Tetrahedron 65 (2009) 9782–9790

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pyridinium *N*-heteroarylaminides: synthesis of *N*-heteroarylpolyamines

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ARTICLE INFO

Article history:
Received 28 July 2009
Received in revised form
11 September 2009
Accepted 18 September 2009
Available online 22 September 2009

ABSTRACT

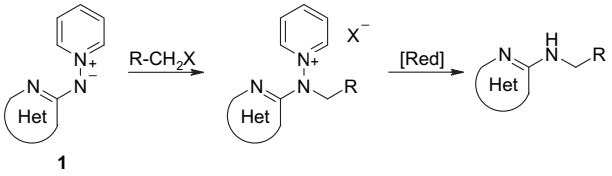
The synthesis of a set of new *N*-heteroarylpolyamines is reported. A multiple and regioselective alkylation on the *exo* nitrogen of pyridinium *N*-(heteroaryl)aminides with several polybromo compounds, followed by a clean N–N bond reduction of the corresponding pyridinium salts, provides an easy and general method to obtain the title compounds.

1. Introduction

Polyamines are a family of compounds that are widely studied as a result of their presence in many biological systems[1a,b] and their use as chelating agents,[1c–e] to mention two of the most representative areas of interest. The polyamines reported to date, however, are mostly aliphatic and very little attention has been paid to polyamines bearing heterocyclic moieties. In the case of the compounds now described, they mostly functionalised with 2-aminopyridine moieties, which combine in their structure two supplementary effects in terms of basicity and coordination properties, because the molecule has two electronically different and complementary unshared electron pairs, which produces an azine nitrogen with high electronic density. In recent articles the advantages of using (poly)aminopyridines within artificial receptors has been described.[1f–h] However, the synthesis and reactivity of other aminoheterocycles have been even less studied.

Monoalkylation on the exocyclic nitrogen of 2-aminopyridines is not an easy task due to the presence of two nucleophilic nitrogen atoms in the structure, for which kinetic control favours alkylation of the azine nitrogen. A review of the literature showed that this problem is usually avoided either by the use of protecting groups,[2a,b] by directly synthesizing the alkylaminopyridine through highly reactive sustrates,[2c] or by preparing the diazonium salt, which is subsequently substituted with the corresponding amine. The synthesis of 2-(*N*-alkylamino)pyridines is also possible from halopyridines through S_N reactions with amines[2d] or by employing amination catalysts.[2e,f] As part of our research programme, we explored the synthetic uses of *N*-(heteroaryl)pyridinium aminides **1**, which offer a clear alternative because substituted alkylaminoheterocycles can be easily obtained in a two-step regioselective and mild procedure.[3]

Alkylation of pyridinium aminides, especially those in which the structure is stabilized with azines, is a well documented procedure for the highly regioselective alkylation of the exocyclic nitrogen atom. A subsequent reduction of the N–N bond under mild conditions yields the corresponding alkylaminoazine (Scheme 1).



Scheme 1.

There are other advantages of the synthesis of alkylaminoazines from pyridinium aminides. For example, multiple alkylations and subsequent reductions are also possible to give, in a controlled manner, families of polyaminopyridines with a range of possibilities for structural variation.[3]

All of these precedents—combining alkylation, reduction and the possibility of using a wide variety of differently functionalized pyridinium aminides[4,5]—allowed us to tackle the synthesis of several geometrically different families of polyaminoazines.[3]

The first target was the preparation of alkyl bromides with two different functionalities: one with halomethyl groups for the alkylation of the corresponding pyridinium aminides and an additional one to explore the possibility of growing the molecule, as typically explored in dendrimer chemistry. The dihalogenated compounds suitable to afford this synthetic route could be easily obtained from dimethylisophthalate derivates **2**, as shown in Scheme 2.[6]

Alkylation of pyridinium aminides[3] **1** with 1-benzyloxy-3,5-bis(bromomethyl) benzene[6d,e] **3** or 3,5-bis(bromomethyl)phenol[6f–i] **4** gave the corresponding bis(heteroarylaminopyridinium)dibromides **5** and **6** in excellent yields (Scheme 2, Table 1).

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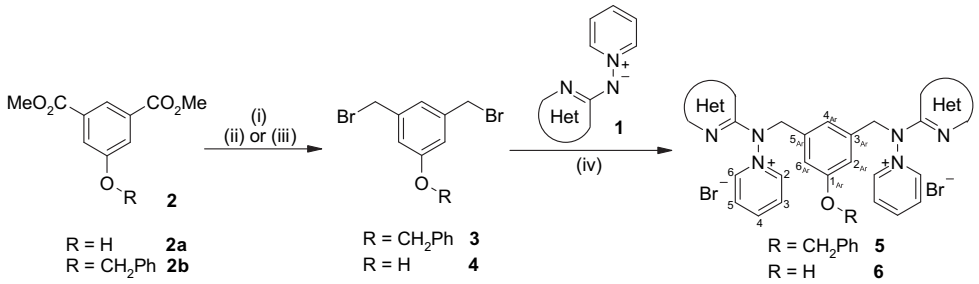
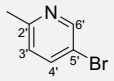
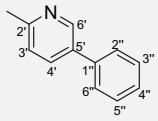
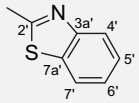
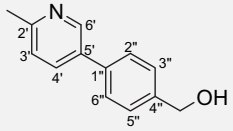
doi:10.1016/j.tet.2009.09.079



Scheme 2. (i) $LiAlH_4$, THF, Δ, 3 h. (ii) NBS, PPh_3, CH_2Cl_2, rt, 12 h, for **3**. (iii) HBr–H_2O/toluene, Δ, 2 h, for **4**. (iv) Acetone, rt, 12 h.

