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Self-assembly of calix[4]arene amine derivatives

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ABSTRACT

Self-assembly can occur spontaneously in solution for calix[4]arenes substituted at both the upper and lower rims with flexible pendant groups containing aromatic rings. This self-assembly occurs in both a head-to-tail and head-to-head manner, as proven by NOESY experiments.

1. Introduction

The concept behind self-assembly is the spontaneous and reversible association of building blocks into well-defined structures via non-covalent interactions.[1] The study of these non-covalent interactions has been greatly enhanced by research into macrocyclic calixarene molecules.[2–6] Calix[4]arenes are one of the most versatile building blocks in supramolecular chemistry, in the fabrication of molecular devices and supramolecular architectures, as they possess a framework, which allows the introduction of appropriate binding cores at either the upper or the lower rim.[7–14] Indeed, over the past 20 years, a great deal of interest has been generated in the self-assembly of calix[4]arenes resulting in the inclusion of small molecules, which can then be separated from the bulk solution.[15–22] As part of our on-going research into calix[4]arene derivatives as potential ligands for energy transfer studies,[23,24] we targeted the attachment of functional groups containing nitrogen donor atoms to both the upper and lower rims of our calix[4]arene scaffolds directly, without using the nitration route we had previously published.[23] This paper reports on the unexpected and spontaneous self-assembly in solution of these calix[4]arene derivatives.

2. Results and discussion

Scheme 1 shows the synthetic approach chosen for the benzyl (**3**–**5**) and pyridyl (**6**–**8**) derivatives. The upper rim chloromethylation of calix[4]arenes has been reported by Gutsche,[25] Ungaro[26] and Pochini[27] for calix[4]arene derivatives containing two *tert*-butyl groups on the upper rim and alkyl derivatives on the lower rim. These methods involved the use of either $SnCl_4$ with chloromethyl *n*-octyl ether or the formation of the methyl alcohol and its conversion to the chloromethyl derivative with thionyl chloride. However, neither of these reactions was successful when we started with tetrahydroxycalix[4]arene (**1**). On the other hand, the reaction of **1** with formaldehyde in the presence of Zn–HBr in glacial acetic acid[28–30] resulted in the formation of **2** in almost quantitative yield. The ^{1}H NMR spectrum of **2** shows sharp signals for the aromatic and hydroxyl protons but broad signals for both the methylene bridges and bromomethylene group, which was taken to be an indication of conformational change in solution since the lower rim and two positions of the upper rim are unsubstituted. The signal for the hydroxyl protons is almost the same in compounds **1** and **2**, indicating that hydrogen bonding between the hydroxyl groups is occurring in both cases, which would suggest that the major form of **2** in solution is the cone conformation.

Derivatisation of the lower rim of **2** with either benzyl groups or methylpyridine groups, using previously reported methods,[23] resulted in the formation of the cone conformers of both **3** and **6**. The attachment of both of those groups was evident in the ^{1}H NMR spectra of both **3** and **6** as a result of the OCH_2 signal at 5.12 and 5.16 ppm, respectively. We have ascertained that the benzyl or pyridylmethyl groups are not attached to the oxygen atom *para* to the bromomethyl substituents through an HMBC NMR experiment.

The reaction at the upper rim of either **3** or **6** with 2-aminomethylpyridine resulted in **4** and **7**, which were waxy

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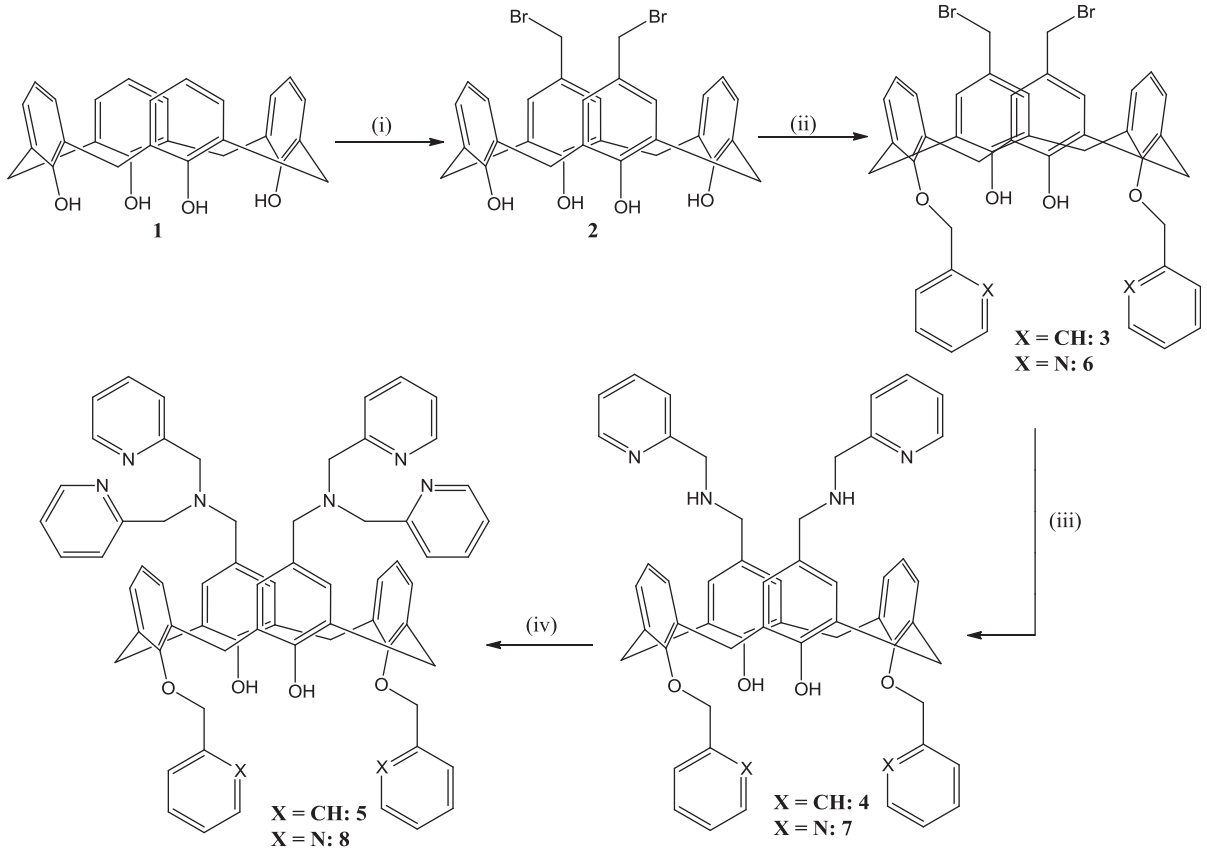


