Supplemental Materials for

Solid Phase Synthesis of Oligo(*p*-benzamide) Foldamers

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Experimental

Technical solvents were purchased from Acros Organics, solvents of p. a. quality from Fisher Scientific, those for spectrometric measurements and all chemical reagents from Acros Organics and were used as received. Wang resin (1.2 mmol OH g⁻¹) and 9-fluorenylmethyl chloroformate was purchased from Iris Biotech GmbH.

N-methylpyrrolidinone was dried by removing water as benzene azeotrope followed by a fractional distillation at 120°C / 44 mbar. Deuterated solvents (DMSO-d₆ and CDCl₃) were purchased from Deutero GmbH and used as received. Standard ¹H and ¹³C nuclear magnetic resonance spectra were recorded at a frequency of 300 MHz (75 MHz for ¹³C) on a Bruker AC 300. For two dimensional NOESY experiments a Bruker AMX 400 was used working at 400 MHz. Infrared spectra were recorded on a Nicolet 5 DXC FT-IR spectrometer, UV-vis spectra on a Shimadzu UV-210 2 PC scanning spectrophotometer. X-ray crystal structures were obtained on a Turbo CAD 4. The RP HPLC analysis was performed on a HP 1090 Liquid Chromatograph (Hewlett Packard) by using a PerfectSil column (MZ Analysentechnik, Mainz, Germany, 250 x 4.0 µm; 120 ODS-2 5 µm). The samples were eluted with an acetonitrile/water gradient that started from 10 % acetonitrile rising to 90 % over a period of 35 min. Both solvents were buffered with 0.1 % TFA. UV-detection was performed at 254 nm. Melting points were recorded on a FP 62 Mettler Toledo in a capillary tube and are uncorrected. Field desorption mass spectra were measured on a Finnigan MAT 95 and ESI mass spectra on a Micromass Q-TOF Ultima 3.

4-(4-Nitrobenzamido)benzoic acid (2):

4-Aminobenzoic acid **1** (80 g, 0.584 mol) and N,N-dimethylaniline (100 ml) was dissolved in dry acetone (530 ml). To this mixture a solution of 4-nitrobenzoyl chloride (108 g, 0.582 mol) in acetone (130 ml) was added dropwise under stirring and cooling with an ice bath. The reaction mixture was allowed to warm to rt and was stirred for one further hour. The resulting yellow precipitate was collected by filtration and washed with hydrochloric acid (2 N, 400 ml) and water until the filtrate was neutral. The resulting solid was dried under vacuum and crystallized from DMF to give **2** (158.2 g, 95%), m.p. > 300°C.

¹H-NMR (DMSO-d₆): δ 7.93 (m 8.8 Hz, 4 H), 8.18 (d, 8.5 Hz, 2 H), 8.36 (d, 8.5 Hz, 2 H), 10.82 (s, 1 H), 12.75 (s, 1H); ¹³C-NMR: δ 119.8, 123.7, 126.2, 129.5, 130.4, 140.4, 142.9, 149.4, 164.4, 167.0; IR: $\tilde{\nu}$ = 3319 (NH); 3108, 3075 (HAr); 1669 (C=O); 1645 (C=O); 1524, 1342 (NO₂) cm⁻¹. Crystal data: M_r = 432.43 (**2** · 2 DMF), 0.25 x 0.40 x 0.40 mm³; monoclinic; space group P 2₁; Z = 2; a = 9.129(6), b = 12.031(3), c = 9.871(7) Å; β = 102.28(3) °; V = 1059.3(10) Å³; ρ_{calc} = 1.356 gcm⁻³; 2θ_{max} = 146.4 °; R1 = 6.53 %.