Table 1
Alkylation of different *N*-(heteroar-2-yl)pyridinium aminides with compounds **3** and **4**

Het	R	Compound	Yield
	–CH_2Ph	**5a**	89%
	–CH_2Ph	**5b**	92%
	–H	**6a**	95%
	–H	**6b**	85%
	–H	**6c**	91%

Compounds **5a** and **5b** were prepared from the corresponding aminides in order to check (by ^{1}H NMR spectroscopy) the evolution of the Suzuki reaction on salt **5a**. The conditions described for the coupling on aminides[5a,b] were not suitable in this case. When the Pd cross-coupling on **5a** was tested using MeCN/EtOH as solvent, decomposition of the salt was observed. A blank test without boronic acid and Pd catalyst demonstrated decomposition of **5a**, giving detectable amounts of pyridin-2-one and 5-benzyloxy-1,3-bis[*N*-(5-bromopyridin-2-yl)aminomethyl]benzene. A mechanism for the process is postulated in Scheme 3.

Due to the failure in the functionalization of the heteroarylaminopyridinium salts **5** and **6**, which would have opened access to more complicated structures, it was decided to prepare branched alkylating agents that would react with functionalized pyridinium aminides,[4] such as 1,3,5-tris-bromomethylbenzene **7**[3a,7] or the *tetrakis*-bromomethyl derivates **10**[3b,8], which synthesis is outlined in Scheme 4.

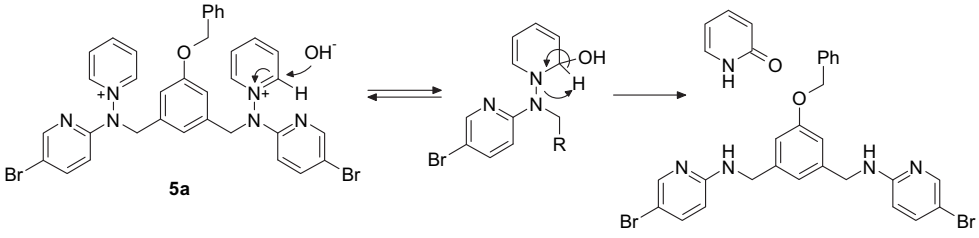
The alkyl bromides **7** and **10** were reacted with pyridinium aminides according to the described procedure.[3a] In this case, however, intermediate mono- and dialkylated salts precipitated together with the fully alkylated compound. In an effort to avoid this problem, a more polar solvent was chosen and the use of DMF was able to retain all compounds in solution, meaning that the reaction could proceed to completion (Schemes 5 and 6).[3b]

Isolation of salts from the mixture was performed by evaporating the solvent, redissolving the residue in the minimum amount of DMF (1–2 mL) and adding this solution dropwise to well stirred AcOEt. This led to precipitation of the heteroarylaminopyridinium bromides, while the uncharged pyridinium aminide remained in solution. The salts **11**, **13** and **14** were collected by filtration and further purified by crystallization.

The N–N bond in the poly(heteroarylamino)aminopyridinium bromides **11**, **13** and **14** was reduced using a metal/acid system such as Zn/AcOH[3b] and in the case of **12c** cleavage of the chlorine was not observed.

Polyamines **12**, **15** and **16** were obtained as solids in good yields except for **12d**, which was obtained as an oil. The different yields obtained in the polyalkylation and reduction processes are shown in Tables 2 and 3 (Schemes 5 and 6).

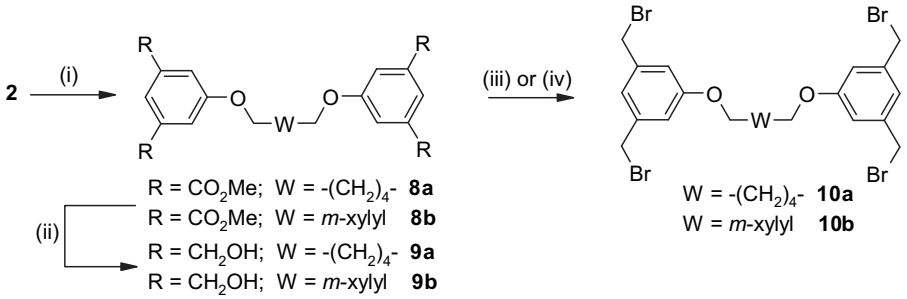
Transformation of the –CH_2OH group into a –CH_2Br group in compounds **11a** and **11b** can be used to grow the molecule. This halogenation was carried out in concentrated hydrobromic acid, in which the salt dissolved slowly. After 12 h the salt was isolated as previously indicated and treated with a basic ionic exchange resin to remove any excess acid. Trihalogenated salt **17**, under the usual conditions, reacted with pyridinium aminides to give hexasalts **18**, as shown in Scheme 7.



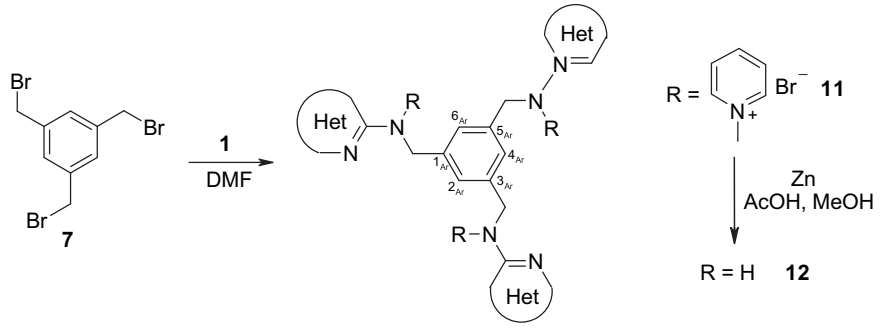
Scheme 3.

On the other hand, the alkylation of the free phenol group in compounds **6** was tested, but substitution with alkyl halides was not observed. This is possibly due to steric hindrance around the phenol group and/or to the association of the phenoxide with the acidic α-positions of the pyridinium rings, both of which would give an intermediate with low reactivity.

