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Pyridinium *N*-heteroarylaminides: synthesis of *N*-heteroaryltetramines based on 1,6-bis(phenoxy)hexane and 1,3-bis(phenoxymethyl)benzene

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Abstract—The synthesis of a set of new *N*-heteroaryltetramines is reported. A regioselective alkylation on the *N-exo* nitrogen of pyridinium *N*-(heteroaryl)aminide with the corresponding tetrabromo compounds, followed by a clean N–N bond reduction of the corresponding tetra-salts, allowed an easy and general method to obtain *N*,*N*′,*N*″,*N*‴-tetrakis(2-heteroaryl)tetramines.

Biogenic polyamines[1] play an important role in various biological and pathological processes[2] and synthetic analogs offer a wide range of therapeutic potential.[3] The biological interest in these compounds has promoted the development of efficient synthetic methods for polyamine analogs and conjugates[4] both in solution and in the solid phase,[5] not only for linear analogs but also for dendrimer-like polyamines.[6] In addition, the pyridine ring takes part in many biological and chemical reactions and the pyridine ring itself—particularly aminopyridinides—are interesting because of their chelating abilities, the reason for which they are commonly used as ligands in inorganic and organometallic chemistry.[7] These characteristics are being used to develop new heterocyclic multidentate molecules for the use in coordination chemistry,[8] and in recent years many related references can be found in the literature that describe 2-aminopyridines,[9] 2-aminoquinolines,[10] and 2-aminobenzothiazoles[11] as part of organometallic complexes. Finally, 2-aminopyridine fragments have been used as part of an abiotic receptor for the recognition of monosaccharides.[12]

The present Letter describes the results obtained in the synthesis of *N*,*N*′,*N*″,*N*‴-tetrakis(2-heteroaryl)tetramines **7** and **8** from 1,6-bis[3,5-bis(bromomethyl)phenoxy]hexane (**2b**) or 1,3-bis[3,5-bis(bromomethyl)phenoxymethyl] benzene (**3b**) and pyridinium *N*-(2-heteroaryl)aminide **4**.

The preparation of the chosen tetrabromo compounds 1,6-bis[3,5-bis(bromomethyl)phenoxy]hexane **2b** and 1,3-bis[3,5-bis(bromomethyl)phenoxymethyl]benzene **3b** (Scheme 1) was achieved from the corresponding alcohols **2a** and **3a**. The preparation of these alcohols was carried out as previously described;[13] dimethyl 5-hydroxyisophthalate, obtained by esterification of 5-hydroxyisophthalic acid with methanol, was treated with the corresponding dibromide in anhydrous DMF and K_2CO_3 as a base[14] to give tetraesters **1a**, **b**, which were then reduced[15] using $LiAlH_4$ in THF to give the desired tetra-alcohols **2a** and **3a**. The preparation of 1,6-bis[3,5-bis(bromomethyl)phenoxy]hexane **2b** was accomplished from tetraester **1a** without the isolation of **2a**, which was transformed into **2b** by the addition of hydrobromic acid in a one-pot process. As expected, the high C–O lability in benzylic derivative **3a** toward acid media made this simple process unsuitable to prepare 1,3-bis[3,5-bis(bromomethyl)phenoxymethyl]benzene **3b**.[16] Alternatively, other bromination methods[17] were tested on **3a** with little or no success. Tetrabromo compound **3b** was finally obtained in good yield using a mixture of *N*-bromosuccinimide (NBS) and triphenylphosphine (Ph_3P) in dichloromethane, treated in an ultrasonic bath for 90 min.[18] The use of ultrasound was essential to keep the alcohol in solution.

Once derivatives **2b** and **3b** had been prepared, alkylation with different *N*-pyridinium aminides **4** was tried