N-Hexyl-4-aminobenzoic acid (3):

1 (54.5 g, 0.397 mol) was dissolved in ethanol (1.5 l) while stirring and cooling with an ice bath. Hexanal (48.7 ml, 0.397 mol) was added and the solution was stirred for 10 minutes. Sodium cyanotrihydroborate (25 g, 0.397 mol) was dissolved in ethanol (200 ml) and added dropwise over a period of 1 h. Subsequently, the solution was stirred at 0°C for one hour and was then allowed to warm to rt stirring further 12 h. The solvent was evaporated and the white solid quenched by adding hydrochloric acid (1 M). After a reaction time of 15 minutes the white precipitate was collected by filtration and washed with water until the filtrate was neutral. The crude product was recrystallized from ethanol-water (4:1) and dried in a vacuum oven at 80°C to give **3** (76.7 g, 87 %), m.p. 121 °C.

¹H-NMR (CDCl₃): δ 0.89 (t, 6.5 Hz, 3 H), 1.30 – 1.38 (m, 6 H), 1.59 – 1.64 (m, 2 H), 3.15 (t, 7.2 Hz, 2 H), 6.55 (d, 8.8 Hz, 2 H), 7.92 (d, 8.8 Hz, 2 H); ¹³C-NMR (CDCl₃): δ 13.97, 22.56, 26.7, 29.22, 31.53, 43.3, 111.27, 116.93, 132.31, 152.77, 172.56; IR: $\tilde{\nu}$ = 3362 (N-H); 3040 (HAr); 2923-2857 (CH₂, CH₃); 1655 (C=O); 1595 (N-H) cm⁻¹.

When N-hexyl-4-aminobenzoic acid 3 was synthesized using 2 equivalents of hexanal and only 0.5 equivalents of sodium borohydride or partially decomposed sodium borohydride, a side reaction takes place giving 6-carboxyl-3-butyl-2-pentylquinoline (3b) ^{*)} in 25 % yield.

6-Carboxyl-3-butyl-2-pentylquinoline (3b):

1 (5 g, 0.036 mol) was dissolved in ethanol (150 ml) while stirring and cooling in an ice bath. To this solution sodium borohydride (1.13 g, 0.018 mol) was added in one portion followed by the rapid addition of hexanal (8.8 ml, 0.072 mol). The reaction mixture was stirred at 0°C for one hour and for another 12 h at room temperature. Then the residue was acidified to pH 2 with conc. hydrochloric acid. After extraction with chloroform, drying the organic layer with magnesium sulphate and evaporation of the solvent, the yellow solid was crystallized from ethanol-water (1: 1) to give **3b** (2.68 g, 25 %), m.p. 154°C.

¹H-NMR (CDCl₃): δ 0.88 (t, 7.4 Hz, 4 H), 1.00 (t, 7.4 Hz, 3 H), 1.33-1.91 (m, 13 H), 2.91 (t, 8.1 Hz, 2 H), 3.47 (t, 7.7 Hz, 2 H), 8.43 (d, 8.6 Hz, 1 H), 8.57 (s, 1 H), 8.72 (s, 1 H), 8.94 (d, 9.2 Hz, 1 H); ¹³C-NMR (CDCl₃): δ 13.34, 21.81, 22.00, 29.67, 30.30, 31.79, 31.85, 31.89, 121.69, 126.20, 129.89, 129.93, 130.47, 132.48, 136.48, 139.02, 143.77, 162.42, 167.23;

FD MS: 299.1 ; ESI MS (m / z): 300.2 [M+H]⁺;

Crystal data: M_r = 453.07, 0.128 x 0.32 x 0.512 mm³ colourless block; monoclinic; space group P 2₁/c; z = 4; a = 10.689(2), b = 7.534(2), c = 22.998(4) Å; β = 101.875(9)°; V = 1812.3(6) Å³; ρ_{calc} = 1.163 gcm⁻³.

Fig SI-1 X-ray crystal structure of **3b**.

*) A possible mechanism for the reaction is given in the following report: Kharasch, M.S.; Richlin, I.; Mayo, F.R. *J. Am. Chem. Soc.* **1940**, 62, 494-497.

N-Hexyl-4-(4-nitrobenzamido)benzoic acid (4):

3 (4 g, 0.018 mol) and N,N-dimethylaniline (4 ml) was dissolved in dry acetone (50 ml). To this mixture a solution of 4-nitrobenzoyl chloride (3.35 g, 0.018 mol) in acetone (10 ml) was added dropwise under stirring and cooling with an ice bath. The reaction mixture was allowed to warm to rt and was stirred for one further hour. After acidification with hydrochloric acid

(1 M), yellow oil precipitated that crystallized in the following two days to give **4** (5.96 g, 90 %).