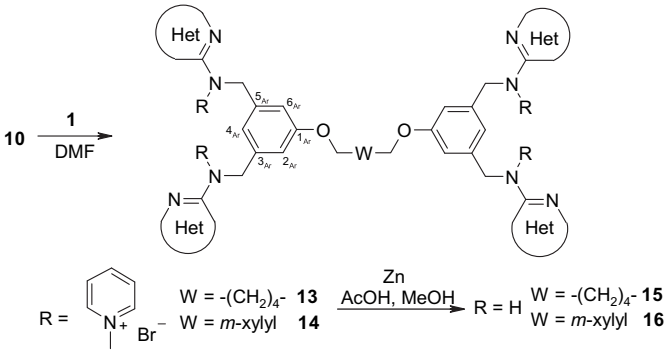
Finally, reduction of hexasalt **18** to the corresponding hexamine was attempted, but the use of either Zn/AcOH[3b] or BEt_3/MeOH[5a] proved unsuccessful and produced only partial reduction, with pyridine detected in the reaction mixture. Tests



Scheme 4. Reagents and conditions: (i) DMF, K_2CO_3, alkyl dibromide, 80 °C, 24 h. (ii) $LiAlH_4$, THF, Δ, 3 h. (iii) HBr/H_2SO_4, Δ, 1 h (for **10a**[7]). (iv) NBS, PPh_3, CH_2Cl_2, ultrasound, 90 min (for **10b**[3b]).



Scheme 5.



Scheme 6.

using ammonium formate and Pd/C (10% dry)[9] allowed the preparation of **19**, although purification of the hexamine was not achieved (Scheme 7).

In conclusion, *N*-(heteroaryl)pyridinium aminides **1** can be used as intermediates to produce polyamines bearing 2-amino-heteroaryl moieties. The process to generate the dendrimeric compounds is simple and straightforward, with a combination of Pd arylation on the heteroaryl ring and *N*-alkylation on the aminide nitrogen. The process, however, becomes more difficult with poly-substituted compounds, as both polypyridinium salts and the resulting polyamines are very insoluble, making it increasingly difficult to manage all processes on increasing the size of the system. Further studies on metal complexation of these polyamines are currently in progress as well as a possible improvement of the reduction in hexasalts.

2. Experimental section

2.1. General

All chemicals and solvents were purchased from commercial sources. Reactions involving ultrasound were carried out in a Branson 1510 ultrasonic bath. Infrared spectra were recorded on a Perkin–Elmer FTIR 1725X spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini (200 MHz), Unity or Mercury (300 MHz) or Unity (500 MHz) spectrometers and values are given in parts per million (δ) downfield from TMS. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus using open capillary tubes and are uncorrected. Elemental analyses were carried out on a Heraeus Rapid CHN analyser and are within ±0.4% of the theoretical values for all compounds described. Mass data were collected, when given, on an Agilent 6210 Time-of-flight LC/MS.

In the NMR analysis, numbering was defined using primes, with the highest priority ring in the molecule labelled without primes and the lowest priority groups labelled with a prime (′), double prime (″), etc. In some cases, substituted central rings are labelled as *Ar* or *Xyl* and alkyl chains with α–γ. In the case of compound **18a**, an extra NMR label appears in the assignment and this denotes a difference between the external (e) and internal (i) pyridinium aminide units.

Note that for reduced compounds the labelling has one fewer prime labels than the precursor (due to the absence of the pyridinium ring). In NMR analyses, 2D experiments were performed for relevant compounds, with the rest assigned on the basis of the values obtained either from the related products or from the literature.

Table 2
Trialkylation and reduction of 3,5-disubstitutedpyridin-2-yl pyridinium aminides[5a]

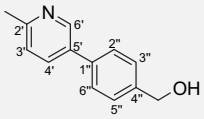
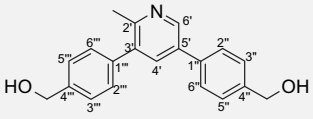
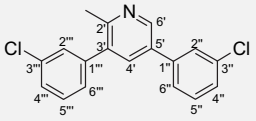
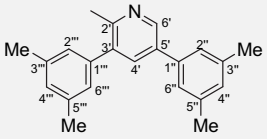
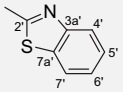
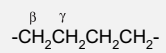
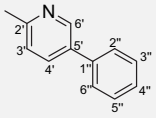
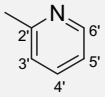
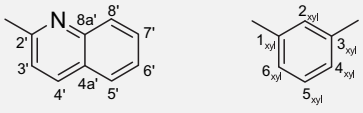
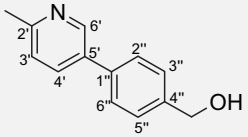
Het	Alkylation		Reduction	
	Compound	Yield	Compound	Yield
	**11a**	85%	**12a**	79%
	**11b**	80%	**12b**	71%
	**11c**	87%	**12c**	79%
	**11d**	76%	**12d**	70%

Table 3
Tetraalkylation and reduction of different heteroarylpyridinium aminides[4,5a]

Het	W	Alkylation		Reduction	
		Compound	Yield	Compound	Yield
		**13a**	85%	**15a**	85%
		**13b**	84%	**15b**	68%
		**13c**	90%	**15c**	74%
		**14a**	87%	**16a**	79%
		**14b**	84%	**16b**	89%
		**14c**	70%	**16c**	73%