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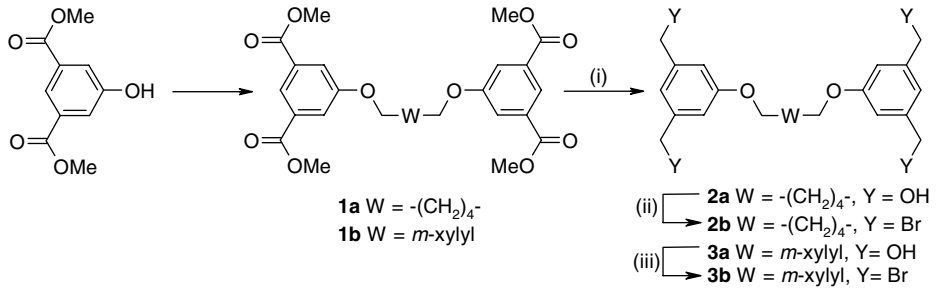
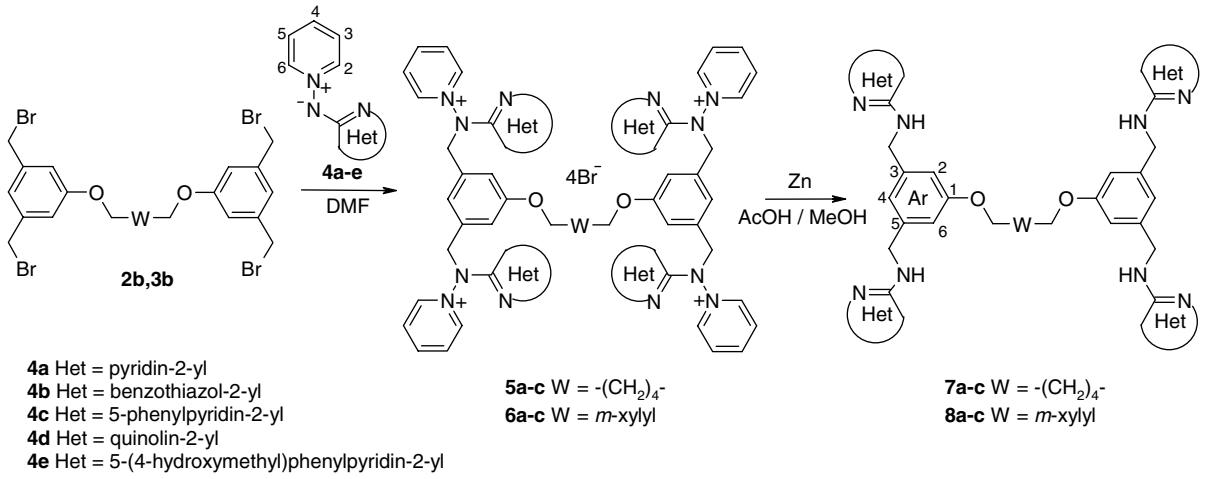


Scheme 1. Reagents and conditions: (i) $LiAlH_4$, THF; (ii) $HBr–H_2SO_4$ (2:1); (iii) PPh_3, NBS, CH_2Cl_2, ultrasound, 90 min.



Scheme 2.

as previously reported,[19] and the products **5** and **6** were only obtained on using DMF as a solvent, where intermediate mono-, di-, and tri-salts were kept in solution and could react to give the final product (Scheme 2). Isolation of **5** and **6** was achieved by concentrating the mixture to a minimum volume of solvent to keep the products in solution, and subsequently adding the solution dropwise to vigorously stirred AcOEt. This produced precipitation of tetra-salts **5** and **6** while the corresponding *N*-aminide **4** remained in solution.[20] The solid obtained in this way was filtered off, washed with AcOEt[21] and dried under vacuum to give the desired salt (Scheme 2). Aminides **4a–d** were prepared as described[19a,b,22] and **4e** was obtained by Suzuki reaction of pyridinium *N*-(5-bromopyridin-2-yl)aminide[23,19b] and 4-hydroxymethylphenylboronic acid.[24]

Finally, salts **5** and **6** had to be converted into *N*-heteroaryltetramines **7** and **8**. In previous papers, conversion of related *N*-aminopyridinium salts into 2-aminopyridines was described with different reducing agents, such as Zn/AcOH,[19a,b,d] Pt/C–Et_3N/HCOOH,[19c,e,23] or BEt_3–MeOH.[25] These methods may be applied to tetra-salts with slight modifications to increase the solubility of the starting materials, and the results obtained in the reduction of **5a** using three different methods are summarized in Table 1.

Although all experiments gave similar good results (conversions between 80% and 90%) the metal–acid system was chosen due to the ease of processing[26] and a series of *N*-heteroaryltetramines (Table 2) were successfully obtained.