Scheme 1. Reaction conditions: (i) formaldehyde, Zn–HBr, glacial acetic acid, 90 °C, 72 h; (ii) K_2CO_3, benzyl bromide or 2-aminomethylpyridine hydrochloride, MeCN, Δ, 18 h; (iii) 2-aminomethylpyridine, MeCN, Δ, 6 h; (iv) 2-aminomethylpyridine hydrochloride, DCM, Δ, 8 h.

solids in both cases. CHN analyses confirmed the formation of **4** and **7**. However, the ^{1}H NMR spectra of both **4** and **7** did not show the expected signals for the proposed structures (see Fig. 1). There appeared to be several species present in solution, which could not be accounted for, given the CHN results. Furthermore, TLC analysis suggested the presence of a single species. Therefore, two possibilities that could explain this unexpected increase in signals in the ^{1}H NMR spectra of **4** and **7** were (i) conformational change in solution, that is, forming the partial cone, 1,2-alternate or 1,3-alternate conformers in solution, or (ii) self-assembly. We did not believe that conformational change was occurring, as such a change had never been previously observed in our laboratory and there was no metal ion present in the reaction to initiate that type of transformation. The alternative explanation of self-assembly was a possibility but required further investigation.

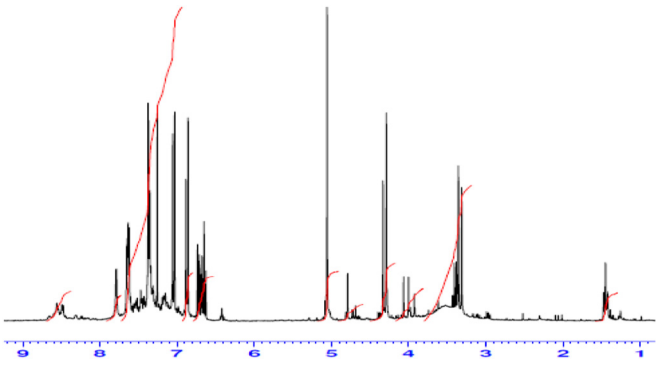


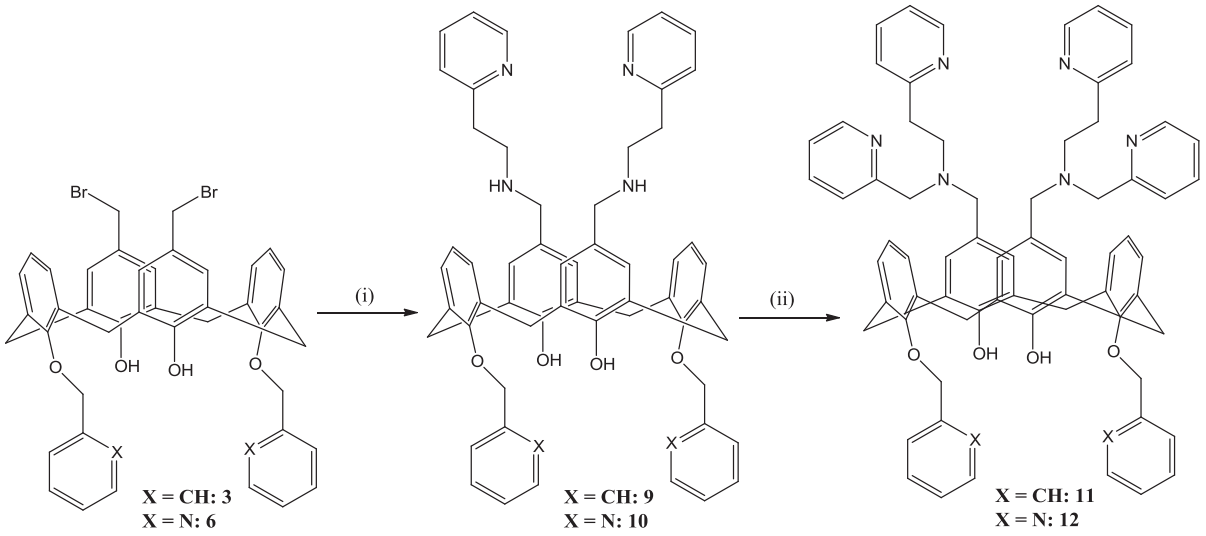
Fig. 1. The ^{1}H NMR spectrum of **4** obtained in $CHCl_3$.

We decided to react **3** and **6** with 2-aminoethylpyridine to give **9** and **10** (see Scheme 2) to see if the ^{1}H NMR spectra obtained would be similar to those obtained for **4** and **7**. We synthesised **9** and **10** in good yields using similar procedures to those for **4** and **7** (see Scheme 2). A similar increase in the number of signals observed in the ^{1}H NMR spectra of compounds **9** and **10** were observed. Again, CHN analyses confirmed the formation of **9** and **10**.

These observations led us to believe that some kind of self-assembly was occurring in solution. To investigate how this self-assembly was occurring, we began by carried out a dilution experiment on **9** using ^{1}H NMR spectroscopy on a 500 MHz instrument to see whether the self-assembly could be prevented if a very dilute solution of the compound was present. We started off with a 1 mM solution of **9** in $CDCl_3$ and obtained the ^{1}H NMR spectrum. Then we carried out a 10-fold dilution and re-ran the spectrum. We repeated this until we had a 1 μM solution. The results of the dilutions are shown in Fig. 2.

It is clearly evident, from Fig. 2, that as the concentration of **9** decreases, so also does the number of signals in each spectrum until the spectrum is simplified to what should be expected for the cone conformation of **9** (Fig. 2). Two distinct doublets for the methylene bridges can be clearly seen as well as four other signals (singlet, doublet, triplet and multiplet) for the remaining methylene groups. A similar effect was observed when this experiment was carried out on either of the compounds **4**, **7** or **10**, which showed this similar phenomenon in solution.