2.2. Alkylation of pyridinium aminides with dibromo derivatives. General procedure

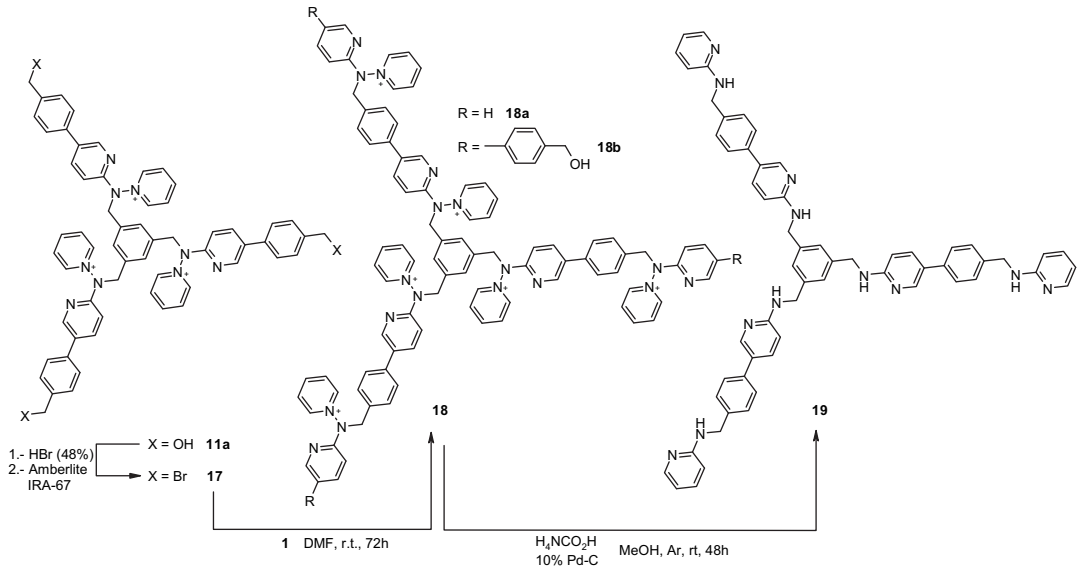
The corresponding dibromoderivative (**3** or **4**) (1.0 mmol) and the corresponding *N*-(heteroaryl)pyridinium aminide (2.2 mmol) were dissolved in acetone (10 mL) in a dried round-bottomed flask. The reaction mixture was stirred at room temperature for 12 h. During the reaction a precipitate appeared and, after completion, the diaminopyridinium bromide was filtered off, washed with acetone, and crystallized from EtOH or *i*PrOH with a few drops of MeOH, to give pure diaminopyridinium bromides **5** and **6** as yellow to brown solids.

*2.2.1. {5-Benzyloxy-1,3-bis[N-(5-bromopyridin-2-yl)-N-(pyridin-1-ium)amino methyl]}benzene dibromide (**5a**).* From 550 mg of the *N*-(5-bromopyridin-2-yl)pyridinium aminide[5c] and 370 mg of **3**, and following the general procedure, 800 mg of the dibromide **5a** were obtained (mp>172 °C dec, EtOH, 92%). IR (KBr), ν_{max} (cm^{-1}): 2998, 2934, 1616, 1571, 1476, 1367, 1299, 1225, 1154, 1048, 996, 829, 748, 673. ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 9.15 (4H, dd, *J*=6.8 and 1.3 Hz, *H*2(6)), 8.74 (2H, tt, *J*=7.8 and 1.3 Hz, *H*4), 8.28 (2H, d, *J*=2.0 Hz, *H*6′), 8.19 (4H, dd, *J*=7.8 and 6.8 Hz, *H*3(5)), 8.03 (2H, dd, *J*=9.0 and 2.4 Hz, *H*4′), 7.38 (5H, m, H_{Ph}), 7.19 (1H, br s, $H4_{Ar}$), 7.14 (2H, d, *J*=9.0 Hz, *H*3′), 7.05 (2H, d, *J*=1.4 Hz, $H2_{Ar}$ (6_{Ar})), 5.36 (4H, s, CH_2N), 5.12 (2H, s, CH_2O). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 160.9, 157.0, 149.8, 149.5, 149.3, 143.0, 138.2, 137.5, 130.7, 129.7, 129.1, 128.5, 122.8, 117.0, 115.8, 112.5, 70.9, 58.5. MS (ESI, MeOH, *m*/*z*): 793/791/789/787 (3/8/8/3, $[M-Br]^+$), 356/354 (74/51), 355 (100), 316 (15), 315 (18). HRMS (ESI-TOF, MeOH): calculated for $C_{35}H_{29}{}^{79}Br_3N_6O$ $[M-Br]^+$: 785.99530, found 785.99497.

*2.2.2. {5-Benzyloxy-1,3-bis[N-(5-phenylpyridin-2-yl)-N-(pyridin-1-ium)amino methyl]}benzene dibromide (**5b**).* From 544 mg of the *N*-(5-phenylpyridin-2-yl)pyridinium aminide[5a] and 370 mg of **3**, and following the general procedure, 770 mg of the dibromide **5b** were obtained (mp>197 °C dec, EtOH, 89%). ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 9.18 (4H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.73 (2H, tt, *J*=7.8 and 1.3 Hz, *H*4), 8.47 (2H, dd, *J*=2.4 and 0.7 Hz, *H*6′), 8.21 (4H, dd, *J*=7.9 and 6.6 Hz, *H*3(5)), 8.14 (2H, dd, *J*=8.6 and 2.4 Hz, *H*4′), 7.62 (4H, dd, *J*=8.3 and 1.4 Hz, *H*2″(6″)), 7.45 (11H, m, *H*3″(5″), H_{Ph} and *H*4″), 7.25 (3H, m, *H*3′ and $H4_{Ar}$), 7.10 (2H, d, *J*=1.2 Hz, $H2_{Ar}$(6_{Ar})), 5.41 (4H, s, CH_2N), 5.15 (2H, s, CH_2O). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 161.0, 157.3, 149.6, 149.1, 147.1, 138.9, 138.3, 137.9, 134.1, 130.6, 130.4, 130.3, 129.7, 129.2, 129.1, 128.5, 127.7, 122.8, 117.0, 111.0, 70.9, 58.7. HRMS (ESI-TOF, MeOH): calculated for $C_{47}H_{40}{}^{79}BrN_6O$ $[M-Br]^+$: 783.2447, found 783.2533.