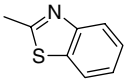
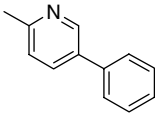
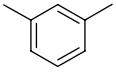
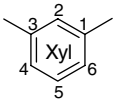
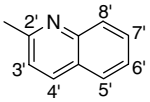
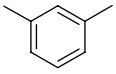
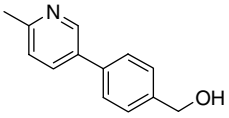
In conclusion, a viable strategy for the formation of *N*,*N*′,*N*″,*N*‴-tetrakis(2-heteroaryl)tetramines has been developed and involves the use of a quadruple and regioselective alkylation and the selective reduction of an N–N-bond. Attempts to apply this methodology to obtain central cores in dendrimer synthesis are in progress.

Table 1. Comparative chart for reduction of **5a** under different conditions

Reduction conditions	Work up conditions	Conversion[a] (%)
BEt_3 (12 equiv)/MeOH, −30 °C, 18 h	Extraction with NaOH (10%) and AcOEt Salt formation with HCl (10%) Rebasify and extract with AcOEt	81
BEt_3 (12 equiv)/MeOH–10% H_2O, −30 °C, 18 h		90
AcOH–MeOH (2:1)/Zn, rt, 12 h	Extraction with NaOH (10%) and AcOEt	85

[a] Measured by HPLC/MS.

Table 2. Results obtained in the alkylation and reduction reactions. Compounds **5a–c**, **6a–c**, **7a–c**, and **8a–c**

–W–	Aminides **4**	Het.	Tetra-salts **5**, **6**		Tetra-amines **7**, **8**	
			Compound	Yield (%)	Compound	Yield (%)
$-CH_2CH_2CH_2CH_2-$ β γ	**4a**		**5a**	85	**7a**	85
$-CH_2CH_2CH_2CH_2-$	**4b**		**5b**	84	**7b**	68
$-CH_2CH_2CH_2CH_2-$	**4c**		**5c**	90	**7c**	74
	**4a**		**6a**	87	**8a**	79
	**4d**		**6b**	84	**8b**	89
	**4e**[24]		**6c**	70	**8c**	73

Acknowledgments

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18. *Synthesis of 1,3-bis[3,5-bis(bromomethyl)phenoxymethyl]benzene* (**3b**): Alcohol **3a**[13] (410 mg, 1 mmol) and PPh_3 (4.4 mmol) were dissolved in dichloromethane (150 mL) in a round-bottom flask and the mixture was cooled to 0 °C. Under vigorous stirring NBS (4.4 mmol) was added portionwise to the reaction mixture. After the addition, the flask was placed in an ultrasonic bath for 90 min. As soon as the starting material had been consumed (detected by TLC) the solvent was removed in vacuo and the residue was purified by chromatography (silica gel/CH_2Cl_2). Compound **3b** was isolated as a white solid (476 mg, 72%), mp: 146–147 °C; IR (KBr): ν_{max} (cm^{-1}) 2938, 2882, 1593, 1443, 1335, 1296, 1212, 1179, 1040, 853, 697, 553; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.49 (1H, br s, $H2_{Xyl}$), 7.40 (3H, m, $H4_{Xyl}(6_{Xyl})$ and 5_{Xyl}), 7.01 (2H, t, $J = 1.5$ Hz, $H4'$), 6.93 (4H, d, $J = 1.5$ Hz, $H2'(6')$), 5.07 (4H, s, CH_2O), 4.41 (4H, s, CH_2Br); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 159.1 ($C1_{Ar}$), 139.7 ($C3_{Ar}(5_{Ar})$), 136.9 ($C1_{Xyl}(3_{Xyl})$), 129.0 ($C2_{Xyl}$), 127.3 ($C4_{Xyl}(6_{Xyl})$), 126.6 ($C5_{Xyl}$), 122.2 ($C4_{Ar}$), 115.5 ($C2_{Ar}(6_{Ar})$), 70.0 (CH_2O), 32.8 (CH_2Br). Anal. Calcd for $C_{24}H_{22}Br_4O_2$: C, 43.54; H, 3.35. Found C, 43.21; H, 3.22.