$^1\text{H-NMR}$ (CDCl_3): δ 0.84-1.63 (m, 11 H), 3.95 (t, 7.7 Hz, 2 H), 7.11 (d, 8.5 Hz, 2 H), 7.45 (d, 8.5 Hz, 2 H), 7.94 (d, 8.4 Hz, 2 H), 8.04 (d, 8.5 Hz, 2 H); $^{13}\text{C-NMR}$ (CDCl_3): δ 13.99, 22.5, 26.5, 27.65, 31.42, 50.56, 123.3, 127.48, 127.97, 129.56, 131.51, 141.84, 147.38, 148.18, 168.13, 170.52; IR: $\tilde{\nu}$ = 3076 (HAr); 2933, 2854 (CH_2 , CH_3); 1648 (C=O); 1520, 1339 (NO_2).

Crystal data: M_r = 370.39, 0.06 x 0.32 x 0.38 mm³ colourless plate; monoclinic; space group P 2₁/c; z = 8; a = 24.997(5), b = 8.6063(9), c = 19.087(4) Å; β = 111.239(8)°; V = 3827(1) Å³; ρ_{calc} = 1.286 gcm⁻³.

N,N-9-Fluorenylmethyloxycarbonyl-hexyl- 4-aminobenzoic acid (5):

Method I. **3** (2 g, 0.009 mol) was dissolved in dry N-methylpyrrolidinone (15 ml). 9-Fluorenylmethyl chloroformate (2.3 g, 0.009 mol) was added and the reaction vessel was equipped with a drying tube. After 15 h the reaction was quenched by the dropwise addition of water (20 ml). The resulting suspension was stored for 12 h at 4°C to complete precipitation. After decanting the solvent the precipitate was crystallized from ethanol/water. By addition of seed crystals colorless crystalline needles of **5** (3.77 g, 94 %), m.p. 206 °C, were obtained.

Method II. **3** (11.07 g, 0.05 mol) was dissolved in 8 % sodium carbonate solution (100 ml) while stirring and cooling with an ice bath. Dioxane (50 ml) was added followed by the dropwise addition of 9-fluorenylmethyl chloroformate (13 g, 0.052 mol) in dioxane (75 ml). The mixture was stirred for 1 h at 0°C and then for 22 h at 30°C.^{**) During the reaction a colorless solid precipitated, which was removed by filtration. The dioxane was evaporated and the aqueous phase extracted twice with ether. The aqueous phase was acidified with hydrochloric acid (1 M) to pH 1 while stirring vigorously and cooling with an ice bath. The reaction mixture was stirred for 30 min. The resulting colorless precipitate was collected by filtration and washed with ice-water until the filtrate was neutral. Further purification was achieved by crystallization from ethanol/water (1:2) to give colorless crystalline needles of **5** (18.03 g, 81 %), m.p. 206°C. From the filtrate of crystallization further product was obtained by the addition of water.}

$^1\text{H-NMR}$ (CDCl_3): δ 0.85 (t, 6.8 Hz, 3 H), 1.19 – 1.28 (m, 6 H), 1.4 (t, 6.6 Hz, 2 H), 3.61 (t, 7.2 Hz, 2 H), 4.12 (t, 6.0, 1 H), 4.52 (d, 6.0 Hz, 2 H), 7.16 – 7.23 (m, 4 H), 7.36 (q, 7.5 Hz, 4 H), 7.7 (d, 7.8 Hz, 2 H), 8.05 (d, 8.5, 2 H); $^{13}\text{C-NMR}$ (CDCl_3): δ 13.97, 22.51, 26.23, 28.23,

31.39, 47.15, 50.11, 67.2, 119.9, 124.76, 126.79, 126.91, 126.95, 127.62, 131.02, 141.34, 143.7, 146.78, 154.85, 171.15; IR: $\tilde{\nu}$ = 3073 (HAr), 2933 (CH₂), 1708 (C=O), 1632 (C=O), 1250 (COOCH₂).