*2.2.3. {5-Hydroxy-1,3-bis[N-(pyridin-2-yl)-N-(pyridin-1-ium)aminomethyl]}benzene dibromide (**6a**).* From 376 mg of the *N*-(pyridin-2-yl)pyridinium aminide[10b] and 280 mg of **4**, and following the general procedure, 614 mg of the dibromide **6a** were obtained (mp=238–239 °C, EtOH, 95%). IR (KBr), ν_{max} (cm^{-1}): 3025, 1614, 1591, 1471, 1321, 1304, 1239, 1158, 797, 773, 682. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.64 (1H, s, O*H*), 9.30 (4H, d, *J*=5.7 Hz, *H*2(6)), 8.75 (2H, t, *J*=7.9 Hz, *H*4), 8.26 (4H, m, *H*3(5)), 8.17 (2H, dd, *J*=5.2 and 1.5 Hz, *H*6′), 7.89 (2H, dd, *J*=7.9 and 1.5 Hz, *H*4′), 7.14 (4H, m, *H*3′ and *H*5′), 6.93 (1H, s, $H4_{Ar}$), 6.69 (2H, s, $H2_{Ar}$(6_{Ar})), 5.28 (4H, s, CH_2N). ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 9.20 (4H, dd, *J*=6.8 and 1.3 Hz, *H*2(6)), 8.44 (2H, tt, *J*=7.8 and 1.3 Hz, *H*4), 8.22 (6H, m, *H*3(5) and *H*6′), 7.90 (2H, ddd, *J*=8.9, 7.9 and 1.8 Hz, *H*4′), 7.18 (4H, m, *H*3′ and *H*5′), 7.08 (1H, m, $H4_{Ar}$), 6.81 (2H, d, *J*=1.5 Hz, $H2_{Ar}$(6_{Ar})), 5.32 (4H, s, CH_2N). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 157.3, 156.0, 147.6, 147.3, 147.0, 138.6, 135.5, 128.7, 118.6, 118.4, 114.9, 108.5, 56.0. MS (ESI, MeOH, *m*/*z*): 543/541 (24/27, $[M-Br]^+$), 232 (35), 231 (100). HRMS (ESI-TOF, MeOH): calculated for $C_{28}H_{26}{}^{79}BrN_6O$ $[M-Br]^+$: 540.12732, found 540.12161.

*2.2.4. {5-Hydroxy-1,3-bis[N-(benzothiazol-2-yl)-N-(pyridin-1-ium)aminomethyl]}benzene dibromide (**6b**).* From 500 mg of the *N*-(benzothiazol-2-yl)pyridinium aminide[4] and 280 mg of **4**, and following the general procedure, 739 mg of the dibromide **6b**



Scheme 7.

were obtained (mp=188–191 °C, EtOH, 87%). IR (KBr), ν_{max} (cm^{-1}): 3485, 3189, 3016, 1685, 1601, 1516, 1441, 1370, 1277, 1165, 767, 737, 670. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.86 (1H, s, O*H*), 9.69 (4H, br d, *J*=5.9 Hz, *H*2(6)), 8.82 (2H, br t, *J*=7.6 Hz, *H*4), 8.38 (4H, ap t, *J*=6.8 Hz, *H*3(5)), 8.02 (2H, br d, *J*=7.9 Hz, *H*7′), 7.58 (2H, br d, *J*=7.9 Hz, *H*4′), 7.40 (2H, ap t, *J*=7.6 Hz, *H*5′ or *H*6′), 7.31 (2H, ap t, *J*=7.6 Hz, *H*6′ or *H*5′), 7.25 (1H, br s, $H4_{Ar}$), 6.92 (2H, br s, $H2_{Ar}(6_{Ar})$), 5.47 (4H, s, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 166.0, 157.6, 149.1, 148.5, 147.3, 134.3, 131.4, 139.2, 126.3, 123.6, 121.6, 120.2, 119.3, 115.9, 58.9. MS (ESI, MeOH, *m*/*z*): 655/653 (16/15, [M−Br]$^+$), 415 (25), 287 (24), 224 (39), 208 (100). HRMS (ESI-TOF, MeOH): calculated for $C_{32}H_{25}{}^{79}BrN_6OS_2$ [M−Br]$^+$: 652.07146, found 652.09369.

*2.2.5. (5-Hydroxy-1,3-bis{N-[(4-hydroxymethylphenyl)pyridin-2-yl]-N-(pyridin-1-ium)aminomethyl})benzene dibromide (**6c**).* From 609 mg of the *N*-[(4-hydroxymethylphenyl)pyridin-2-yl]pyridinium aminide[3b] and 280 mg of **4**, and following the general procedure, 815 mg of the dibromide **6c** were obtained (mp=188–190 °C, EtOH, 91%). IR (KBr), ν_{max} (cm^{-1}): 3368, 3023, 1599, 1475, 1372, 1014, 810, 676. ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.69 (1H, s, O*H*), 9.38 (4H, d, *J*=5.9 Hz, *H*2(6)), 8.77 (2H, t, *J*=7.9 Hz, *H*4), 8.49 (2H, br s, *H*6′), 8.30 (4H, m, *H*3(5)), 8.20 (2H, d, *J*=8.6 Hz, *H*4′), 7.63 (4H, ap d, *J*=7.9 Hz, *H*2″(6″)), 7.40 (4H, ap d, *J*=7.9 Hz, *H*3″(5″)), 7.26 (2H, d, *J*=8.6 Hz, *H*3′), 7.00 (1H, br s, $H4_{Ar}$), 6.74 (2H, br s, $H2_{Ar}(6_{Ar})$), 5.35 (4H, s, CH_2N), 4.52 (4H, br s, CH_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 157.5, 155.4, 147.7, 147.5, 144.7, 141.8, 136.6, 135.7, 133.9, 130.5, 128.9, 126.6, 125.6, 118.6, 114.9, 108.7, 71.7, 56.3. MS (ESI, MeOH *m*/*z*): 755/753 (11/11, [M−Br]$^+$), 337(23), 298 (18), 278 (67), 258 (100). HRMS (ESI-TOF, MeOH): calculated for $C_{44}H_{38}{}^{79}BrN_6O_3$ [M−Br]$^+$: 752.21105, found 752.20476.