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20. *General procedure for the alkylation of pyridinium N-aminides* **4** *with tetrabromo derivatives* **2b** *or* **3b**: In a flame-dried round-bottom flask under an inert atmosphere, the corresponding tetrabromo derivative **2b** or **3b** (0.2 mmol) and aminide **4** (1 mmol) were suspended in DMF (5 mL). The reaction was stirred at room temperature for 72 h until the halogenated derivative had been consumed (detected by TLC). The solvent was removed under vacuum, the crude product was redissolved in the minimum volume of DMF (~1 mL) and the solution was added to vigorously stirred AcOEt (50 mL). The solid precipitate was filtered off and recrystallized from EtOH and a few drops of MeOH to give the corresponding pure tetra-salts **5** and **6** as brownish solids.

1,6-Bis[3,5-bis(pyridin-1-ium-pyridin-2-ylaminomethyl)phenoxy]hexane tetrabromide (**5a**): brownish solid (225 mg, 85%), mp > 162 °C (dec); IR (KBr): ν_{max} (cm^{-1}): 3010, 2935, 1595, 1470, 1432, 1298, 1160, 776, 746, 685; ^1H NMR (500 MHz, CD_3OD): δ (ppm) 9.23 (8H, dd, $J = 6.4$ and 1.4 Hz, $H2(6)$), 8.74 (4H, tt, $J = 7.8$ and 1.4 Hz, $H4$), 8.22 (12H, m, $H3(5)$ and $6'$), 7.90 (4H, ddd, $J = 8.7$, 7.5 and 1.7 Hz, $H4'$), 7.19 (10H, m, $H3'$, $H5'$ and $H4_{Ar}$), 7.00 (4H, d, $J = 1.0$ Hz, $H2_{Ar}$ ($H6_{Ar}$)), 5.58 (8H, s, CH_2N), 3.98 (4H, t, $J = 6.4$ Hz, CH_2O), 1.76 (4H, m, $CH_2\beta$), 1.52 (4H, m, $CH_2\gamma$); ^{13}C NMR (125 MHz, CD_3OD): δ (ppm) 161.6 ($C1_{Ar}$), 158.3 ($C2'$), 149.7 ($C2(6)$), 149.2 ($C6'$), 149.2 ($C4$), 140.6 ($C4'$), 137.8 ($C3_{Ar}(5_{Ar})$), 130.6 ($C3(5)$), 122.4 ($C4_{Ar}$), 120.8 ($C3'$), 116.5 ($C2_{Ar}(6_{Ar})$), 111.0 ($C5'$), 69.4 (CH_2O), 58.6 (CH_2N), 30.2 ($CH_2\beta$), 26.9 ($CH_2\gamma$).

1,3-Bis[3,5-bis(pyridin-1-ium-quinolin-2-ylaminomethyl)phenoxymethyl]benzene tetrabromide (**6b**): Brown solid, (259 mg, 84%), mp > 190 °C (dec); IR (KBr): ν_{max} (cm^{-1}) 3004, 2932, 1617, 1598, 1504, 1471, 1430, 1324, 1214, 1163, 1046, 813, 676; ^1H NMR (500 MHz, CD_3OD): δ (ppm) 9.18 (8H, dd, $J = 6.9$ and 1.3 Hz; $H2(6)$), 8.72 (4H, tt, $J = 7.7$ and 1.3 Hz, $H4$), 8.34 (4H, d, $J = 8.9$ Hz, $H4'$), 8.21 (8H, dd, $J = 7.7$ and 6.9 Hz, $H3(5)$), 7.89 (4H, br d, $J = 8.2$ Hz, $H5'$), 7.67 (4H, ddd, $J = 8.5$, 6.9 and 1.4 Hz, $H7'$), 7.57 (4H, br d, $J = 8.5$ Hz, $H8'$), 7.51 (4H, ddd, $J = 8.2$, 6.9 and 1.3 Hz, $H6'$), 7.35 (4H, m, $H2_{Xyl}$, $H4_{Xyl}(6_{Xyl})$ and $H5_{Xyl}$), 7.29 (4H, d, $J = 8.9$ Hz, $H3'$), 7.28 (2H, ap t, $J = 1.4$ Hz, $H4_{Ar}$), 7.15 (8H, d, $J = 1.4$ Hz, $H2_{Ar}(6_{Ar})$), 5.53 (8H, s, CH_2N), 5.12 (4H, s, CH_2O); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 161.0 ($C1_{Ar}$), 156.5 ($C2'$), 149.8 ($C2(6)$), 149.3 ($C4$), 147.3 ($C8'a$), 141.3 ($C4'$), 138.7 ($C1_{Xyl}(3_{Xyl})$), 138.2 ($C3_{Ar}(5_{Ar})$), 131.9 ($C7'$), 130.6 ($C3(5)$), 129.9 ($C5_{Xyl}$), 128.9 ($C5'$), 128.6 ($C8'$), 128.3 ($C4_{Xyl}(6_{Xyl})$), 127.9 ($C2_{Xyl}$), 127.0 ($C4'a$), 126.9 ($C6'$), 122.8 ($C4_{Ar}$), 117.1 ($C2_{Ar}(6_{Ar})$), 111.0 ($C3'$), 70.9 (CH_2O), 58.6 (CH_2N).