Using NOESY experiments, it should be possible to ascertain whether the self-assembly is occurring in a head-to-tail manner or in a head-to-head/tail-to-tail manner (see Fig. 3). We will define the processes as being either a Homo process, where like ends are connected together, either head-to-head or tail-to-tail, or a Hetero



Scheme 2. Reaction conditions: (i) 2-aminoethylpyridine, MeCN, 6 h; (ii) 2-aminomethylpyridine hydrochloride, DCM, 8 h.

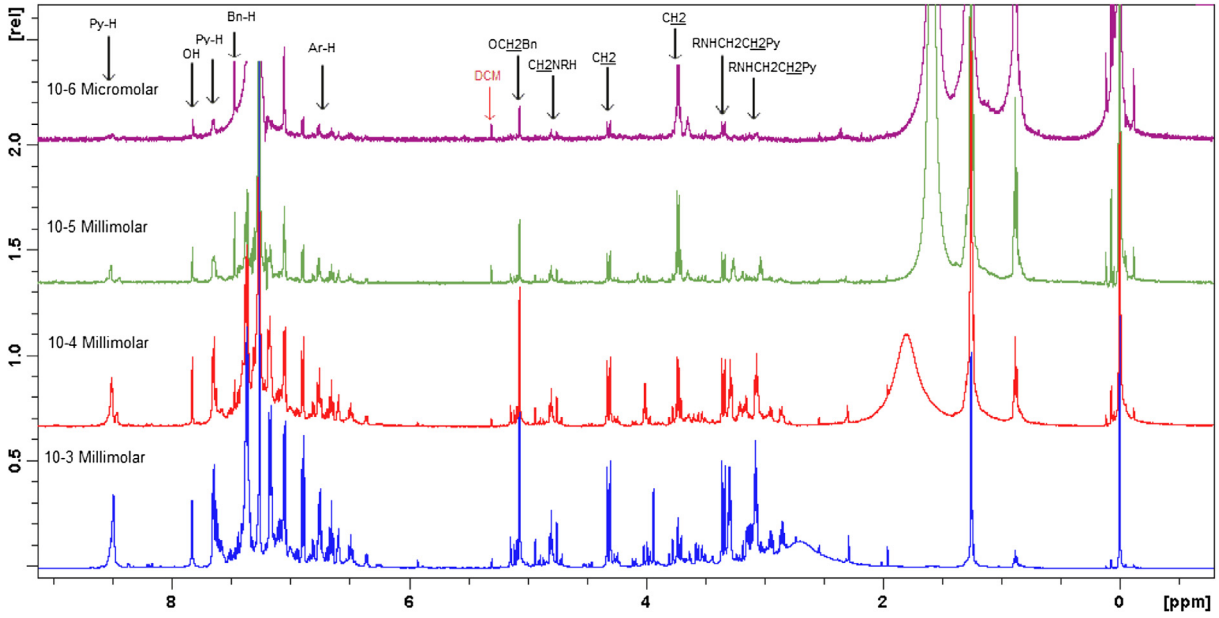


Fig. 2. ^{1}H NMR spectra of **9** in $CDCl_3$ at various concentrations of **9** with assignment of 1×10^{-6} M spectrum: blue=1×10^{-3} M, red=1×10^{-4} M, green=1×10^{-5} M and purple=1×10^{-6} M.

process, where opposite ends join together, as in head-to-tail, similar to those reported on tetraurea calix[4]arene systems by Böhmer.[11] The upper and lower rim substituents are colour coded blue (upper) and red (lower) to make it easier to distinguish the different possible self-assembly processes. These experiments were initially carried out on the 500 MHz instrument using compound **9**.

Analysis of the 2D NOESY spectra was initiated at H2 of the pyridine ring (δ 8.50). This is a convenient starting point from which conformational assignments can be inferred, as any interaction with the lower rim benzyl protons can only occur if a head-to-tail self-assembly mechanism has occurred. The NOESY correlation observed with the doublets at δ 4.35 and 3.39 indicated proximity to the methylene bridges of the calix[4]arene and, more importantly, observed with the singlet at δ 5.06 indicated proximity to the methylene bridge of the benzyl group. This latter NOE interaction supports the theory of a head-to-tail interaction resulting in the self-assembly process occurring. Further correlation was observed between the methylene group attached to the amine (CH_2–NHR group) and the singlet at δ 5.06, which is the CH_2 of the benzyl group again. The key NOESY correlations for **9** are outlined in Fig. 4 and include the interactions between the benzyl linker and the pyridyl protons (green line), the pyridyl protons and the benzyl ring (purple line) and a second pyridyl proton and the benzyl linker (red line) suggesting a hetero dimerisation and the interactions of the calix[4]arene ring protons with the pyridyl group and benzyl group (blue line) and the pyridyl proton and a pyridine ring (red line) suggesting a homo dimerisation. The orange line indicates the interactions of the Ar–CH_2–NHR protons with both the pyridyl ring and the benzyl linker, suggesting both homo and hetero dimerisations are evident. So from the NOE studies, it is clear that both homo and hetero dimerisations are occurring and that both processes are present in solution.