2.3. Alkylation of pyridinium aminides with tribromo and tetrabromo derivatives. General procedure

To a dried round-bottomed flask, either tris-(bromomethyl) benzene **7** (71.4 mg, 0.2 mmol) and the corresponding *N*-(heteroaryl)pyridinium aminide (0.66 mmol) or the corresponding tetrahaloderivative (0.2 mmol, **10a**: 128.4 mg or **10b**: 132.4 mg) and the *N*-(heteroaryl)pyridinium aminide (1.0 mmol) were suspended in DMF (5 mL). The reaction mixture was stirred at room temperature for up to 72 h, or until the halogenated derivative had been consumed (detected by TLC). Once the process was complete, purification of aminopyridinium salts was carried out as described previously.[3b] The tri- and tetra-aminopyridinium bromides **11**, **13** and **14** appeared as yellow to brown solids.

*2.3.1. 1,3,5-Tris{pyridin-1-ium-[5-(4-hydroxymethylphenyl)pyridin-2-yl]amino methyl}benzene bromide (**11a**).* From 183.0 mg of the *N*-[5-(4-hydroxymethylphenyl)pyridin-2-yl]pyridinium aminide,[3b] 312 mg of compound **11a** were obtained as a dark yellow solid (mp>192 °C dec, EtOH/MeOH, 85%). IR (KBr), ν_{max} (cm^{-1}): 3351, 3023, 1615, 1599, 1475, 1372, 1222, 1047, 1014, 810, 678. ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 9.31 (6H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.73 (3H, tt, *J*=7.7 and 1.3 Hz, *H*4), 8.46 (3H, dd, *J*=2.4 and 0.9 Hz, *H*6′), 8.26 (6H, dd, *J*=7.9 and 6.8 Hz, *H*3(5)), 8.08 (3H, dd, *J*=8.1 and 2.4 Hz, *H*4′), 7.73 (3H, s, H_{Ar}), 7.57 (6H, ap d, *J*=8.6 Hz, *H*2″(6″)), 7.45 (6H, ap d, *J*=8.6 Hz, *H*3″(5″)), 7.13 (3H, dd, *J*=8.8 and 0.9 Hz, *H*3′), 5.49 (6H, s, CH_2N), 4.68 (6H, s, CH_2O). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 157.1, 149.6, 149.1, 147.0, 142.9, 138.7, 137.9, 133.9, 136.6, 130.8, 130.3, 128.8, 127.6, 111.2, 64.7, 58.6. Elemental Analysis: Calculated for $C_{60}H_{54}Br_3N_9O_3\cdot 3H_2O$: C=57.98, H=4.87, N=10.14, Found C=57.61, H=4.72, N=10.14.

*2.3.2. 1,3,5-Tris{pyridin-1-ium-[3,5-bis(4-hydroxymethyl)phenyl-pyridin-2-yl]amino methyl}benzene bromide (**11b**).* From 253 mg of the *N*-[3,5-bis(4-hydroxymethylphenyl)pyridin-2-yl]pyridinium aminide,[5a] 254 mg of compound **11b** were obtained as a brown solid (mp>162 °C dec, EtOH/MeOH, 80%). IR (KBr), ν_{max} (cm^{-1}): 3368, 2928, 1615, 1473, 1438, 1405, 1205, 1046, 1007, 822, 785, 680, 529. ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 8.84 (6H, ap d, *J*=5.9 Hz, *H*2(6)), 8.59 (3H, d, *J*=2.4 Hz, *H*6′), 8.40 (3H, ap t, *J*=7.7 Hz, *H*4), 7.83 (6H, ap t, *J*=7.1 Hz, *H*3(5)), 7.80 (3H, d, *J*=2.4 Hz, *H*4′), 7.60 (3H, s, H_{Ar}), 7.45 (18H, m, *H*2‴(6‴), *H*2″(6″) and *H*3‴(5‴) or *H*3″(5″)), 7.28 (6H, ap d, *J*=8.0 Hz, *H*3″(5″) or *H*3‴(5‴)), 5.22 (6H, s, CH_2N), 5.22 (12H, m, CH_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 152.3, 146.4, 146.0, 143.7, 142.5, 142.4, 138.5, 134.2, 134.1, 133.5, 133.3, 128.8, 128.3, 128.1, 127.8, 126.7, 126.4, 126.2, 61.9, 61.9, 56.6. Elemental Analysis: Calculated for $C_{81}H_{72}Br_3N_9O_6\cdot 6H_2O$: C=60.23, H=5.24, N=7.80, Found C=60.38, H=5.06, N=8.02.

