

Synthesis of aromatic and heteroaromatic oligoamides on methoxypoly(ethylene glycol) as solubilizing polymer support

Burkhard König,* Ulrich Papke and Martin Rödel

Institut für Organische Chemie Universität Regensburg, D-93040, Regensburg, Germany

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A protecting-group-free procedure for the synthesis of short carbo- and heteroaromatic oligoamide chains on MeO-PEG as solubilizing support is introduced. Starting from nitrocarboxylic acids, oligoamides of carboxylic acids derived from *N*-methylpyrrole, *N*-methylimidazole and aniline are synthesized that contain up to five arene units. The polymer support facilitates work up procedures and markedly improves the otherwise poor solubility of the products. Each coupling step is monitored by ^1H -NMR spectroscopy without cleavage of the product from the polymeric support.

Heteroaromatic oligoamides containing *N*-methylpyrrole (Py) and *N*-methylimidazole (Im) amino acids are an essential part of the structure of DNA-binding natural products, such as netropsin¹ or distamycin.² Inspired by these compounds and their properties, Dervan, Wemmer and others have developed synthetic heteroaromatic oligoamides that bind sequence specifically to DNA.³ The recently reported fascinating results of highly specific binding at nanomolar concentrations⁴ and *in vivo* gene regulation⁵ by such compounds makes their future application in gene therapy or biotechnology very likely. Baird and Dervan have provided a procedure for the synthesis of heteroaromatic oligoamides by automated solid phase synthesis, by which even extended oligoamides are available in almost every desirable combination using Boc-protected heteroaromatic amino acids as building blocks.⁶

We report here the synthesis of short heteroaromatic oligoamides on a soluble polymer support.⁷ A protecting-group-free procedure using methoxypoly(ethylene glycol) (MeO-PEG-OH), **1**, with an average molecular weight of 5000 g mol⁻¹ as an inexpensive support⁸ provides practical access to oligoamides for the synthesis of DNA binding agents or other purposes. Readily available nitrocarboxylic acids are used as the starting material. They are reduced to the corresponding amine after being successfully coupled to the support. It is not intended to provide a competing procedure to the reported automated solid phase synthesis⁶ of extended oligoamides: the well known restrictions of the MeO-PEG support in the synthesis of large peptides⁹ and the difficulty of automation limit the synthesis to short oligoamides. However, synthesis on a MeO-PEG-OH solid support does offer some advantages: the handling and characterization of insoluble oligoamides is facilitated, commercially or readily available nitro compounds are employed as starting materials and every reaction step can be monitored by NMR without cleavage of the oligoamide from the polymer. This promotes the optimization of the coupling conditions for each step, which is usually required because of the significant differences in reactivity of aromatic and heteroaromatic amino acids in amide bond formation. We provide here general procedures for oligoamide synthesis on a liquid–solid support and illustrate the feasibility of the synthetic route by some examples.

Results and discussion

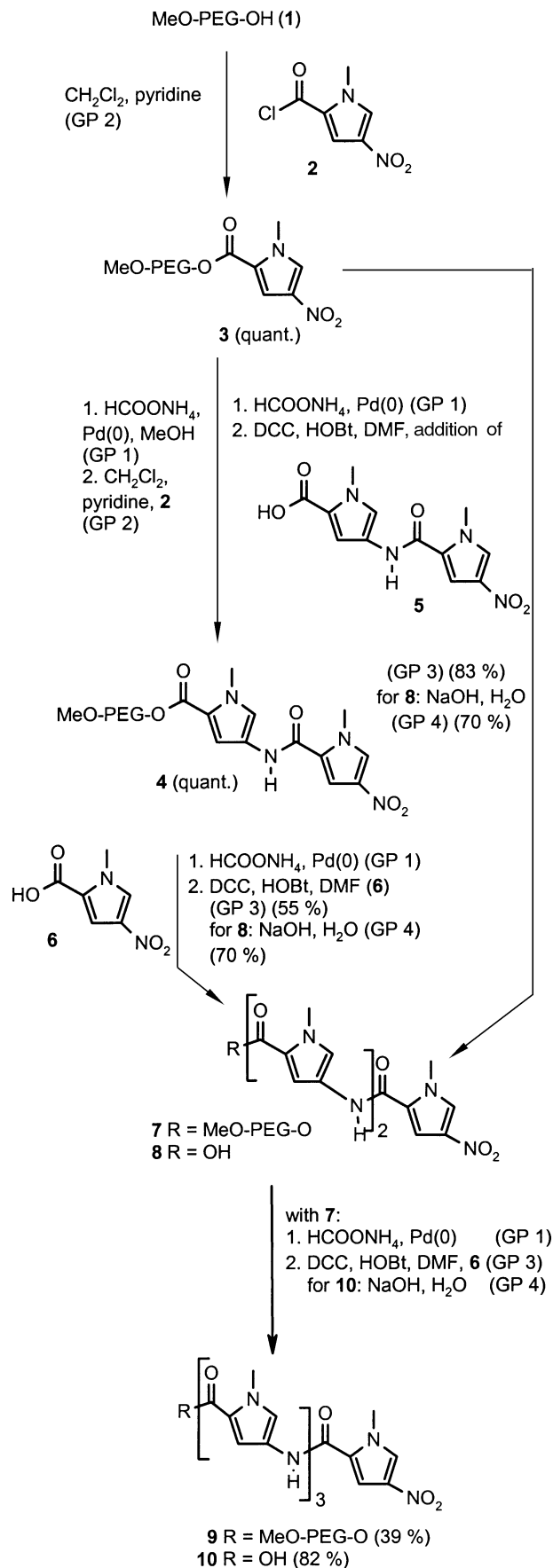
In the first step 1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl chloride, **2**,¹⁰ is quantitatively bound to MeO-PEG-OH (**1**) *via* an

ester linkage using standard conditions (Scheme 1). For purification the polymer-bound product **3** is precipitated by addition of Et₂O and collected by filtration (see general procedure 2 in the Experimental section). The excess of acid chloride is removed by washing with ether. In the next step the nitro group is reduced with HCOONH₄–Pd/C in methanol solution for 1 h at room temperature (see general procedure 1 in the Experimental section). The catalyst is removed by filtration over Celite and Et₂O is added to precipitate both the amine and excess HCOONH₄. The solid is dissolved in dichloromethane leaving behind excess HCOONH₄ and the obtained solution is used directly in the next reaction step. Reaction with **2** leads to the polymer-bound amide **4** with quantitative loading of the polymer, which is determined by NMR spectroscopy (*vide infra*). Repetition of the reduction–coupling cycle gives diamide **7**, but the loading of the polymer decreases to 55%. A polymer loading of 83% is obtained with compound **5**,¹⁰ which illustrates that the ester linkage of the heteroarene chain to MeO-PEG is not fully stable under the coupling conditions.¹¹ Introduction of the next pyrrole yields pure triamide **9**, but the loading of the support decreases to 39%. Finally, the oligoamides are cleaved from the polymer support by treatment with base, which provides **8**¹² and **10** as carboxylic acids in good yield (see general procedure 4 in the Experimental section).