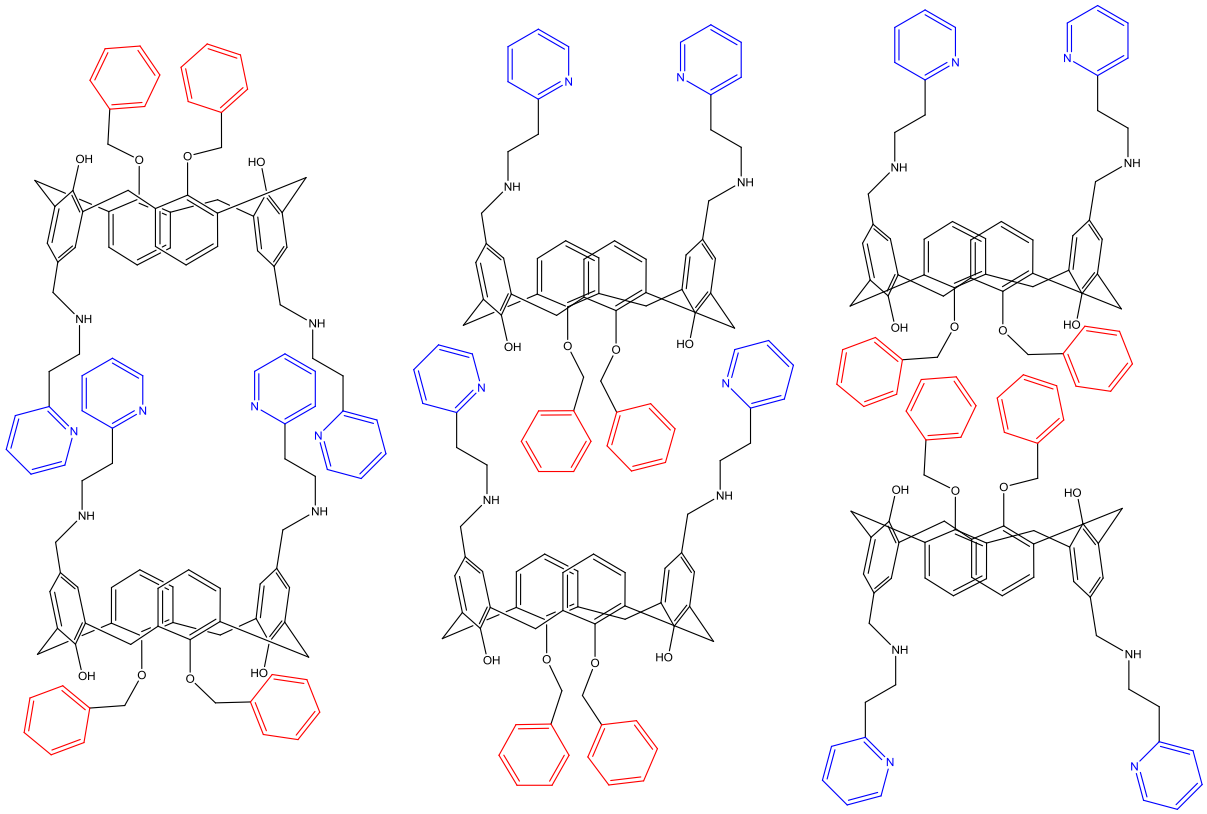


Fig. 3. The three possible head-to-head, head-to-tail and tail-to-tail dimerisations that could occur for **9** in solution. The head-to-head and tail-to-tail dimerisations are homo dimerisations and the head-to-tail dimerisation is a hetero dimerisation.

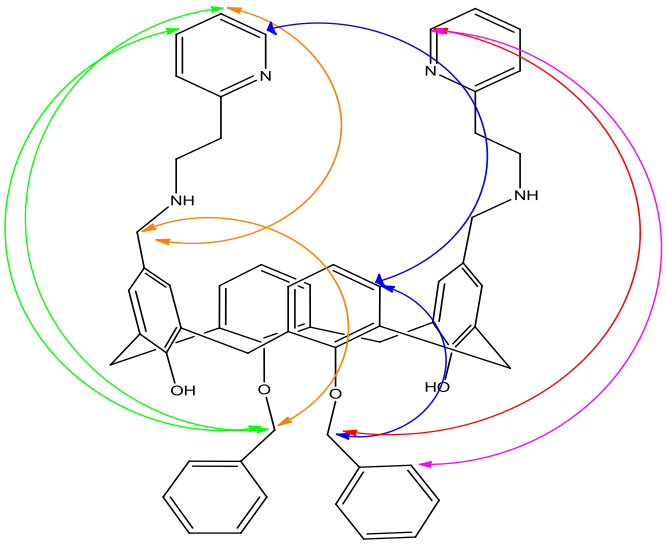


Fig. 4. Key NOSEY correlations observed for **9**.

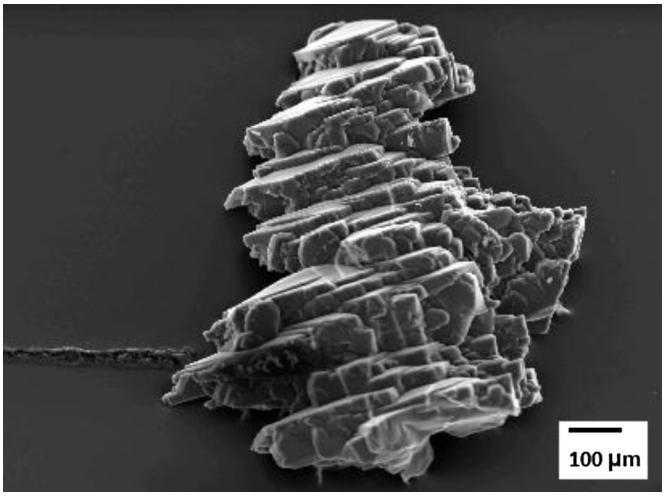


Fig. 5. Scanning electron micrograph of self-assembled **9**.

Efforts to grow crystals of **4**, **5**, **9** and **10**, suitable for an X-ray crystallography study, were unsuccessful. However, long, strand-like growths were observed at the bottom of the flasks in all cases after evaporation of most of the solvent. The difficulty in trying to obtain single crystals suitable for an X-ray structural determination is that, as the amount of solvent decreases, the concentration of the compounds increase and promotes the self-assembly process, resulting in polymeric materials. These polymeric strands were analysed using scanning electron microscopy (SEM, Hitachi S-3200N at 14 kV), as shown in Fig. 5. The sample was sputter coated with gold under argon for 10 cycles and then transferred into the main chamber of the SEM where the sample was subjected to high vacuum conditions at room temperature. The sample was viewed between 14 and 16 kV. The images for **4**, **5**, **9** and **10** were all similar and showed these long strand-like morphologies with smooth surfaces.

The subsequent reaction of **4** and **7** with 2-picolyl chloride afforded **5** and **8**. Again, CHN analyses confirmed the formation of **5** and **8**. The ^{1}H NMR spectra of **5** and **8** show an increase in the number of signals in both the aromatic and methylene bridge regions of the spectra, suggesting that self-assembly in solution is also occurring in these materials.

3. Conclusions

In conclusion, we have shown that self-assembly can occur spontaneously in solution for calix[4]arenes substituted at both the upper and lower rims with flexible pendant groups containing aromatic rings. This self-assembly occurs in a head-to-tail and head-to-head manner, as proven by NOESY experiments.