) Chang, C. D.; Waki, M.; Ahmad, M.; Meienhofer, J.; Lundell, E. O.; Haug, J. D. *Int. J. Peptide Protein Res.* **1980, *15*, 59-66

N-(4-Methoxybenzyl)-4-aminobenzoic acid (7):

1 (80 g, 0.583 mol) and *p*-anisaldehyde (80 g, 0.587 mol) were dissolved in toluene (450 ml) and heated until reflux by using a Dean-Stark apparatus. After 24 h all water had been removed from the reaction mixture. Toluene was evaporated and the yellow solid residue dissolved in dry THF (400 ml). Under stirring and cooling with an ice bath sodium borohydride (46 g, 1.216 mol) was added in small portions. After 3 days the reaction was quenched by adding 300 ml of water resulting in a vigorous hydrogen formation. Hydrochloric acid (1 M) was added until the reaction mixture was neutral. The resulting white precipitate was collected by filtration, and dried at 40°C in a vacuum oven to give **7** (103 g, 69 %), m.p. 204°C.

¹H-NMR (DMSO-d₆): δ 3.71 (s, 3 H), 4.23 (d, 5.9 Hz, 2 H), 6.59 (d, 8.5 Hz, 2 H), 6.89 (d, 8.1 Hz, 2 H), 6.95 (t, 5.9, 1 H), 7.24 (d, 8.4 Hz, 2 H), 7.61 (d, 8.4 Hz, 2 H), 11.99 (s, 1 H); ¹³C-NMR (DMSO-d₆): δ 45.37, 55.02, 111.18, 113.79, 117.07, 128.47, 131.06, 152.42, 158.24, 167.5 ; IR $\tilde{\nu}$ = 3359 (NH); 3023 (HAr), 2933 (CH₂); 2837 (CH₃); 1652 (C=O); 1592 (NH).

N-(4-Methoxybenzyl)-4-(4-nitrobenzamido)benzoic acid (8):

1 (10g, 0.038 mol) and triethylamin (6 ml) were dissolved in dichloromethane (50 ml). To this mixture a solution of 4-nitrobenzoyl chloride (8 g, 0.043 mol) in dichloromethane (20 ml) was added dropwise under stirring and cooling with an ice bath. The reaction mixture was allowed to warm to rt and was stirred for one further hour. The resulting yellow precipitate was collected by filtration and washed with hydrochloric acid (2 N, 400 ml) and then with water until the filtrate was neutral. After crystallization from ethanol yellow plates of **8** precipitated (14 g, 98 %), m.p. 188.3°C.

¹H-NMR (CDCl₃): δ 3.77 (s, 3 H), 5.09 (s, 2 H), 6.82 (d, 8.9 Hz, 2 H), 6.98 (d, 8.5 Hz, 2 H), 7.19 (d, 8.5 Hz, 2 H), 7.48 (d, 8.4 Hz, 2 H), 7.9 (d, 8.5 Hz, 2 H), 8.04 (d, 8.5 Hz, 2 H); ¹³C-NMR (CDCl₃): δ 53.24, 55.21, 114.06, 123.27, 127.78, 128.04, 128.32, 129.58, 129.94, 131.38, 141.58, 147.13, 148.27, 159.26, 168.25, 170.38; IR: $\tilde{\nu}$ = 3076 (HAr); 2993 (CH₂); 2834 (CH₃); 1711 (C=O); 1632 (C=O); 1512, 1343 (NO₂).

Crystal data: $M_r = 406.38$, $0.1 \times 0.66 \times 0.9 \text{ mm}^3$ colourless plate; orthorhombic; space group $Pna2_1$; $z = 4$; $a = 16.0866(8)$, $b = 17.8033(10)$, $c = 7.1185(4) \text{ \AA}$; $V = 2038.7(2) \text{ \AA}^3$; $\rho_{\text{calc}} = 1.324 \text{ gcm}^{-3}$.