Fig. 1 shows part of the ^1H -NMR spectra of **3** (top), **4** (middle) and **7** (bottom), making the growth of the oligoamide chain visible. Resonance signals of *N*-methyl groups successively appear, indicating the incorporation of a new pyrrole ring. Comparison of the integral of each signal with the methoxy resonance of MeO-PEG ($\delta = 3.37$), which is used as an internal standard, allows the determination of reaction yields and polymer loading.

A particular advantage of oligoamide synthesis on a liquid–solid support is the possibility to control the success of coupling without cleavage from the polymer. This is illustrated by the synthesis of *N*-methylimidazole *N*-methylpyrrole diamide, **15**, in Scheme 2. Though the nitrocarboxylic acid **11** can be coupled to the preceding amine, the reaction of compound **12**, after reduction, with **6** is not successful. The low reactivity of the imidazole amine group in amide formation under standard conditions has been observed previously.⁶ To obtain **14** the use of **13**⁶ in the amide coupling is required, which was confirmed by the analysis of the polymer-bound reaction products by NMR.

Starting from the corresponding nitrocarboxylic acids new aromatic or heteroaromatic amino acids, which have not been



used for the synthesis of oligoamides so far, can be introduced. This is illustrated (Scheme 3) by the reaction of *m*-nitrobenzoic acid, **16-OH**, which leads to the synthesis of an analog, **19**, of the distamycin amide core in which the central *N*-methylpyrrole unit is replaced by a 1,3-disubstituted benzene

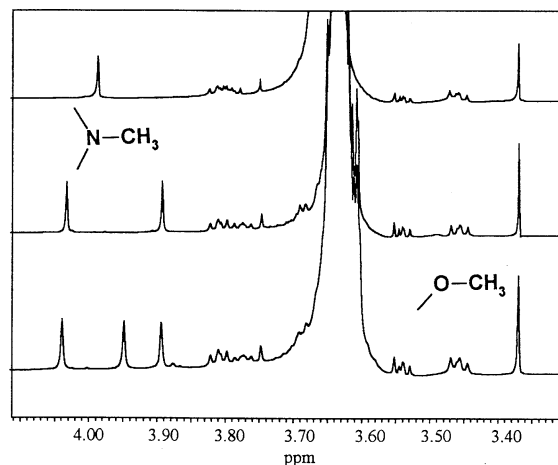
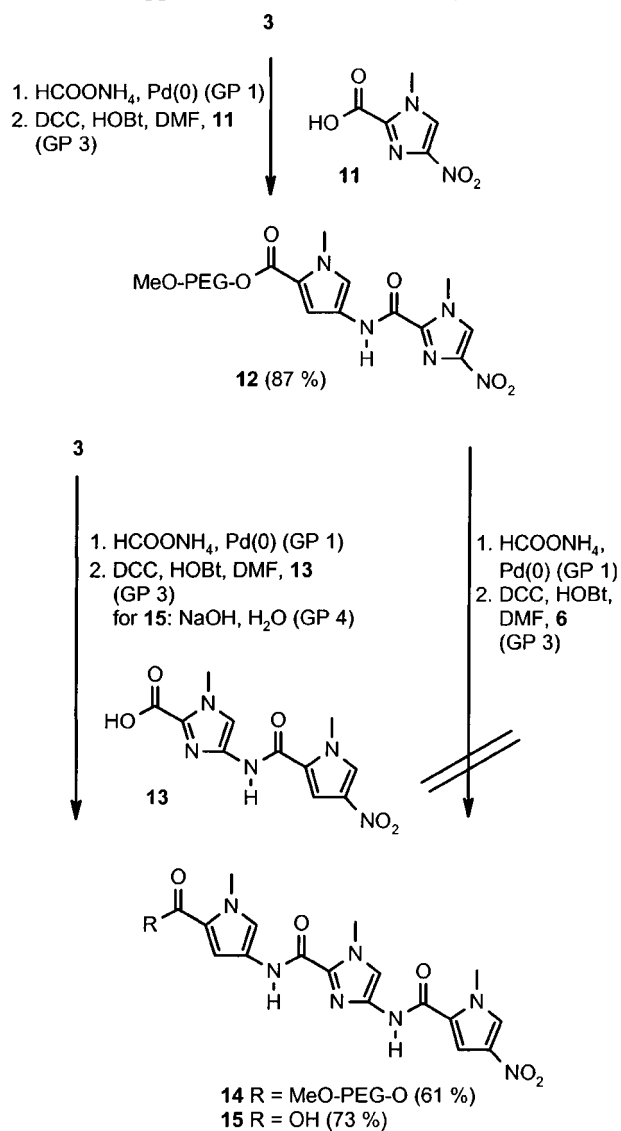
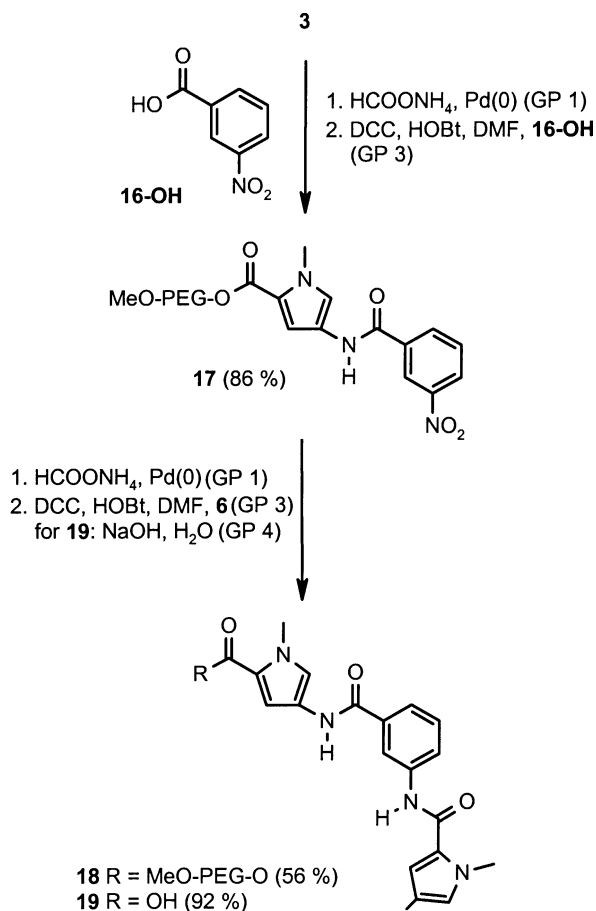


Fig. 1 Part of the ¹H-NMR (400 MHz, CDCl₃) spectrum of polymer-bound *N*-methylpyrrole oligoamides. From top to bottom: compounds 3, 4 and 7.