4. Experimental

4.1. Equipment and materials

^{1}H and ^{13}C NMR (δ ppm; J Hz) spectra were recorded on either a Bruker Advance DPX-300 spectrometer or a Bruker Advance 500 MHz spectrometer using saturated $CDCl_3$ solutions with Me_4Si reference, unless indicated otherwise, with resolutions of 0.18 Hz and 0.01 ppm, respectively. Infrared spectra (cm^{-1}) were recorded as KBr discs or liquid films between KBr plates using a Nicolet Impact 410 FT-IR spectrometer. Melting point analyses were carried out using a Stewart Scientific SMP 1 melting point apparatus and are uncorrected. Electrospray (ESI) mass spectra were collected on an Agilent Technologies 6410 Time of Flight LC/MS. Compounds were dissolved in acetonitrile/water (1:1) solutions containing 0.1% formic acid, unless otherwise stated. The interpretation of mass spectra was made with the help of the program 'Agilent Mass-hunter Workstation Software'. Microanalyses were carried out at the Microanalytical Laboratory of the National University of Ireland Maynooth. Standard Schlenk techniques were used throughout. The particle morphologies of the as-prepared samples were observed by JSM-5610LV scanning electron microscopy (SEM) at 20 kV. Starting materials were commercially obtained and used without further purification.

4.2. Syntheses

*4.2.1. Compound **2**.* Zinc powder (0.18 g, 2.8 mmol) was added to glacial acetic acid (100 mL) followed by HBr (33% in acetic acid, 12 mL) and stirred for 30 min under nitrogen. Compound **1** (3.0 g, 7.1 mmol), paraformaldehyde (0.11 g, 3.5 mmol) and HBr (60 mL) were added and heated to reflux at 90 °C for 72 h. On cooling, the solvent was removed under reduced pressure and the residue was washed with water (30 mL) and ether (30 mL) to give a brown solid (**2**). Yield: 2.98 g, 99%; mp 255–260 °C. IR (KBr, cm^{-1}): 3175 (OH), 1608, 1594, 1448, 753. ^{1}H NMR (300 MHz, $CDCl_3$): 10.19 (4H, s, Ar–OH), 7.26 (1H, d, J=12.1 Hz, Ar–H), 7.05 (1H, d, J=12.1 Hz, Ar–H), 6.72 (1H, t, J=8.6 Hz, Ar–H), 4.73 (4H, s, CH_2Br), 4.24 (4H, d, J=14.0 Hz, CH_2), 3.51 (4H, d, J=14.0 Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 148.8, 131.6, 129.0, 128.2, 122.2, 76.6, 34.1, 31.7. ESI-MS (DMSO/MeOH) calcd for $C_{30}H_{26}Br_2O_4$ $[M-1]^+$ 609.3280, found 609.3280. Found C 59.10, H 4.31; $C_{30}H_{26}Br_2O_4$ requires C 59.04, H 4.29%.

*4.2.2. Compound **3**.* To compound **2** (1.00 g, 1.64 mmol) dissolved in acetonitrile (100 mL) were added benzyl bromide (0.39 mL, 3.28 mmol) and potassium carbonate (0.45 g, 3.28 mmol) and the resulting suspension was heated to reflux under nitrogen overnight. The suspension was allowed to cool, the inorganic salts were removed by filtration and the volatiles were removed under reduced pressure to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy burgundy solid (**3**). Yield: 0.65 g, 89%; IR (KBr, cm^{-1}): 3361 (OH), 1608, 1595, 1448, 1088, 753. ^{1}H NMR (300 MHz, $CDCl_3$): 7.94 (2H, s, Ar–OH), 7.72 (4H, t, J=2.8 Hz, Bn–H), 7.43 (4H, s, Ar–H), 7.40 (2H, t, J=2.2 Hz, Bn–H), 7.12 (4H, d, J=6.9 Hz, Bn–H), 6.96 (4H, d, J=7.7 Hz, Ar–H), 6.77 (2H, t, J=10.0 Hz, Ar–H), 6.72 (4H, d, J=10.0 Hz, Ar–H), 5.12 (4H, s, OCH_2Bn), 4.54 (4H, s, CH_2Br), 4.38 (4H, d, J=13.1 Hz, CH_2), 3.42 (4H, d, J=13.1 Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 153.4, 151.9, 136.8, 133.2, 129.0, 128.7, 128.5, 128.0, 127.5, 125.5, 118.4, 78.4, 76.6, 31.4. Found C 66.65, H 4.42; $C_{44}H_{38}Br_2O_4$ requires C 66.85, H 4.84%.

*4.2.3. Compound **4**.* To compound **3** (0.65 g, 0.89 mmol) dissolved in acetonitrile (60 mL) were added triethylamine (0.18 g, 1.77 mmol) and 2-aminomethylpyridine (0.28 mL, 1.77 mmol). The resulting solution was heated to reflux for 6 h under nitrogen. After cooling, the solvent was removed under reduced pressure to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy red oil (**4**). Yield: 0.72 g, 95%. IR (KBr, cm^{-1}): 3414 (OH), 3388, 3028, 1590, 1448, 1089, 755. ^{1}H NMR (300 MHz, $CDCl_3$): 8.59 (2H, d, J=3.8 Hz, Py–H), 7.79 (4H, d, J=2.0 Hz, Bn–H), 7.73 (2H, t, J=2.1 Hz, Py–H), 7.42 (2H, t, J=1.9 Hz, Py–H), 7.39 (2H, s, Ar–OH), 7.37 (2H, d, J=2.1 Hz, Py–H), 7.34 (4H, t, J=2.3 Hz, Bn–H), 7.14 (2H, t, J=1.8 Hz, Bn–H), 7.10 (4H, s, Ar–H), 6.89 (4H, d, J=6.9 Hz, Ar–H), 6.57 (2H, t, J=8.2 Hz, Ar–H), 5.13 (4H, s, OCH_2Bn), 4.79 (4H, s, CH_2NH), 4.41 (4H, d, J=13.2 Hz, CH_2), 3.91 (4H, s, CH_2Py), 3.23 (4H, d, J=13.2 Hz, CH_2), 2.43 (2H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 149.2, 135.6, 134.0, 133.3, 130.0, 128.9, 128.7, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 123.7, 121.4, 75.3, 71.7, 54.6, 31.5. Found C 79.64, H 5.97, N 6.82; $C_{56}H_{52}N_4O_4$ requires C 79.59, H 6.20, N 6.63%.