21. For compounds **5b** and **6c**, due to the low solubility of aminides **4b** and **4e** in AcOEt, washing was done with acetone.

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24. *Synthesis of N-[5-(4-hydroxymethylphenyl)pyridin-2-yl]-pyridinium aminide* (**4e**): $Pd(PPh_3)_4$ (57 mg, 5 mmol %), 4-hydroxymethylphenylboronic acid (1.5 mmol) and pyridinium *N*-(5-bromo-pyridin-2-yl) aminide[23] (1 mmol) were dissolved in a toluene:ethanol mixture (4:1, 15 mL). K_2CO_3 (10 mmol) was added and the mixture was stirred under argon and heated under reflux for 8 h. The system was allowed to reach room temperature, the catalyst and inorganic salts were filtered off through Celite and washed with acetonitrile until no color was observed in the filtrate. The combined filtrates were evaporated to dryness. The crude residue was purified by flash chromatography on a silica gel column with ethanol as the eluent. Compound **4e** was obtained as a red solid (255 mg, 92%, toluene), mp 168–169 °C; IR (KBr): ν_{max} (cm^{-1}) 3233, 2850, 1599, 1465, 1374, 1328, 1146, 1042, 1008, 808, 761, 518; ^1H NMR (300 MHz, CD_3OD): δ (ppm) 8.80 (2H, dd, $J = 7.0$ and 1.2 Hz, $H2(6)$); 8.05 (1H, tt, $J = 7.7$ and 1.2 Hz, $H4$); 7.98 (1H, dd, $J = 2.5$ and 0.7 Hz, $H6'$); 7.83 (2H, dd, $J = 7.7$ and 7.0 Hz, $H3(5)$); 7.72 (1H, dd, $J = 8.8$ and 2.5 Hz, $H4'$); 7.50 (2H, ap d, $J = 8.4$ Hz, $H2''(6'')$); 7.39 (2H, ap d, $J = 8.4$ Hz, $H3''(5'')$); 6.62 (1H, dd, $J = 8.8$ and 0.7 Hz, $H3'$); 4.63 (2H, s, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 164.9 ($C2'$), 144.8 ($C2(6)$), 144.6 ($C6'$), 140.7 ($C4''$), 139.0 ($C1''$), 137.8 ($C4$), 137.0 ($C4'$), 128.7 ($C3''(5'')$), 128.5 ($C3(5)$), 126.4 ($C2''(6'')$), 125.3 ($C5'$), 112.3 ($C3'$), 70.0 (CH_2). MS (CI, *m/z*): 278 (100, M + 1), 277 (47), 260 (25), 201 (65). HRMS (ESI-TOF, CH_3OH): $[M+H]^+$ calcd for $C_{17}H_{16}N_3O$, 278.12879; found, 278.13210.

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26. *General procedure for the reduction of pyridinium tetrakis salts* **5** *and* **6**: In a round-bottom flask the corresponding tetra-salt **5** or **6** (0.1 mmol) was dissolved in AcOH/MeOH (2:1, 30 mL). Zn dust (40 mmol) was added and the mixture was stirred at room temperature for 12 h. During this time a color change was observed. The crude mixture was evaporated to dryness and treated with a mixture of

NaOH (10%) (15 mL) and AcOEt (30 mL). Two layers were separated and the organic phase was dried over $MgSO_4$, the solvent was removed in vacuo and the residue purified by chromatography through a silica gel column, using a suitable solvent as the eluent, and finally recrystallized to give the corresponding tetra-aminopyridine **8** and **9** as a pale yellow solids.