*2.3.3. 1,3,5-Tris{pyridin-1-ium-[3,5-bis(3-chlorophenyl)pyridin-2-yl]aminomethyl}-benzene bromide (**11c**).* From 259 mg of the *N*-[3,5-bis(3-chlorophenyl)pyridin-2-yl]pyridinium aminide,[5a]

266 mg of compound **11c** were obtained as a brown solid (mp=174–176 °C, *i*PrOH/MeOH, 87%). IR (KBr), ν_{max} (cm^{-1}): 3401, 3011, 1595, 1570, 1473, 1439, 1234, 1195, 1100, 1080, 787, 678. ^1H NMR (300 MHz, CD_3OD), δ (ppm): 8.98 (6H, ap d, J=5.4 Hz, *H*2(6)), 8.67 (3H, d, J=2.3 Hz, *H*6′), 8.51 (3H, ap t, J=7.7 Hz, *H*4), 7.94 (6H, ap t, J=6.9 Hz, *H*3(5)), 7.82 (3H, d, J=2.3 Hz, *H*4′), 7.48 (24H, m, *H*2″ or *H*2‴, *H*4″, *H*5″, *H*6″, *H*4‴, *H*5‴, *H*6‴ and H_{Ar}), 7.17 (3H, t, J=1.9 Hz, *H*2″ or *H*2‴), 5.23 (6H, s, C*H*$_2$N). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 153.7, 148.0, 147.8, 146.9, 140.4, 139.1, 138.9, 137.2, 136.3, 136.0, 135.9, 132.2, 131.9, 131.5, 131.1, 130.1, 130.0, 129.9, 129.8, 128.8, 127.9, 126.4, 60.7. Elemental Analysis: Calculated for $C_{75}H_{54}Br_3Cl_6N_9 \cdot 8H_2O$: C=53.69, H=4.21, N=7.51, Found C=53.60, H=3.83, N=7.62.

*2.3.4. 1,3,5-Tris{pyridin-1-ium-[3,5-bis(3,5-dimethylphenyl)pyridin-2-yl]amino methyl}benzene bromide (**11d**).* From 250 mg of the *N*-[3,5-bis(3,5-dimethylphenyl)pyridin-2-yl]pyridinium aminide,[5a] 258 mg of compound **11d** were obtained as a brown solid (mp=173–174 °C, *i*PrOH/MeOH, 76%). IR (KBr), ν_{max} (cm^{-1}): 3401, 3013, 1604, 1440, 1221, 849, 702, 676. ^1H NMR (300 MHz, CD_3OD), δ (ppm): 8.81 (6H, dd, J=6.7 and 1.3 Hz, *H*2(6)), 8.49 (3H, d, J=2.3 Hz, *H*6′), 8.45 (3H, tt, J=7.7 and 1.3 Hz, *H*4), 7.87 (6H, dd, J=7.7 and 6.7 Hz, *H*3(5)), 7.63 (3H, s, H_{Ar}), 7.52 (3H, d, J=2.3 Hz, *H*4′), 7.10 (3H, br s, *H*4‴ or *H*4″), 7.04 (3H, br s, *H*4″ or *H*4‴), 6.92 (6H, br s, *H*2‴(6‴) or *H*2″(6″)), 6.73 (6H, br s, *H*2″(6″) or *H*2‴(6‴)), 5.29 (6H, s, C*H*$_2$N), 2.36 (18H, s, C*H*$_3$), 2.35 (18H, s, C*H*$_3$). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 153.0, 147.5, 147.4, 146.0, 140.2, 140.1, 140.0, 137.7, 137.4, 137.2, 136.8, 132.7, 131.3, 131.0, 129.9, 127.6, 125.5, 116.2, 60.4, 21.5, 21.4. Elemental Analysis: Calculated for $C_{87}H_{84}Br_3N_9 \cdot 4H_2O$: C=66.67, H=5.92, N=8.04, Found C=66.89, H=5.69, N=8.09.

*2.3.5. 1,6-Bis{3,5-bis[N-(pyridin-2-yl)-N-(pyridin-1-ium)aminomethyl]phenoxy}hexane tetrabromide (**13a**).* See Ref. 3b.

*2.3.6. 1,6-Bis{3,5-bis[N-(benzothiazol-2-yl)-N-(pyridin-1-ium)aminomethyl]phenoxy}-hexane tetrabromide (**13b**).* From **10a** and 227 mg of the *N*-(benzothiazol-2-yl)pyridinium aminide,[4] 264 mg of **13b** were obtained as a yellow solid (mp>186 °C dec, 84%). IR (KBr), ν_{max} (cm^{-1}): 3009, 2931, 1614, 1596, 1520, 1471, 1440, 1297, 1170, 1047, 760, 672. ^1H NMR (300 MHz, CD_3OD), δ (ppm): 9.52 (8H, dd, J=6.9 and 1.6 Hz, *H*2(6), 8.75 (4H, tt, J=7.8 and 1.6 Hz, *H*4), 8.29 (8H, dd, J=7.8 and 6.9 Hz, *H*3(5)), 7.88 (4H, dd, J=8.0 and 1.3 Hz, *H*4′), 7.60 (4H, dd, J=8.2 and 1.3 Hz, *H*7′), 7.45 (4H, m, *H*5′ or *H*6′), 7.35 (4H, m, *H*6′ or *H*5′), 7.19 (4H, d, J=1.7 Hz, *H*2$_{Ar}$(6$_{Ar}$)), 7.16 (2H, br t, J=1.7 Hz, *H*4$_{Ar}$)), 5.51 (8H, s, C*H*$_2$N), 4.06 (4H, br t, J=6.2 Hz, C*H*$_2$O), 1.81 (4H, m, C*H*$_2\beta$), 1.56 (4H, m, C*H*$_2\gamma$). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 167.4 (*C*2′), 161.7 (*C*1$_{Ar}$), 151.3 (*C*3a′), 150.0 (*C*4), 149.2 (*C*2(6)), 136.4 (*C*3$_{Ar}$(5$_{Ar}$)), 133.6 (*C*7a′), 131.0 (*C*3(5)), 128.7 (*C*4′ or *C*7′), 125.8 (*C*7′ or *C*4′), 122.8 (*C*4$_{Ar}$), 122.8 (*C*5′ or *C*6′), 122.4 (*C*5′ or *C*6′), 117.5 (*C*2$_{Ar}$(6$_{Ar}$)), 69.5 (*C*H$_2$O), 61.2 (*C*H$_2$N), 30.2 (*C*H$_2\beta$), 26.9 (*C*H$_2\gamma$). Elemental Analysis: Calculated for $C_{70}H_{62}Br_4N_{12}O_2S_4 \cdot 8H_2O$: C=49.59, H=4.64, N=9.91, S=7.57, Found C=49.72, H=4.53, N=9.78, S=7.27.