*4.2.4. Compound **5**.* To compound **4** (1.0 g, 1.18 mmol) dissolved in dichloromethane (60 mL) were added triethylamine (0.21 g, 2.12 mmol) and 2-picolyl chloride hydrochloride (0.35 g, 2.12 mmol). The resulting solution was then heated to reflux under nitrogen for 8 h. After cooling, the solvent was removed under reduced pressure to give an oil. The oil was washed with chloroform (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy red solid (**5**). Yield: 1.04 g, 96%. IR (KBr, cm^{-1}): 3388 (OH), 1590, 1571, 1448, 1384, 1090, 758. ^{1}H NMR (300 MHz, $CDCl_3$): 8.56 (4H, d, J=5.5 Hz, Py–H), 7.85 (2H, s, Ar–OH), 7.65 (4H, t, J=7.8 Hz, Py–H), 7.63 (4H, t, J=5.1 Hz, Py–H), 7.58 (4H, d, J=8.1 Hz, Py–H), 7.43 (4H, d, J=1.7 Hz, Bn–H), 7.37 (4H, t, J=1.3 Hz, Bn–H), 7.19 (2H, t, J=2.6 Hz, Bn–H), 7.05 (4H, d, J=6.6 Hz, Ar–H), 6.84 (4H, d, J=7.7 Hz, Ar–H), 6.65 (2H, t, J=5.8 Hz, Ar–H), 5.05 (4H, s, OCH_2Bn), 4.68 (8H, s, CH_2Py), 4.27 (4H, d, J=13.8 Hz, CH_2), 3.89 (4H, s, NCH_2), 3.34 (4H, d, J=13.8 Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 149.2, 137.7, 137.2, 136.8, 135.6, 134.8, 133.3, 133.1, 131.1, 128.8, 128.6, 128.5, 128.4, 128.2, 128.0, 124.1, 123.7, 78.6, 76.9, 52.9, 31.4. Found C 79.42, H 6.01, N 7.90; $C_{68}H_{62}N_6O_4$ requires C 79.51, H 6.08, N 8.18%.

*4.2.5. Compound **6**.* 2-Aminomethylpyridine hydrochloride (0.27 g, 1.6 mmol) was dissolved in acetonitrile (10 mL) and to this was added Na_2CO_3 (0.17 g, 1.6 mmol) to remove the hydrochloride salt and the resulting suspension was stirred for 30 min. The resulting inorganic salts were removed by filtration and to the filtrate were added **2** (0.50 g, 0.8 mmol) and NaH (0.04 g, 1.6 mmol) in acetonitrile (60 mL). This suspension was then heated to reflux under nitrogen overnight. After cooling, the inorganic solids were removed by filtration and the volatiles were removed under reduced pressure to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a sticky red solid (**6**). Yield: 1.24 g, 95%; IR (KBr, cm^{-1}): 3404, 2919, 1592, 1448, 1247, 1089, 909, 757. ^{1}H NMR (300 MHz, $CDCl_3$): 8.51 (2H, d, J=7.5 Hz, Py–H), 7.59 (2H, t, J=4.8 Hz, Py–H), 7.51 (2H, s, Ar–OH), 7.39 (2H, t, J=5.3 Hz, Py–H), 7.15 (2H, d, J=6.8 Hz, Py–H), 7.09 (4H, s, Ar–H), 6.89 (4H, d, J=6.9 Hz, Ar–H), 6.63 (2H, t, J=8.6 Hz, Ar–H), 5.16 (4H, s, CH_2–Py), 4.64 (4H, s, CH_2–Br), 4.37 (4H, d, J=13.2 Hz,

CH_2), 3.42 (4H, d, J=13.4 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 156.2, 155.6, 152.6, 148.7, 136.6, 133.6, 132.4, 128.7, 128.6, 128.2, 125.1, 125.0, 120.9, 78.2, 46.3, 31.6. Found C 63.54, H 4.49, N 3.48; $C_{42}H_{36}Br_2N_2O_4$ requires C 63.64, H 4.58, N 3.53%.

4.2.6. Compound **7**. To compound **6** (0.44 g, 0.55 mmol) dissolved in acetonitrile (70 mL) were added triethylamine (0.112 g, 1.11 mmol) and 2-aminomethylpyridine (0.11 mL, 1.11 mmol). The resulting solution was heated to reflux overnight under nitrogen. After cooling, the solvent was removed under reduced pressure to give an oil. The oil was washed with chloroform (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy red-brown solid (**7**). Yield: 0.46 g, 99%; IR (KBr, cm^{-1}): 3418, 2923, 1591, 1571, 1467, 1435, 1088, 755. ^{1}H NMR (300 MHz, $CDCl_3$): 8.59 (2H, d, J=4.8 Hz, Py−H), 8.50 (2H, d, J=4.3 Hz, Py−H), 7.52 (2H, t, J=5.5 Hz, Py−H), 7.49 (2H, t, J=6.6 Hz, Py−H), 7.47 (2H, t, J=7.6 Hz, Py−H), 7.27 (2H, d, J=7.8 Hz, Py−H), 7.21 (2H, d, J=7.4 Hz, Py−H), 6.94 (2H, d, J=7.6 Hz, Py−H), 6.81 (4H, d, J=7.1 Hz, Ar−H), 6.54 (2H, t, J=7.1 Hz, Ar−H), 5.16 (4H, s, OCH_2Py), 4.5 (2H, s, CH_2NH), 4.35 (4H, d, J=12.6 Hz, CH_2), 3.95 (4H, s, $NHCH_2Py$), 3.43 (4H, s, J=12.6 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 158.3, 156.0, 154.7, 152.3, 50.8, 149.9, 136.4, 135.6, 133.4, 131.9, 128.4, 127.8, 127.5, 126.9, 125.1, 124.6, 120.7, 120.5, 77.7, 59.2, 53.7, 30.9. Found C 76.41, H 5.74, N 9.56; $C_{54}H_{50}N_6O_4$ requires C 76.57, H 5.95, N 9.92%.