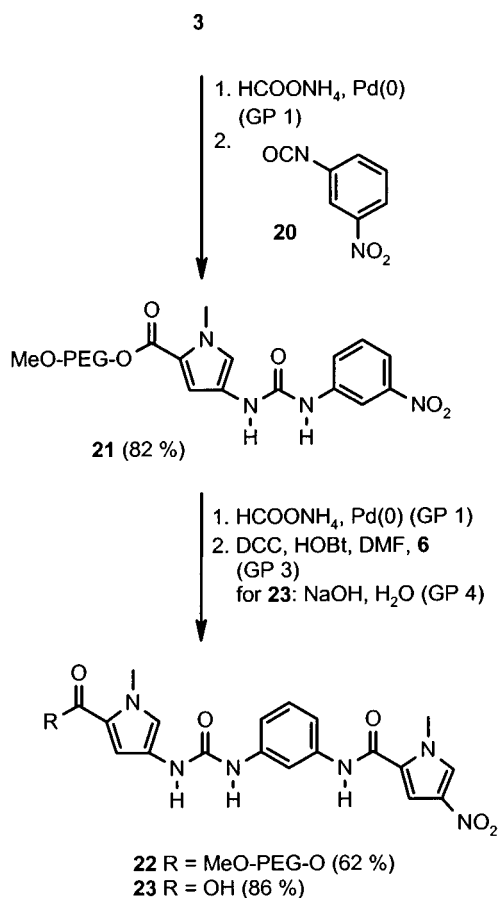
ring. Again, the success of amide formation for each step is monitored by NMR. Compounds in which one amide linkage is replaced by a urea moiety, such as **23**, are obtained from the reaction (Scheme 4) with nitroisocyanates (**20**).

Extended aromatic oligoamides are known for their low solubility in organic solvents.¹³ The unique properties of the MeO-PEG support facilitates the handling and character-

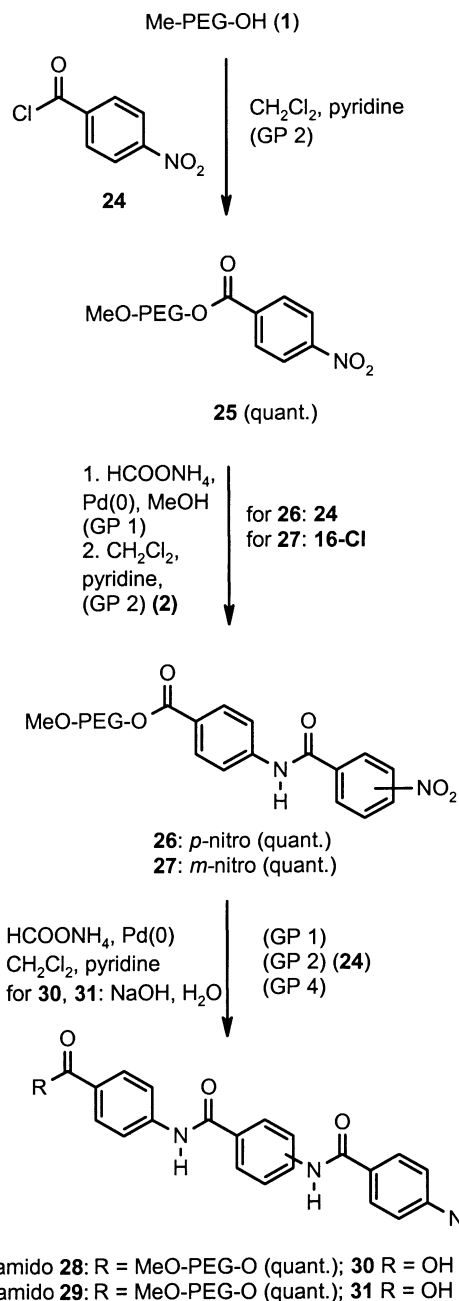




Scheme 3



Scheme 4

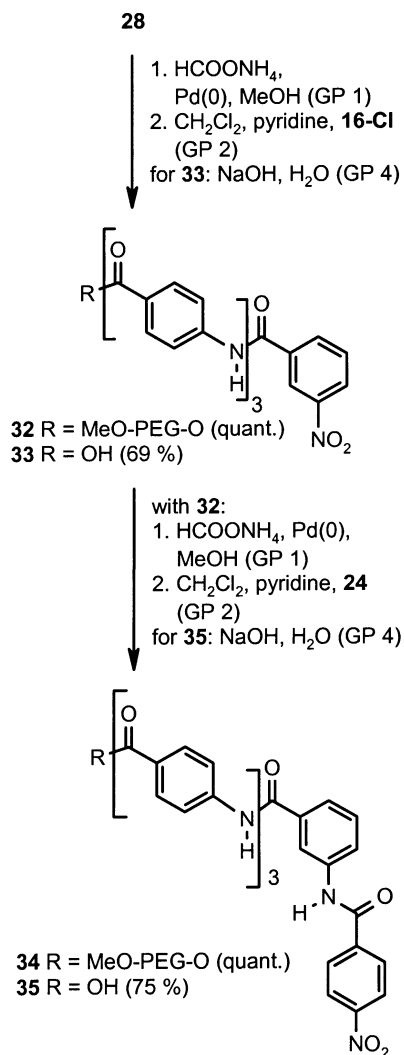


Scheme 5

ization of such compounds markedly, as shown by the synthesis of **30**, **31** and **35** (see Schemes 5 and 6). With nitrobenzoic acids as building blocks for oligoamide synthesis we observed a constant quantitative loading of the polymer support and complete conversion for all coupling and reduction steps up to the tetraamide **34**. The growth of the aromatic oligoamide chain is monitored by the ^1H -NMR resonances of the amide signals of compounds **26**, **28**, **32** and **34** (Fig. 2, from top to bottom).