N,N-9-Fluorenylmethyloxycarbonyl-(4-methoxybenzyl)-4-aminobenzoic acid (9):

7 (20 g, 0.077 mol) was dissolved in dry N-methylpyrrolidinone (150 ml). 9-Fluorenylmethyl chloroformate (20.1 g, 0.077 mol) was added and the reaction vessel was equipped with a drying tube. After 15 h the reaction was quenched by the dropwise addition of water (200 ml). The resulting suspension was stored for 12 h at 4°C until the solvent phase became clear. The liquid phase was decanted and stored for two days to give crystals of **9** (31.4 g, 85 %), m.p. 154°C . By the addition of small amounts of water further product was obtained. The solid residue, which was leftover from decantation, was crystallized from ethanol/water. After crystallization brown oil precipitated. The liquid phase was decanted and nucleation was started by adding seed crystals.

$^1\text{H-NMR}$ (CDCl_3): δ 3.77 (s, 3 H), 4.11 (t, 6.2 Hz, 1 H), 4.54 (d, 6.2 Hz, 2 H), 4.76 (s, 2 H), 6.79 (d, 8.5 Hz, 2 H), 6.98 (d, 8.4 Hz, 2 H), 7.06 – 7.38 (m, 8 H), 7.68 (d, 7.7 Hz, 2 H), 7.97 (d, 8.5 Hz, 2 H); $^{13}\text{C-NMR}$ (CDCl_3): δ 47.12, 53.2, 55.18, 67.5, 113.91, 119.9, 124.79, 126.84, 126.99, 127.11, 127.66, 129.1, 129.19, 130.96, 141.31, 143.56, 146.53, 155.09, 158.94, 171.2; IR: $\tilde{\nu} = 3065$ (HAr); 2950 (CH_2); 2834 (CH_3), 1701 (C=O); 1652 (C=O); 1243 (COOCH_2).

N,N-9-Fluorenylmethyloxycarbonyl-(4-methoxybenzyl)-4-aminobenzoic acid dimer (10):

9 (10 g, 0.02 mol) was dissolved in dry N-methylpyrrolidinone (100 ml) at rt followed by the dropwise addition of thionyl chloride (1.45 ml, 0.02 mol). After 60 minutes compound **7** (5.14g, 0.02 mol) was added, which was dissolved in dry N-methyl-pyrrolidinone (100 ml). The solution was stirred over night equipped with a drying tube. By the dropwise addition of water (200 ml) a solid precipitated that was purified by column chromatography (silica, ethyl acetate:hexane = 7:3) to give **10** (5.23g, 36 %), m.p. 93.8°C .

$^1\text{H-NMR}$ (CDCl_3): δ 4.00 (t, 6.2 Hz, 1 H), 4.38 (d, 6.7 Hz, 2 H), 4.63 (s, 2 H), 5.1 (s, 2 H), 6.73 (d, 8.8 Hz, 2 H), 6.92 (d, 8.4 Hz, 2 H), 6.79-6.9 (m, 8 H), 7.13-7.34 (m, 12 H), 7.65 (d, 7.7 Hz, 2 H), 7.73 (d, 8.4 Hz, 2 H); $^{13}\text{C-NMR}$ (CDCl_3): δ 14.15, 46.94, 53.04, 53.25, 55.18, 60.39, 67.64, 113.76, 113.95, 119.88, 124.88, 126.89, 127.07, 127.28, 127.61, 129.02, 129.14, 129.29, 129.56, 129.62, 130.98, 133.56, 141.24, 143.07, 143.61, 148.25, 155.12,

158.9, 159.05, 169.05, 169.74, 170.15; IR: $\tilde{\nu}$ = 3066 (HAr); 2947 (CH₂); 2831 (CH₃); 1705 (C=O); 1645 (C=O); 1240 (COOCH₂).