1,6-Bis[3,5-bis(pyridin-2-ylaminomethyl)phenoxy]hexane (**7a**): White solid (59 mg, 85%, ethyl acetate); mp: 92–94 °C; IR (KBr): ν_{max} (cm^{-1}) 3251, 2924, 1600, 1455, 1328, 1291, 1154, 1049, 979, 845, 771; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.06 (4H, ap dd, $J = 5.0$ and 1.8 Hz, *H*6), 7.36 (4H, ddd, $J = 8.6$, 7.2 and 1.8 Hz, *H*4), 6.90 (2H, br s, $H4_{Ar}$), 6.78 (4H, d, $J = 1.6$ Hz, $H2_{Ar}(6_{Ar})$), 6.56 (4H, ddd, $J = 7.2$, 5.0 and 1.0 Hz, *H*5), 6.32 (4H, br d, $J = 8.6$ Hz, *H*3), 4.94 (4H, br s, N*H*), 4.42 (8H, d, $J = 5.7$ Hz, CH_2N), 3.88 (4H, t, $J = 6.4$ Hz, CH_2O), 1.73 (4H, m, $CH_2\beta$), 1.45 (4H, m, $CH_2\gamma$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 159.7 ($C1_{Ar}$), 158.5 (*C*2), 148.0 (*C*6), 141.1 ($C3_{Ar}(5_{Ar})$), 137.4 (*C*4), 118.3 ($C4_{Ar}$), 113.1 ($C2_{Ar}(6_{Ar})$), 112.2 (*C*5), 106.8 (*C*3), 67.8 (CH_2O), 46.3 (CH_2N), 29.7 ($CH_2\beta$), 25.8 ($CH_2\gamma$); HRMS (ESI-TOF, CH_3OH): $[M+H]^+$ calcd for $C_{42}H_{46}N_8O_2$, 695.3812; found, 695.3860.

1,3-Bis[3,5-bis(quinolin-2-ylaminomethyl)phenoxymethyl]-benzene (**8b**): Yellow solid (81 mg, 89%, ethyl acetate); mp: 133–135 °C. IR (KBr): ν_{max} (cm^{-1}) 3417, 2925, 1618, 1400, 1290, 1154, 1049, 893, 818, 756, 456. ^1H NMR (500 MHz, $(CD_3)_2CO$): δ (ppm) 7.81 (4H, d, $J = 8.9$ Hz, *H*4), 7.58 (4H, dd, $J = 8.0$ and 1.5 Hz, *H*5), 7.55 (4H, dd, $J = 8.4$ and 1.5 Hz, *H*8), 7.44 (4H, ddd, $J = 8.4$, 7.1 and 1.5 Hz, *H*6), 7.41 (1H, br s, $H2_{Xyl}$), 7.26 (3H, m, $H4_{Xyl}(6_{Xyl})$ and $H5_{Xyl}$), 7.13 (4H, ddd, $J = 8.0$, 6.9 and 1.1 Hz, *H*7), 7.10 (2H, br s, $H4_{Ar}$), 6.98 (4H, d, $J = 1.3$ Hz, $H2_{Ar}(6_{Ar})$), 6.81 (4H, d, $J = 8.9$ Hz, *H*3), 4.99 (4H, s, CH_2O), 4.69 (4H, s, CH_2N). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ (ppm) 159.7 ($C1_{Ar}$), 157.5 (*C*2), 148.8 (*C*8a), 142.7 ($C3_{Ar}(5_{Ar})$), 138.3 ($C1_{Xyl}(3_{Xyl})$), 137.1 (*C*4), 129.5 (*C*7), 129.0 ($C5_{Xyl}$), 128.0 (*C*5), 127.5 ($C4_{Xyl}(6_{Xyl})$), 127.2 ($C2_{Xyl}$), 126.7 (*C*8), 124.1 (*C*4a), 122.0 (*C*6), 120.1 ($C4_{Ar}$), 113.3 (*C*3), 113.1 ($C2_{Ar}(6_{Ar})$), 69.9 (CH_2O), 44.9 (CH_2N); HRMS (ESI-TOF, CH_3OH): $[M+H]^+$ calcd for $C_{60}H_{50}N_8O_2$, 915.4124; found, 915.4162.