Conclusion

In summary we have presented a simple and affordable procedure for the synthesis of short heteroaromatic and aromatic oligoamides. The described synthesis on MeO-PEG as solid support combines the convenience of solid phase procedures, such as simplified work up and removal of excess coupling reagents, with the advantages of solution reactions, such as short reaction times and the use of heterogeneous catalysts. Starting from readily available nitrocarboxylic acids, carbo- and heteroaromatic oligoamides with up to five arene units



Scheme 6

were obtained, whereby neither protecting groups, nor expensive chemicals or special apparatus are necessary. The synthesis of libraries of oligoamides from nitrocarboxylic acids may be envisaged. We hope that the reported procedure will make heteroaromatic and aromatic oligoamides more widely available and stimulate their application in biotechnology or separation techniques, such as new stationary chromatography phases.¹⁴

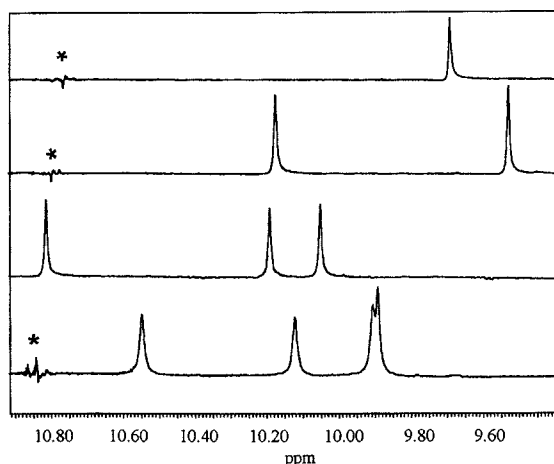


Fig. 2 Amide proton resonance region of the ¹H-NMR spectrum (400 MHz, CDCl₃) of polymer-bound aromatic oligoamides. From top to bottom: compounds **26**, **28**, **32** and **34**. * denotes a noise signal.

Experimental

General

NMR spectra were recorded at 400 (¹H) and 100 (¹³C) MHz in [D]₃-chloroform solutions unless otherwise stated. The multiplicity of the ¹³C signals was determined with the DEPT technique and are denoted as (+) for CH₃ or CH, and (C_{quat}) for quaternary carbons. Direct inlet EI mass spectra were recorded at 70 eV on a double focusing sector field instrument (Finnigan MAT, MS8430). The source temperature was set to 200 °C. High resolution experiments were performed at a resolution of 10 000 (10% valley) by peak matching. In some cases where molecular ion intensities were too low for exact mass determination characteristic fragment ions (*e.g.*, M⁺ – CO₂) were used instead. The percentage of polymer loading with oligoamide product was determined from comparison of the integrals of the ¹H-NMR resonance of the terminal MeO-PEG methoxy group and a significant signal of the oligoamide residue. Py and Im indicate pyrrole and imidazole amino acids, respectively. HOBT·H₂O stands for hydroxybenzotriazole and DIEA for *N,N*-diisopropylethylamine. *m*Ph and *p*Ph denote 1,3- and 1,4-benzoic amino acid, respectively.

General procedure 1 (GP 1) for the reduction step

The MeO-PEG-bound nitro compound was dissolved in methanol (not more than 100 ml). For large-scale reactions a minimum amount of dichloromethane had to be added until all of the solid was dissolved. Excess HCOONH₄ and 10% palladium on carbon were added, and the reaction mixture was stirred for 1 h at room temperature. The start of the reaction was indicated by the evolution of gas. In cases where this could not be observed the reaction mixture was heated with a heat gun for a short period. After 1 h at room temperature the catalyst was removed by filtration over Celite and Et₂O was added (250–1000 ml depending on the scale of the reaction) to precipitate the generated MeO-PEG-bound amine and excess HCOONH₄. The solid was collected by suction and dissolved in dichloromethane leaving behind excess HCOONH₄, which was filtered off. The obtained solution is directly used in GP 2 or GP 3.

General procedure 2 (GP 2) for coupling with acid chlorides

To the solution obtained from GP 1 or to a solution of MeO-PEG-OH in dichloromethane, an excess of pyridine and 3–5 equiv. of the appropriate acid chloride were added and the reaction mixture was stirred for 12 h. The product was precipitated by addition of Et₂O and collected by filtration. The polymer was redissolved and precipitated twice for purification, then dried *in vacuo*.

General procedure 3 (GP 3) for the coupling step with activated acids

The appropriate acid (3–5 equiv.) was activated with DCC and HOBT·H₂O (1.0 equiv. of each, corresponding to the amount of acid) in DMF (25 ml) for 4 h. To this reaction mixture the solution obtained from GP 1 was added, followed by an excess of DIEA. After 12 h stirring at room temperature the reaction mixture was filtered and the product was precipitated by addition of Et₂O, and collected by filtration. The polymer was redissolved, precipitated twice and dried *in vacuo*.

General procedure 4 (GP 4) for the cleavage of oligoamide from the polymer

The MeO-PEG-bound oligoamide was dissolved in 10 ml of aqueous 2 N NaOH and stirred at room temperature for 12 h.

The solution was acidified with HCl, the precipitated oligoamide was collected by filtration and dried *in vacuo*.

Syntheses and product characterization

MeO-PEG-Py-NO₂ (3). MeO-PEG-OH (1, 50.0 g, 10.0 mmol) was allowed to react with **2** (5.67 g, 30.0 mmol) following GP 2 (pyridine: 10 ml) to yield **3** with quantitative loading of the polymer. ¹H-NMR: δ = 3.99 (s, 3H), 7.43 (d, ⁴J = 2.0 Hz, 1H), 7.68 (d, ⁴J = 2.0 Hz, 1H).

MeO-PEG-Py-Py-NO₂ (4). Compound **3** (5.0 g, 1.0 mmol) was reduced using GP 1 (HCOONH₄: 1.0 g, 15.9 mmol; Pd/C: 100 mg) and subsequently allowed to react with **2** (567 mg, 3.0 mmol) following GP 2 (pyridine: 1 ml) to yield **4** with quantitative loading of the polymer. ¹H-NMR: δ = 3.90 (s, 3H), 4.03 (s, 3H), 7.05 (d, ⁴J = 2.0 Hz, 1H), 7.45 (d, ⁴J = 2.0 Hz, 1H), 7.60 (d, ⁴J = 2.0 Hz, 1H), 7.68 (d, ⁴J = 2.0 Hz, 1H), 8.98 (s, 1H).

MeO-PEG-Py-Py-Py-NO₂ (7). Compound **3** (1.0 g, 0.2 mmol) was reduced using GP 1 (HCOONH₄: 0.5 g, 7.9 mmol; Pd/C: 120 mg) and subsequently allowed to react with **5** (175 mg, 0.6 mmol) following GP 3 (DCC: 124 mg, 0.6 mmol; HOBT·H₂O: 92 mg, 0.6 mmol; DIEA: 1 ml) to yield **7** with 83% loading of the polymer. ¹H-NMR: δ = 3.90 (s, 3H), 3.95 (s, 3H), 4.05 (s, 3H), 6.86 (d, ⁴J = 2.0 Hz, 1H), 6.91 (s, 1H), 7.32 (s, 1H), 7.46 (d, ⁴J = 1.5 Hz, 1H), 7.50 (d, ⁴J = 1.5 Hz, 1H), 7.60 (d, ⁴J = 1.5 Hz, 1H), 8.51 (s, 1H), 9.18 (s, 1H).