Solid Phase Synthesis of decamer 11j using the N-Fmoc protected PBM-Monomer (9):

Wang resin (500 mg, initial loading 1.2 mmol/g, 0.6 mmol, 1 equiv.) was swollen in dry NMP (5 ml) for 30 min. The surmounting solvent was removed with a pipette. **9** (863 mg, 1.8 mmol, 3 equiv.) was dissolved in dry NMP (2 ml) and the solution was evacuated four times (1×10^{-2} mbar). Then SOCl₂ (130.5 μ l, 1.8 mmol, 3 equiv.) was added dropwise under nitrogen. After 1 h reaction time the solution was added to the resin and the suspension was allowed to react for 1 h while shaking. The resin was filtered and washed with NMP (5 x 1 min). To determine the loading of **9**, the resin was reacted with 4-nitrobenzoyl chloride (556 mg, 3 mmol, 5 equiv.) in dry NMP (3 ml) for 30 min. Using TFA/CH₂Cl₂ (50%, 1 ml) as cleaving reagent analytical amounts of sample were cleaved from the resin within a time of 30 min and were analysed by RP HPLC. By comparing the height of the elution signal of the cleaved 4-nitrobenzoic acid with the one of cleaved monomer (which is equal to compound **9**) the loading turned out to be nearly 100 % of the desired product.

The Fmoc protection was removed by the use of 20% piperidine in NMP (20 ml, 5 x 2 min). After washing the resin with NMP (3 x 1 min) and CH₂Cl₂ (5 x 1 min) the coupling was monitored by ESI MS (pos. mode).

Following this synthetic strategy, all further coupling steps were lead through. Monitoring of each coupling step was performed by RP HPLC experiments by comparing elugrams of former couplings with the current one. After each coupling step, capping was carried out by the use of acetyl chloride/NMP (50 %) before removal of the Fmoc group.

Solid Phase Synthesis of decamer 11j using the N-Fmoc protected PBM-Dimer (10):

Wang resin (250 mg, initial loading 1.2 mmol/g, 0.3 mmol, 1 equiv.) was swollen in dry NMP (5 ml) for 30 min. The surmounting solvent was removed with a pipette. **10** (1.795 g, 2.4 mmol, 8 equiv.) was dissolved in dry NMP (4 ml) and the solution was evacuated four times (1×10^{-2} mbar). Then SOCl₂ (174 μ l, 2.4 mmol, 8 equiv.) was added dropwise under nitrogen. After 1 h reaction time the solution was added to the resin and the suspension was allowed to react for 18-20 h while shaking. The resin was filtered and washed with NMP (5 x 1 min). To determine the loading of **10**, the resin was reacted with 4-nitrobenzoyl chloride (250 mg, 1.5 mmol, 1.5 equiv.) in dry NMP (1.5 ml) for 30 min. Using TFA/CH₂Cl₂ (50%, 1 ml) as cleaving reagent analytical amounts of sample were cleaved from the resin within a

time of 30 min and were analysed by RP HPLC. The loading was determined to vary between 50 to 90%.

The Fmoc protection was removed by the use of 20% piperidine in NMP (20 ml, 5 x 2 min). After washing the resin with NMP (3 x 1 min) and CH₂Cl₂ (5 x 1 min) the coupling was monitored by ESI MS (pos. mode).

Following this synthetic strategy, all further coupling steps were lead through. Monitoring of each coupling step was performed by RP HPLC experiments by comparing elugrams of former couplings with the current one. After each coupling step, capping was carried out by the use of acetyl chloride/NMP (50 %) before removal of the Fmoc group.

Solid phase coupling of (9) with HBTU^{*}):**

Compound **9** (72 mg, 0.15 mmol, 5 equiv.) and HBTU (55 mg, 0.147 mmol, 4.9 equiv.) was weighed out into a dry glass vial. Then a minimum of NMP was added to effect total dissolution. After addition of DIPEA (39 mg, 0.3 mmol, 10 equiv.) the solution was mixed thoroughly and was added to monomer loaded, N-deprotected resin (Wang resin, initial loading 1.2 mmol/g, 25 mg, 0.03 mmol, 1 equiv.; loaded with one unit of **9**). After a reaction time of 1 h, the resin was washed with NMP (3 x 1 min) and CH₂Cl₂ (5 x 1min) and an analytical amount of sample was cleaved from the resin by the use of 50 % TFA in CH₂Cl₂ within 30 min. RP HPLC monitoring showed no product formation.