4.2.7. Compound ***8***. 2-Aminomethylpyridine hydrochloride (0.209 g, 1.27 mmol) was dissolved in acetonitrile (20 mL) and to this was added Na_2CO_3 (0.135 g, 1.27 mmol) to remove the hydrochloride salt and the resulting suspension was stirred for 10 min. The resulting inorganic salts were removed by filtration and to the filtrate were added **7** (0.54 g, 0.64 mmol) and NaH (0.03 g, 1.27 mmol) in acetonitrile (50 mL). This suspension was then heated to reflux under nitrogen overnight. After cooling, the inorganic solids were removed by filtration and the volatiles were removed under reduced pressure to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a sticky red solid (**8**). Yield=0.52 g, 76%; IR (KBr, cm^{-1}): 3432, 1630, 1592, 1448, 1384, 1091, 757. ^{1}H NMR (300 MHz, $CDCl_3$): 8.60 (2H, d, J=4.5 Hz, Py−H), 8.49 (4H, d, J=4.5 Hz, Py−H), 7.90 (2H, s, Ar−OH), 7.69 (2H, t, J=8.2 Hz, Py−H), 7.52 (4H, t, J=7.4 Hz, Py−H), 7.23 (2H, t, J=5.8 Hz, Py−H), 7.17 (4H, t, J=5.4 Hz, Py−H), 7.09 (4H, s, Ar−H), 7.03 (2H, t, J=5.7 Hz, Py−H), 7.00 (4H, t, J=6.7 Hz, Py−H), 6.74 (4H, d, J=7.7 Hz, Ar−H), 6.50 (2H, t, J=7.5 Hz, Ar−H), 5.21 (4H, s, OCH_2−Py), 4.62 (12H, s, CH_2−Py), 4.36 (4H, d, J=13.7 Hz, CH_2), 3.39 (4H, d, J=12.1 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 154.5, 153.9, 151.4, 150.0, 149.0, 148.7, 136.5, 136.2, 132.7, 131.3, 127.6, 127.3, 127.1, 126.8, 126.5, 126.0, 120.6, 120.0, 76.5, 48.8, 44.9, 29.9. Found C 76.85, H 5.65, N 10.78; $C_{66}H_{60}N_8O_4$ requires C 77.02, H 5.88, N 10.89%.

4.2.8. Compound ***9***. Compound **3** (0.50 g, 0.71 mmol), triethylamine (0.14 g, 1.42 mmol) and 2-aminoethylpyridine (0.17 g, 1.42 mmol) were heated to reflux in acetonitrile (60 mL) under nitrogen for 2 days. The suspension was allowed to cool to room temperature. The triethylammonium bromide was removed by filtration and the volatiles were removed under reduced pressure to give an oil. The oil was washed with chloroform (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy dark yellow solid (**9**). Yield: 0.72 g, 66.7%. IR (KBr, cm^{-1}): 3394, 3351, 2926, 1608, 1594, 1448, 1088, 753. ^{1}H NMR (300 MHz, $CDCl_3$): 8.55 (2H, d, J=3.6 Hz, Py−H), 7.63 (2H, t, J=7.4 Hz, Py−H), 7.61 (2H, t, J=8.5 Hz, Py−H), 7.59 (2H, d, J=7.4 Hz, Py−H), 7.37 (4H, d, J=6.7 Hz, Bn−H), 7.34 (4H, s, Ar−H), 7.31 (2H, t, J=7.8 Hz, Bn−H), 7.14 (4H, t, J=6.7 Hz, Bn−H), 7.05 (4H, d, J=7.7 Hz, Ar−H), 6.87 (4H, d, J=7.6 Hz, Ar−H), 6.70 (2H, t, J=7.7 Hz, Ar−H), 6.65 (2H, t, J=7.7 Hz, Ar−H), 5.05 (4H, s, OCH_2Bn), 4.31 (4H, d, J=13.7 Hz, CH_2), 4.12 (4H, s, CH_2Py), 3.93 (4H, s, CH_2Py), 3.33 (4H, d, J=13.7 Hz, CH_2), 2.91 (2H, br m, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 158.6, 154.1, 152.3, 149.3, 135.6, 135.2, 133.1, 130.0, 128.8, 128.3, 127.7, 127.5, 127.0, 125.0, 123.7, 74.3, 53.4, 48.9, 36.1, 31.0. Found C 79.56, H 6.08, N 6.21; $C_{58}H_{56}N_4O_4$ requires C 79.79, H 6.47, N 6.42%.

4.2.9. Compound ***10***. Compound **6** (1.24 g, 1.56 mmol), triethylamine (0.32 g, 3.12 mmol) and 2-aminoethylpyridine (0.37 mL, 3.12 mmol) were heated to reflux in a 1:1 acetonitrile/chloroform mixture (50 mL) under nitrogen overnight. The solution was allowed to cool to room temperature, filtered and the volatiles removed under reduced pressure. The residue was then washed with dichloromethane and water to remove any remaining triethylamine to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy red-brown solid (**10**), yield=1.20 g, 63%; IR (KBr, cm^{-1}): 3404, 3007, 2916, 1591, 1569, 1435, 1088. ^{1}H NMR (300 MHz, $CDCl_3$): 8.62 (2H, d, J=4.6 Hz, Py−H), 8.51 (2H, d, J=5.5 Hz, Py−H), 7.75 (2H, t, J=8.0 Hz, Py−H), 7.63 (2H, d, J=7.6 Hz, Py−H), 7.59 (2H, t, J=6.4 Hz, Py−H), 7.41 (2H, t, J=6.3 Hz, Py−H), 7.08 (4H, d, J=7.2 Hz, Ar−H), 7.06 (2H, t, J=7.53 Hz, Py−H), 7.04 (2H, d, J=7.6 Hz, Py−H), 6.99 (4H, d, J=6.8 Hz, Ar−H), 6.89 (2H, s, Ar−H), 6.62 (2H, t, J=7.7 Hz, Ar−H), 5.14 (4H, s, OCH_2Py), 4.36 (4H, d, J=13.4 Hz, CH_2), 3.94 (4H, s, CH_2−NHR), 3.33 (4H, d, J=14.0 Hz, CH_2), 3.04 (4H, t, J=6.7 Hz, N−CH_2CH_2−Py), 2.94 (4H, t, J=6.1 Hz, NCH_2CH_2−py); ^{13}C NMR (75 MHz, $CDCl_3$): 160.0, 159.6, 156.1, 153.4, 149.4, 149.1, 136.6, 136.5, 133.7, 130.0, 128.5, 128.2, 127.8, 125.5, 123.9, 123.5, 123.3, 122.9, 78.7, 55.0, 53.6, 38.8, 31.3. Found C 76.52, H 6.14, N 9.12; $C_{56}H_{54}N_6O_4$ requires C 76.86, H 6.22, N 9.60%.