HO₂C-Py-Py-Py-NO₂ (8)¹². Compound **7** (400 mg, 0.074 mmol) was treated according to GP 4 and yielded 21 mg (0.05 mmol) of **8** (70%) as a yellow solid. IR(KBr): $\tilde{\nu}$ = 3408, 2953, 1665, 1438 cm⁻¹. UV(CH₃CN): λ_{\max} (log ϵ) = 240 (4.36), 296 (4.43) nm. ¹H-NMR (400 MHz, DMSO-d₆): δ = 3.82 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 6.85 (d, ⁴J = 1.9 Hz, 1H), 7.05 (d, ⁴J = 1.8 Hz, 1H), 7.26 (d, ⁴J = 1.6 Hz, 1H), 7.42 (d, ⁴J = 1.8 Hz, 1H), 7.59 (d, ⁴J = 1.9 Hz, 1H), 8.18 (d, ⁴J = 1.8 Hz, 1H), 9.94 (s, 1H), 10.28 (s, 1H), 12.16 (s, 1H). ¹³C-NMR (100 MHz, DMSO-d₆): δ = 36.1 (+), 36.2 (+), 37.5 (+), 104.6 (+), 107.6 (+), 108.4 (+), 118.7 (+), 119.6 (C_{quat}), 120.3 (+), 121.5 (C_{quat}), 122.6 (C_{quat}), 122.9 (C_{quat}), 126.3 (C_{quat}), 128.3 (+), 133.8 (C_{quat}), 156.9 (C_{quat}), 158.3 (C_{quat}), 162.0 (C_{quat}). MS (EI) m/z (%) = 370 (74) [M - CO₂]⁺, 275 (100).

MeO-PEG-Py-Py-Py-NO₂ (9). Compound **7** (620 mg, 0.12 mmol) was reduced using GP 1 (HCOONH₄: 0.45 g, 7.1 mmol; Pd/C: 50 mg) and subsequently allowed to react with **6** (63 mg, 0.37 mmol) following GP 3 (DCC: 77 mg, 0.37 mmol; HOBT·H₂O: 57 mg, 0.37 mmol; DIEA: 1 ml) to yield **9** with 39% loading of the polymer. ¹H-NMR: δ = 3.89 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 6.87 (m, 2H), 6.94 (m, 1H), 7.40 (m, 1H), 7.45 (m, 2H), 7.56 (m, 1H), 7.60 (m, 1H), 8.75 (s, 1H), 9.33 (br s, 2H).

HO₂C-Py-Py-Py-NO₂ (10). Compound **9** (754 mg, 0.137 mmol) was treated according to GP 4 and yielded 20 mg (0.037 mmol) of **10** (82%) as a yellow solid. Mp: 245 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3427, 1701, 1648 cm⁻¹. UV(CH₃CN): λ_{\max} (log ϵ) = 192 (4.49), 240 (4.43), 300 (4.50) nm. ¹H-NMR (400 MHz, DMSO-d₆): δ = 3.82 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.97 (s, 3H), 6.86 (d, ⁴J = 1.8 Hz, 1H), 7.06 (m, 2H), 7.25 (d, ⁴J = 1.5 Hz, 1H), 7.28 (d, ⁴J = 1.5 Hz, 1H), 7.43 (d, ⁴J = 1.8 Hz, 1H), 7.62 (d, ⁴J = 1.9 Hz, 1H), 8.19 (d, ⁴J = 1.7 Hz, 1H), 9.91 (s, 1H), 10.00 (s, 1H), 10.33 (s, 1H). ¹³C-NMR (100 MHz, DMSO-d₆): δ = 36.1 (+), 36.1 (+), 36.2 (+), 37.5 (+), 104.6 (+), 104.8 (+), 107.7 (+), 108.4 (+), 118.6 (+), 118.7 (+), 119.5 (C_{quat}), 120.3 (+), 121.5 (C_{quat}), 122.2 (C_{quat}), 122.6 (C_{quat}), 122.7 (C_{quat}), 123.0 (C_{quat}), 126.3 (C_{quat}), 128.2 (+), 133.8 (C_{quat}), 156.9 (C_{quat}), 158.4 (C_{quat}), 158.5

(C_{quat}), 162.0 (C_{quat}). MS (EI) m/z (%) = 492 (100) [M - CO₂]⁺, 397 (18), 275 (49), 153 (36). HRMS: C₂₃H₂₄N₈O₅, [M - CO₂]⁺ = 492.1865 ± 2 ppm.

MeO-PEG-Py-Im-NO₂ (12). Compound **3** (1.0 g, 0.2 mmol) was reduced using GP 1 (HCOONH₄: 0.5 g, 7.9 mmol; Pd/C: 100 mg) and was afterwards allowed to react with **11** (136 mg, 0.8 mmol) following GP 3 (DCC: 247 mg, 1.2 mmol; HOBT·H₂O: 162 mg, 1.2 mmol; DIEA: 1 ml) to yield **12** with 87% loading of the polymer. ¹H-NMR: δ = 3.92 (s, 3H), 4.21 (s, 3H), 6.98 (d, ⁴J = 2.0 Hz, 1H), 7.41 (d, ⁴J = 2.0 Hz, 1H), 7.93 (s, 1H), 9.29 (s, 1H).

MeO-PEG-Py-Im-Py-NO₂ (14). Compound **3** (0.5 g, 0.2 mmol) was reduced using GP 1 (HCOONH₄: 0.9 g, 14.3 mmol; Pd/C: 50 mg) followed by reaction with **13** (88 mg, 0.3 mmol) according to GP 3 (DCC: 62 mg, 0.3 mmol; HOBT·H₂O: 46 mg, 0.3 mmol; DIEA: 1 ml) to yield **14** with 61% loading of the polymer. ¹H-NMR: δ = 3.92 (s, 3H), 4.05 (s, 3H), 4.10 (s, 3H), 6.89 (m, 1H), 7.44 (m, 1H), 7.48 (m, 1H), 7.49 (m, 1H), 7.64 (m, 1H), 9.05 (s, 1H), 9.16 (s, 1H).

HO₂C-Py-Im-Py-NO₂ (15). Compound **7** (293 mg, 0.054 mmol) was treated according to GP 4 and yielded 10 mg (0.024 mmol) of **15** (73%) as a yellow solid. Mp: 220 °C. IR(KBr): $\tilde{\nu}$ = 3428, 1672, 1572 cm⁻¹. UV(CH₃CN): λ_{\max} (log ϵ) = 192 (2.36), 236 (2.21), 292 (2.20) nm. ¹H-NMR (400 MHz, DMSO-d₆): δ = 3.83 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.93 (d, ⁴J = 2.0 Hz, 1H), 7.40 (d, ⁴J = 1.9 Hz, 1H), 7.57 (s, 1H), 7.76 (d, ⁴J = 2.0 Hz, 1H), 8.20 (d, ⁴J = 2.0 Hz, 1H), 10.08 (s, 1H), 10.80 (s, 1H). ¹³C-NMR (100 MHz, DMSO-d₆): δ = 36.4 (+), 37.0 (+), 37.6 (+), 107.8 (+), 108.5 (+), 120.0 (C_{quat}), 120.6 (+), 122.0 (C_{quat}), 126.3 (C_{quat}), 126.8 (+), 128.4 (+), 134.0 (C_{quat}), 135.6 (C_{quat}), 145.3 (C_{quat}), 157.1 (C_{quat}), 159.4 (C_{quat}), 162.0 (C_{quat}). MS (EI) m/z (%) = 414 (9) [M - 1]⁺, 399 (100).