Solid phase coupling of (9) with HATU^{*}):**

Compound **9** (72 mg, 0.15 mmol, 5 equiv.) and HATU (56 mg, 0.147 mmol, 4.9 equiv.) was weighed out into a dry glass vial. Then a minimum of NMP was added to effect total dissolution. After addition of DIPEA (39 mg, 0.3 mmol, 10 equiv.) the solution was mixed thoroughly and was added to monomer loaded, N-deprotected resin (Wang resin, initial loading 1.2 mmol/g, 25 mg, 0.03 mmol, 1 equiv.; loaded with one unit of **9**). After a reaction time of 1 h, the resin was washed with NMP (3 x 1 min) and CH₂Cl₂ (5 x 1min) and an analytical amount of sample was cleaved from the resin by the use of 50 % TFA in CH₂Cl₂ within 30 min. RP HPLC monitoring showed no product formation.

***) "Fmoc Solid Phase Peptide Synthesis: a Practical Approach", Eds. W.C. Chang, P.D. White, Oxford University Press, Oxford, **2000**, p. 58.

Removal of the *N*-(4-methoxybenzyl) protecting group:

Compound **8** (1 g, 2.4 mmol) was dissolved in TFA (5 ml) and stirred for 24 h at rt. The colourless precipitate was obtained by filtration in near quantitative yield (0.673 g, 98 %). ¹H-NMR analysis showed that it was identical to compound **2**.

Synthesis of compounds as HPLC references (see Fig. SI-3)**4-(4-amino-N-(4-methoxybenzyl)benzamido)benzoic acid (SI-01)**

A Schlenk-flask flushed with nitrogen was equipped with ammonium formate (4g), **8** (4g, 9.8 mmol) and methanol (30 ml). Under a slight stream of nitrogen, Pd/C (10%, 100 mg) was added to the mixture under vigorous stirring. The reaction mixture was stirred at rt for 3d under a N₂-atmosphere. The mixture was filtered through Celite and all volatiles were removed under vacuum. The residue was taken up in water. The insoluble fraction was isolated by filtration and the filtrate acidified with HCl (1M) until a white precipitate was formed. (NMR analysis revealed that both solid fractions were identical.) The combined solids were dried under vacuum to yield 3.1 g (85%).

¹H-NMR (DMSO-d₆): δ 3.68 (s, 3 H), 5.03 (s, 2 H), 6.32 (d, 8.8 Hz, 2 H), 6.81 (d, 8.8 Hz, 2 H), 7.01 (d, 8.8 Hz, 2H), 7.08 (d, 8.5 Hz, 2H), 7.17 (d, 8.8 Hz, 2H), 7.73 (d, 8.5 Hz, 2H)

FD MS: 376.5

N-Fmoc-4-(4-amino-N-(4-methoxybenzyl)benzamido)benzoic acid (SI-02)

SI-01 (2.6 g, 7 mmol) and Fmoc-Cl (1.8 g, 7 mmol) were added as solids to a one-neck flask. Dry NMP (20 ml) was added and the mixture stirred for 12h at rt. Water was added slowly

until a white solid precipitated. The solid was collected by filtration, dried under vacuum and recrystallized from ethanol to give 3.56 g (86%).

$^1\text{H-NMR}$ (DMSO- d_6): δ 3.68 (s, 3H), 4.27 (t, 6.3 Hz, 1H), 4.47 (d, 6.25 Hz, 2H), 5.05 (s, 2H), 6.81 (d, 8.5 Hz, 2H), 7.10 (d, 8.5 Hz, 2H), 7.16-7.25 (m, 6H), 7.30-7.35 (m, 2H), 7.38-7.43 (m, 2H), 7.69-7.75 (m, 4H), 7.87 (d, 7.4 Hz, 2H), 9.84 (s, 1H)

FD MS: 599.3; HPLC analysis, see Fig. SI-3.