4.2.10. Compound ***11***. 2-Aminomethylpyridine hydrochloride (0.07 g, 0.46 mmol) was dissolved in acetonitrile (20 mL) and to this was added Na_2CO_3 (0.048 g, 0.457 mmol) to remove the hydrochloride salt and the resulting suspension was stirred for 10 min. The resulting inorganic salts were removed by filtration and to the filtrate were added **9** (0.2 g, 0.23 mmol) and NaH (0.01 g, 0.46 mmol) in acetonitrile (50 mL). This suspension was then heated to reflux under nitrogen overnight. After cooling, the inorganic solids were removed by filtration and the volatiles were removed under reduced pressure to give an oil. The oil was washed with dichloromethane (3×25 mL) to remove any unreacted starting material and the volatiles were removed under reduced pressure to give a waxy yellow solid (**11**), yield=0.24 g, 92.3%; IR (KBr, cm^{-1}): 3429 (OH), 2921, 1592, 1456, 1195, 1089, 759; ^{1}H NMR (300 MHz, $CDCl_3$): 8.50 (2H, d, J=4.6 Hz, Py−H), 8.47 (2H, d, J=4.9 Hz, Py−H), 7.86 (2H, s, Ar−OH), 7.65 (4H, d, J=6.8 Hz, Bn−H), 7.57 (6H, t, J=7.7 Hz, Bn−H), 7.50 (2H, t, J=4.7 Hz, Py−H), 7.43 (2H, t, J=8.0 Hz, Py−H), 7.38 (2H, d, J=4.6 Hz, Py−H), 7.31 (2H, t, J=6.4 Hz, Py−H), 7.25 (2H, t, J=7.7 Hz, Py−H), 7.20 (2H, d, J=6.7 Hz, Py−H), 7.13 (4H, s, Ar−H), 7.08 (4H, d, J=7.7 Hz, Ar−H), 6.76 (2H, t, J=8.1 Hz, Ar−H), 5.06 (4H, s, OCH_2Bn), 4.75 (4H, s, CH_2NR_2), 4.31 (4H, d, J=13.0 Hz, CH_2), 3.91 (4H, s, CH_2Py), 3.34 (4H, d, J=13.0 Hz, CH_2), 3.15 (4H, t, J=14.4 Hz, CH_2CH_2Py), 3.02 (4H, t, J=14.4 Hz, CH_2CH_2Py); ^{13}C NMR (75 MHz, $CDCl_3$): 160.4, 159.4, 154.1, 151.9, 149.0, 148.6, 137.7, 136.5, 136.4, 134.0, 129.0, 128.8, 128.6, 128.4, 128.2, 127.7, 127.2, 126.4, 125.4, 123.1, 122.3, 121.2, 71.6, 60.2, 58.6, 54.4, 39.2, 31.9. Found C 79.31, H 6.13, N 7.86; $C_{70}H_{66}N_6O_4$ requires C 79.67, H 6.30, N 7.96%.

4.2.11. Compound ***12***. 2-Aminomethylpyridine hydrochloride (0.28 mL, 2.74 mmol) was dissolved in acetonitrile (20 mL) and to this was added Na_2CO_3 (0.29 g, 2.74 mmol) to remove the

hydrochloride salt and the resulting suspension was stirred for 10 min. The resulting inorganic salts were removed by filtration and to the filtrate were added **10** (1.20 g, 1.37 mmol) and triethylamine (0.23 g, 2.74 mmol) in acetonitrile (50 mL). This suspension was then heated to reflux under nitrogen overnight. The solution was allowed to cool to room temperature, filtered and the volatiles removed under reduced pressure. The residue was then washed with DCM and water to remove any residual triethylamine to give a dark red/brown waxy solid (**12**), yield=0.95 g, 65%; IR (KBr, cm^{-1}): 3431, 1591, 1570, 1466, 1435, 1088, 755; ^1H NMR (300 MHz, $CDCl_3$): 8.70 (2H, d, J=5.1 Hz, Py–H), 8.63 (2H, d, J=5.0 Hz, Py–H), 8.52 (2H, d, J=5.1 Hz, Py–H), 8.22 (2H, t, J=5.9 Hz, Py–H), 8.16 (2H, t, J=7.6 Hz, Py–H), 7.86 (2H, d, J=1.7 Hz, Py–H), 7.79 (2H, t, J=6.0 Hz, Py–H), 7.60 (2H, t, J=1.7 Hz, Py–H), 7.57 (2H, t, J=1.6 Hz, Py–H), 7.55 (2H, t, J=1.7 Hz, Py–H), 7.53 (2H, d, J=1.9 Hz, Py–H), 7.40 (2H, s, Ar–OH), 7.29 (2H, d, J=1.9 Hz, Py–H), 7.06 (4H, s, Ar–H), 7.04 (4H, d, J=2.8 Hz, Ar–H), 6.49 (2H, t, J=7.1 Hz, Ar–H), 5.18 (4H, s, CH_2Py), 4.24 (4H, d, J=14.9 Hz, CH_2), 3.94 (4H, s, R_2NCH_2Py), 3.44 (4H, d, J=13.7 Hz, CH_2), 3.05 (4H, t, J=4.6 Hz, CH_2CH_2Py), 3.00 (4H, t, J=3.8 Hz, CH_2CH_2Py); ^{13}C NMR (75 MHz, $CDCl_3$): 159.9, 159.4, 156.8, 156.6, 156.1, 154.4, 149.4, 149.0, 148.7, 137.2, 136.6, 136.3, 133.7, 128.8, 128.5, 128.2, 127.9, 125.4, 123.8, 123.5, 123.2, 121.9, 121.5, 121.1, 78.7, 63.5, 60.1, 54.3, 38.4, 32.2. Found C 76.91, H 6.05, N 10.45; $C_{68}H_{64}N_8O_4$ requires C 77.25, H 6.10, N 10.60%.

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