MeO-PEG-Py-*m*Ph-NO₂ (17). Compound **3** (1.24 g, 0.25 mmol) was reduced using GP 1 (HCOONH₄: 0.33 g, 5.2 mmol; Pd/C: 120 mg) followed by reaction with *m*-nitrobenzoic acid (**16-OH**, 567 mg, 3.0 mmol) according to GP 3 (DCC: 155 mg, 0.75 mmol; HOBT·H₂O: 115 mg, 0.75 mmol; DIEA: 1 ml) to yield **17** with 86% loading of the polymer. ¹H-NMR: δ = 3.93 (s, 3H), 7.02 (d, ⁴J = 2.0 Hz, 1H), 7.59 (d, ⁴J = 2.0 Hz, 1H), 7.67 (t, ³J = 8.0 Hz, 1H), 8.35 (m, 1H), 8.42 (m, 1H), 8.90 (m, 1H), 9.48 (s, 1H).

MeO-PEG-Py-*m*Ph-Py-NO₂ (18). Compound **17** (760 mg, 0.15 mmol) was reduced using GP 1 (HCOONH₄: 0.45 g, 7.1 mmol; Pd/C: 50 mg) and then allowed to react with **6** (76 mg, 0.45 mmol) following GP 3 (DCC: 93 mg, 0.45 mmol; HOBT·H₂O: 69 mg, 0.45 mmol; DIEA: 1 ml) to yield **18** with 56% loading of the polymer. ¹H-NMR: δ = 3.92 (s, 3H), 4.07 (s, 3H), 6.90 (d, ⁴J = 2.0 Hz, 1H), 7.44 (t, ³J = 7.9 Hz, 1H), 7.57 (d, ⁴J = 1.9 Hz, 1H), 7.65 (m, 2H), 7.70 (m, 1H), 8.09 (m, 1H), 8.15 (m, 1H), 9.01 (s, 1H), 9.14 (s, 1H).

HO₂C-Py-*m*Ph-Py-NO₂ (19). Compound **18** (510 mg, 0.094 mmol) was treated according to GP 4 and gave 20 mg (0.05 mmol) of **19** (92%) as a yellow solid. Mp: 225 °C (decomp.). IR(KBr): $\tilde{\nu}$ = 3402, 1677, 1315 cm⁻¹. UV(CH₃CN): λ_{\max} (log ϵ) = 276 (4.47), 240 (4.42), 214 (4.44), 192 (4.42) nm. ¹H-NMR (400 MHz, DMSO-d₆): δ = 3.85 (s, 3H), 3.98 (s, 3H), 6.91 (d, ⁴J = 1.4 Hz, 1H), 7.49 (m, 2H), 7.66 (d, ³J = 7.6 Hz, 1H), 7.77 (d, ⁴J = 1.6 Hz, 1H), 7.93 (d, ³J = 8.0 Hz, 1H), 8.24 (m, 2H), 10.31 (s, 1H), 10.32 (s, 1H), 12.23 (br s, 1H). ¹³C-NMR (100 MHz, DMSO-d₆): δ = 36.2 (+), 37.6 (+), 108.6 (+), 108.8 (+), 119.6 (+), 119.8 (C_{quat}), 120.6 (+), 122.3 (+), 122.6 (C_{quat}), 122.9 (+), 126.0 (C_{quat}), 128.7 (+), 128.8 (+), 133.9 (C_{quat}), 135.2 (C_{quat}), 138.9 (C_{quat}), 158.6 (C_{quat}), 161.9 (C_{quat}), 163.6 (C_{quat}). MS (EI) m/z (%) = 411

(8) $[M]^+$, 367 (100), 272 (84), 153 (36), 107 (20), 95 (22). HRMS: $C_{19}H_{17}N_5O_6$, $[M]^+ = 411.1175 \pm 2$ ppm.

MeO-PEG-Py-mNHCONHPh-NO₂ (21). Compound **3** (1.17 g, 0.23 mmol) was reduced using GP 1 ($HCOONH_4$: 0.5 g, 7.9 mmol; Pd/C: 60 mg) and then allowed to react with 3-nitrophenyl isocyanate (**20**, 192 mg, 1.17 mmol) to yield **21** with 82% loading of the polymer. For purification the product was precipitated three times with Et_2O . 1H -NMR: $\delta = 3.89$ (s, 3H), 6.73 (d, $^4J = 2.0$ Hz, 1H), 7.26 (d, $^4J = 1.8$ Hz, 1H), 7.39 (t, $^3J = 8.1$ Hz, 1H), 7.78 (m, 1H), 7.85 (m, 1H), 8.04 (br s, 1H), 8.41 (m, 1H), 8.54 (s, 1H).

MeO-PEG-Py-mNHCONHPh-Py-NO₂ (22). Compound **21** (0.65 g, 0.13 mmol) was reduced using GP 1 ($HCOONH_4$: 0.5 g, 7.9 mmol; Pd/C: 50 mg) and was afterwards allowed to react with **6** (66 mg, 0.39 mmol) following GP 3 (DCC: 80 mg, 0.39 mmol; HOBT·H₂O: 60 mg, 0.39 mmol; DIEA: 1 ml) to yield **22** with 62% loading of the polymer. 1H -NMR: $\delta = 3.87$ (s, 3H), 4.02 (s, 3H), 6.70 (m, 1H), 7.2–7.3 (m, 3H), 7.42 (m, 1H), 7.53 (d, $^4J = 1.8$ Hz, 1H), 7.61 (m, 1H), 7.68 (m, 1H), 7.74 (m, 1H), 7.92 (s, 1H), 8.72 (s, 1H).