HPLC and ESI-MS characterization of oligomers 11a-j

- coupling with activated 9 -

Fig. SI-2 HPLC elugrams of **11a-j** cleaved with TFA from an analytical resin sample. The oligomers are still Fmoc-protected. After each coupling step with activated monomer **9**, capping with acetyl chloride was carried out. The elugram clearly shows that with increasing oligomer length the elution times become longer. This is expected as the hydrophobicity increases with increasing oligomer length. Impurities corresponding to capped (acetylated) shorter oligomers can not be detected in the elugrams.

Fig. SI-3 HPLC elugrams of **11a** and **11b** (see Fig. SI-2) as well as pure **9**, **10**, an analytical sample of *N*-Fmoc-*p*-aminobenzoic acid and **SI-02**. The coupling times between unfunctionalized Wang resin, **11a** and **11b** were 1 hour each. The elugram for **11a** shows the desired product as well as product from which the PMB-group was cleaved. This loss of the PMB-protecting group occurred most likely during acidic cleavage from the resin. Comparisson of the elugrams of **11a** and **11b** shows that none of the peaks of **11a** are present in the elugram of **11b**. The peak at ca. 32 min. in the **11b** elugram is the desired fully protected product, the peak at ca. 29 min. is most likely the PMB-deprotected species **SI-02**. As the oligomer length increases the probability of cleaving one or more PMB-groups increases. The isomers that have lost one PMB-group will elute at slightly different times giving rise to a complex elugram as for example seen for **11j** (Fig. SI-2).

Fig. SI-4 ESI-MS spectrum of **11b**.

Fig. SI-5 ESI-MS spectrum of **11c**.

Fig. SI-6 ESI-MS spectrum of **11d**.

Fig. SI-7 ESI-MS spectrum of **11e**.

Fig. SI-8 ESI-MS spectrum of **11f**.

Fig. SI-9 ESI-MS spectrum of **11g**.

Fig. SI-10 ESI-MS spectrum of **11h**.

Fig. SI-11 ESI-MS spectrum of **11i**.

Fig. SI-12 ESI-MS spectrum of **11j**.

HPLC and ESI-MS characterization of oligomers **11b,d,f,h,j** - coupling with activated **10** -

Fig. SI-13 HPLC elugrams of **11b**, **11d**, **11f**, **11h**, **11j** cleaved with TFA from an analytical resin sample. The oligomers are Fmoc-deprotected. Coupling was carried out with activated monomer **10**. The coupling time for each step is ca. 20 hours.

Fig. SI-14 ESI-MS of **11d**.

Fig. SI-15 ESI-MS of **11f**.

Fig. SI-16 ESI-MS of **11h**.

Figure SI-17. ESI-MS of **11j** as cleaved from the resin.

Determination of amide conformation via x-ray crystallographic and NMR-spectroscopic data

4-(4-Nitrobenzamido)benzoic acid (2):

Fig. SI-18 X-ray crystal structure of **2**.

Fig. SI-19 COSY NMR spectrum (DMSO- d_6 , 400MHz) of **2**.

Fig. SI-20 NOESY NMR spectrum (DMSO- d_6 , 400MHz) of **2**.

N-Hexyl-4-(4-nitrobenzamido)benzoic acid (4**):**

Fig. SI-21 X-ray crystal structure of **4**.

Fig. SI-22 COSY NMR spectrum (CDCl_3 , 400MHz) of **4**.

Sig. SI-23 NOESY NMR spectrum (CDCl_3 , 400MHz) of **4**. The cross-peaks between protons **2** and **3** are circled, showing the cis-conformation of the amide bond.

N-(4-Methoxybenzyl)-4-(4-nitrobenzamido)benzoic acid (8**):**

Fig. SI-24 X-ray crystal structure of **8**.

Fig. SI-25 COSY NMR spectrum (CDCl₃, 400MHz) of **8**.

Fig. SI-26 NOESY NMR spectrum (CDCl₃, 400MHz) of **8**. The cross-peaks between protons **2** and **3** are circled, showing the cis-conformation of the amide bond.