HO₂C-Py-mNHCONHPh-Py-NO₂ (23). Compound **22** (285 mg, 0.053 mmol) was treated according to GP 4 and yielded 12 mg (0.028 mmol) of **23** (86%) as a yellow solid. Mp: 230 °C. IR(KBr): $\tilde{\nu} = 3408, 1676, 1547, 1314$ cm⁻¹. UV(CH₃CN): λ_{max} (log ϵ) = 256 (4.58), 216 (4.38), 192 (4.31) nm. 1H -NMR (400 MHz, DMSO-*d*₆): $\delta = 3.81$ (s, 3H), 3.91 (s, 3H), 6.65 (d, $^4J = 2.1$ Hz, 1H), 7.15–7.25 (m, 3H), 7.29 (m, 1H), 7.73 (d, $^4J = 2.0$ Hz, 1H), 7.93 (m, 1H), 8.22 (d, $^4J = 1.7$ Hz, 1H), 8.30 (s, 1H), 8.66 (s, 1H), 10.09 (s, 1H). ^{13}C -NMR (100 MHz, DMSO-*d*₆): $\delta = 36.1$ (+), 37.6 (+), 107.7 (+), 108.5 (+), 109.9 (+), 113.4 (+), 113.5 (+), 119.1 (+), 119.8 (C_{quat}), 122.7 (C_{quat}), 126.3 (C_{quat}), 126.8 (+), 128.8 (+), 133.8 (C_{quat}), 139.0 (C_{quat}), 140.4 (C_{quat}), 152.3 (C_{quat}), 158.4 (C_{quat}), 162.0 (C_{quat}). MS (FAB⁻): m/z (%) = 425 (4) $[M - 1]^-$, 306 (100).

MeO-PEG-pPh-NO₂ (25). **1** (50.0 g, 10.0 mmol) was allowed to react with 4-nitrobenzoyl chloride (**24**, 9.25 g, 50.0 mmol) following GP 2 (pyridine: 5 ml) to yield **25** with quantitative loading of the polymer. 1H -NMR: $\delta = 8.27$ (m, 4H).

MeO-PEG-pPh-pPh-NO₂ (26). Compound **25** (11.5 g, 2.3 mmol) was reduced using GP 1 ($HCOONH_4$: 1.5 g, 23.8 mmol; Pd/C: 100 mg) followed by reaction with **24** (2.13 g, 11.5 mmol) according to GP 2 (pyridine: 1.6 ml) to yield **26** with quantitative loading of the polymer. 1H -NMR: $\delta = 7.93$ (d, $^3J = 8.8$ Hz, 2H), 8.05 (d, $^3J = 8.6$ Hz, 2H), 8.31 (m, 4H), 9.69 (s, 1H).

MeO-PEG-pPh-mPh-NO₂ (27). Compound **25** (11.5 g, 2.3 mmol) was reduced using GP 1 ($HCOONH_4$: 1.5 g, 23.8 mmol; Pd/C: 100 mg) and was afterwards allowed to react with 3-nitrobenzoyl chloride (**16-Cl**, 2.13 g, 11.5 mmol) following GP 2 (pyridine: 1.6 ml) to yield **27** with quantitative loading of the polymer. 1H -NMR: $\delta = 7.70$ (t, $^3J = 8.0$ Hz, 1H), 7.97 (d, $^3J = 8.8$ Hz, 2H), 8.05 (d, $^3J = 8.8$ Hz, 2H), 8.38 (m, 1H), 8.50 (m, 1H), 8.99 (m, 1H), 9.74 (s, 1H).

MeO-PEG-pPh-pPh-pPh-NO₂ (28). Compound **26** (8.25 g, 1.65 mmol) was reduced using GP 1 ($HCOONH_4$: 1.5 g, 23.8 mmol; Pd/C: 100 mg) and was afterwards allowed to react with **24** (1.53 g, 8.25 mmol) following GP 2 (pyridine: 1.2 ml) to yield **28** with quantitative loading of the polymer. 1H -NMR: $\delta = 8.00$ (m, 8H), 8.28 (d, $^3J = 8.8$ Hz, 2H), 8.38 (d, $^3J = 8.8$ Hz, 2H), 9.53 (s, 1H), 10.18 (s, 1H).

MeO-PEG-pPh-mPh-pPh-NO₂ (29). Compound **27** (8.25 g, 1.65 mmol) was reduced using GP 1 ($HCOONH_4$: 1.5 g, 23.8 mmol; Pd/C: 100 mg) and was afterwards allowed to

react with **24** (1.53 g, 8.25 mmol) following GP 2 (pyridine: 1.2 ml) to yield **29** with quantitative loading of the polymer. 1H -NMR: $\delta = 7.46$ (t, $^3J = 7.9$ Hz, 1H), 7.79 (d, $^3J = 7.8$ Hz, 1H), 7.92 (d, $^3J = 8.7$ Hz, 2H), 8.01 (d, $^3J = 10.2$ Hz, 2H), 8.3–8.4 (m, 6H), 9.44 (s, 1H), 10.04 (s, 1H).

HO₂C-pPh-pPh-pPh-NO₂ (30). Compound **28** (4.55 g, 0.84 mmol) was treated according to GP 4 to yield 295 mg (0.73 mmol) of **30** (86%) as a white solid. Mp: >300 °C. IR(KBr): $\tilde{\nu} = 3336, 1524, 1320$ cm⁻¹. UV(CH₃CN): λ_{max} (log ϵ) = 196 (4.70), 298 (4.52) nm. 1H -NMR (400 MHz, DMSO-*d*₆): $\delta = 8.08$ (s, 4H), 8.09 (m, 2H), 8.16 (m, 2H), 8.31 (m, 2H), 8.46 (m, 2H), 10.61 (s, 1H), 10.97 (s, 1H). ^{13}C -NMR (100 MHz, DMSO-*d*₆): $\delta = 119.6$ (+), 119.8 (+), 123.7 (+), 126.0 (C_{quat}), 128.9 (+), 129.4 (+), 130.0 (C_{quat}), 130.3 (+), 140.4 (C_{quat}), 142.1 (C_{quat}), 143.5 (C_{quat}), 149.4 (C_{quat}), 164.4 (C_{quat}), 165.4 (C_{quat}), 167.3 (C_{quat}). MS (EI): m/z (%) = 405 (8) $[M]^+$, 269 (100), 150 (19), 121 (18), 104 (16), 92 (10), 76 (9). HRMS: $C_{21}H_{15}N_3O_6$, $[M]^+ = 405.0955 \pm 2$ ppm. Elem. anal. $C_{21}H_{15}N_3O_6$: calcd. C 62.22, H 3.73, N 10.37; found C 62.24, H 3.70, N 10.19%.

HO₂C-pPh-mPh-pPh-NO₂ (31). Compound **29** (6.9 g, 1.28 mmol) was treated according to GP 4 to yield 454 mg (1.12 mmol) of **31** (88%) as a white solid. Mp: >300 °C. IR(KBr): $\tilde{\nu} = 3315, 1645, 1526, 1323$ cm⁻¹. UV(CH₃CN): λ_{max} (log ϵ) = 194 (4.65), 216 (4.46), 278 (4.47) nm. 1H -NMR (400 MHz, DMSO-*d*₆): $\delta = 7.57$ (t, $^3J = 8.0$ Hz, 1H), 7.76 (d, $^3J = 7.3$ Hz, 1H), 7.94 (m, 4H), 8.06 (m, 1H), 8.24 (m, 2H), 8.35 (s, 1H), 8.40 (m, 2H), 10.61 (s, 1H), 10.81 (s, 1H). ^{13}C -NMR (100 MHz, DMSO-*d*₆): $\delta = 119.5$ (+), 120.2 (+), 123.3 (+), 123.6 (+), 125.7 (C_{quat}), 128.9 (+), 129.3 (+), 130.3 (+), 135.4 (C_{quat}), 139.0 (C_{quat}), 140.3 (C_{quat}), 143.3 (C_{quat}), 149.3 (C_{quat}), 164.1 (C_{quat}), 165.9 (C_{quat}), 167.0 (C_{quat}). MS (EI): m/z (%) = 405 (6) $[M]^+$, 269 (100), 150 (17), 121 (20), 104 (12), 92 (8), 76 (10). HRMS: $C_{21}H_{15}N_3O_6$, $[M]^+ = 405.0955 \pm 2$ ppm. Elem. anal. $C_{21}H_{15}N_3O_6$: calcd. C 62.22, H 3.73, N 10.37; found C 62.01, H 3.71, N 10.07%.

MeO-PEG-pPh-pPh-pPh-mPh-NO₂ (32). Compound **28** (2.65 g, 0.49 mmol) was reduced using GP 1 ($HCOONH_4$: 1.0 g, 15.9 mmol; Pd/C: 100 mg) and was afterwards allowed to react with **16-Cl** (454 mg, 2.45 mmol) following GP 2 (pyridine: 1.0 ml) to yield **32** with quantitative loading of the polymer. 1H -NMR: $\delta = 7.68$ (t, $^3J = 8.0$ Hz, 1H), 7.96 (d, $^3J = 8.7$ Hz, 2H), 8.1 (m, 10H), 8.31 (m, 1H), 8.74 (d, $^3J = 7.8$ Hz, 1H), 9.04 (m, 1H), 10.05 (s, 1H), 10.19 (s, 1H), 10.81 (s, 1H).

HO₂C-pPh-pPh-pPh-mPh-NO₂ (33). Compound **32** (920 mg, 0.167 mmol) was treated according to GP 4 to yield 60 mg (0.115 mmol) of **33** (69%) as a white solid. Mp: >300 °C. IR(KBr): $\tilde{\nu} = 3325, 1650, 1519, 1321$ cm⁻¹. UV(CH₃CN): λ_{max} (log ϵ) = 192 (4.39), 216 (4.33), 306 (4.37) nm. 1H -NMR (400 MHz, DMSO-*d*₆): $\delta = 7.88$ (t, $^3J = 8.0$ Hz, 1H), 7.9–8.1 (m, 12H), 8.46 (m, 2H), 8.84 (m, 1H), 10.45 (s, 1H), 10.48 (s, 1H), 10.87 (s, 1H). ^{13}C -NMR (100 MHz, DMSO-*d*₆): $\delta = 119.3$ (+), 119.7 (+), 122.5 (+), 125.3 (C_{quat}), 126.3 (+), 128.58 (+), 128.63 (+), 129.0 (C_{quat}), 129.6 (C_{quat}), 130.1 (+), 130.2 (+), 134.2 (+), 135.9 (C_{quat}), 141.9 (C_{quat}), 142.5 (C_{quat}), 143.3 (C_{quat}), 147.7 (C_{quat}), 163.6 (C_{quat}), 165.1 (C_{quat}), 165.2 (C_{quat}), 166.9 (C_{quat}). MS (EI): m/z (%) = 524 (2) $[M]^+$, 507 (2), 480 (4), 388 (72), 286 (36), 269 (60), 150 (100), 120 (51), 104 (41), 76 (38). HRMS: $C_{27}H_{20}N_4O_5$, $[M - CO_2]^+ = 480.1429 \pm 5$ ppm. Elem. anal. $C_{28}H_{20}N_4O_7(H_2O)$: calcd. C 61.99, H 4.09, N 10.33; found C 62.23, H 3.98, N 9.80%.

MeO-PEG-pPh-pPh-pPh-mPh-pPh-NO₂ (34). Compound **32** (1.9 g, 0.35 mmol) was reduced using GP 1 ($HCOONH_4$: 1.0 g, 15.9 mmol; Pd/C: 100 mg) and then allowed to react with **24** (320 mg, 1.73 mmol) following GP 2 (pyridine: 1.0 ml) to yield **34** with quantitative loading of the

polymer. $^1\text{H-NMR}$: δ = 7.80 (d, 3J = 7.5 Hz, 1H), 7.92 (d, 3J = 8.1 Hz, 1H), 7.97 (d, 3J = 8.6 Hz, 2H), 8.1 (m, 11H), 8.25 (m, 3H), 8.43 (d, 3J = 8.6 Hz, 2H), 9.89 (s, 1H), 9.91 (s, 1H), 10.12 (s, 1H), 10.55 (s, 1H).

HO₂C-*p*Ph-*p*Ph-*p*Ph-*m*Ph-*p*Ph-NO₂ (35). Compound **34** (1160 mg, 0.207 mmol) was treated according to GP 4 to yield 100 mg (0.156 mmol) of **35** (75%) as a brownish solid. Mp: > 300 °C. IR(KBr): $\tilde{\nu}$ 3307, 1648, 1518, 1321 cm⁻¹. UV(CH₃CN): λ_{max} (log ϵ) = 194 (4.60), 252 (4.38) nm. $^1\text{H-NMR}$ (400 MHz, DMSO-*d*₆): δ = 7.59 (t, 3J = 7.9 Hz, 1H), 7.79 (d, 3J = 7.9 Hz, 1H), 7.9–8.1 (m, 13H), 8.24 (m, 2H), 8.40 (m, 3H), 10.45 (s, 1H), 10.46 (s, 1H), 10.61 (s, 1H), 10.81 (s, 1H), 12.74 (br s, 1H). $^{13}\text{C-NMR}$ (100 MHz, DMSO-*d*₆): δ = 119.3 (+), 119.4 (+), 120.1 (+), 123.2 (+), 123.5 (+), 123.6 (+), 125.2 (C_{quat}), 128.6 (+), 128.8 (+), 129.0 (C_{quat}), 129.2 (+), 130.1 (+), 135.3 (C_{quat}), 138.9 (C_{quat}), 140.2 (C_{quat}), 142.4 (C_{quat}), 142.5 (C_{quat}), 143.4 (C_{quat}), 149.2 (C_{quat}), 164.0 (C_{quat}), 165.1 (C_{quat}), 165.2 (C_{quat}), 165.7 (C_{quat}), 166.9 (C_{quat}). MS (EI): m/z (%) = 599 (0.1) [M – CO₂]⁺, 507 (2), 286 (18), 269 (16), 167 (21), 150 (35), 120 (100). Elem. anal. C₃₅H₂₅N₅O₈(H₂O): calcd. C 63.54, H 4.11, N 10.59; found C 63.46, H 4.04, N 10.08%.

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