*2.3.7. 1,6-Bis{3,5-bis[N-(5-phenylpyridin-2-yl)-N-(pyridin-1-ium)-aminomethyl] phenoxy}hexane tetrabromide (**13c**).* From **10a** and 247 mg of the *N*-(5-phenylpyridin-2-yl)pyridinium aminide,[5a] 295 mg of **13c** were obtained as a light brown solid (mp>179 °C dec, 90%). IR (KBr), ν_{max} (cm^{-1}): 3026, 2935, 1597, 1472, 1376, 1299, 1165, 1050, 768, 698, 680. ^1H NMR (500 MHz, CD_3OD), δ (ppm): 9.27 (8H, dd, J=6.4 and 1.3 Hz, *H*2(6)), 8.74 (4H, tt, J=7.7 and 1.3 Hz, *H*4), 8.46 (4H, d, J=2.2 Hz, *H*6′), 8.25 (8H, dd, J=7.7 and 6.4 Hz, *H*3(5)), 8.13 (4H, dd, J=8.6 and 2.2 Hz, *H*4′), 7.61 (8H, dd, J=8.3 and 1.4 Hz, *H*2″(6″)), 7.48 (8H, dd, J=8.3 and 7.2 Hz, *H*3″(5″)), 7.41 (4H, tt, J=7.2 and 1.4 Hz, H4″), 7.26 (4H, d, J=8.6 Hz, *H*3′), 7.25 (2H, br s, *H*4$_{Ar}$), 7.04 (4H, d, J=1.4 Hz, *H*2$_{Ar}$(6$_{Ar}$)), 5.42 (8H, s, C*H*$_2$N), 3.99 (4H, t, J=6.4 Hz, C*H*$_2$O), 1.78 (4H, m, C*H*$_2\beta$), 1.53 (4H, m, C*H*$_2\gamma$). ^{13}C NMR (125 MHz, CD_3OD), δ (ppm): 161.7 (*C*1$_{Ar}$), 157.4 (*C*2′), 149.7 (*C*2(6)), 149.2 (*C*4), 147.1 (*C*6′), 138.9 (*C*4′), 137.9 (*C*3$_{Ar}$(5$_{Ar}$)), 134.2 (*C*5′), 130.6 (*C*1″), 130.5 (*C*3(5)), 130.3 (*C*3″(5″)), 129.4 (*C*4″), 127.8 (*C*2″(6″)), 122.3 (*C*4$_{Ar}$), 116.5 (*C*2$_{Ar}$(6$_{Ar}$)), 111.1 (*C*3′), 69.4 (*C*H$_2$O), 58.8 (*C*H$_2$N), 30.2 (*C*H$_2\beta$), 26.9 (*C*H$_2\gamma$). Elemental Analysis: Calculated for $C_{86}H_{78}Br_4N_{12}O_2 \cdot 6H_2O$: C=59.39, H=5.22, N=9.66, Found C=59.69, H=4.89, N=9.87.

*2.3.8. 1,3-Bis{3,5-bis[N-(pyridin-2-yl)-N-(pyridin-1-ium)aminomethyl]phenoxy methyl}benzene tetrabromide (**14a**).* From **10b** and 171 mg of the *N*-(pyridin-2-yl)pyridinium aminide,[10b] 234 mg of **14a** were obtained as a light brown solid (mp>147 °C dec, 87%). IR (KBr), ν_{max} (cm^{-1}): 3013, 1595, 1471, 1432, 1297, 1159, 1044, 776, 686. ^1H NMR (300 MHz, CD_3OD), δ (ppm): 9.17 (8H, dd, J=6.7 and 1.5 Hz, *H*2(6)), 8.71 (4H, tt, J=7.8 and 1.5 Hz, *H*4), 8.19 (12H, m, *H*3(5) and *H*6′), 7.89 (4H, ddd, J=8.5, 7.3 and 1.8 Hz, *H*4′), 7.54 (1H, br s, *H*2$_{xyl}$), 7.41 (3H, m, *H*4$_{xyl}$(6$_{xyl}$) and *H*5$_{xyl}$), 7.18 (10H, m, *H*3′, 5′ and 4$_{Ar}$), 7.11 (4H, d, J=1.5 Hz, *H*2$_{Ar}$(6$_{Ar}$)), 5.34 (8H, s, C*H*$_2$N), 5.14 (4H, s, C*H*$_2$O). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 161.0 (*C*1$_{Ar}$), 158.3 (*C*2′), 149.6 (*C*2(6)), 149.2 (*C*6′), 149.1 (*C*4), 140.7 (*C*4′), 138.7 (*C*1$_{xyl}$(3$_{xyl}$)), 137.9 (*C*3$_{Ar}$(5$_{Ar}$)), 130.6 (*C*3(5)), 130.0 (*C*5$_{xyl}$), 128.3 (*C*4$_{xyl}$(6$_{xyl}$)), 128.0 (*C*2$_{xyl}$), 122.8 (*C*4$_{Ar}$), 120.9 (*C*5′), 116.9 (*C*2$_{Ar}$(6$_{Ar}$)), 111.0 (*C*3′), 70.9 (*C*H$_2$O), 58.6 (*C*H$_2$N). Elemental Analysis: Calculated for $C_{64}H_{58}Br_4N_{12}O_2 \cdot 5H_2O$: C=53.50, H=4.77, N=11.70, Found C=53.63, H=4.62, N=11.87.

*2.3.9. 1,3-Bis{3,5-bis[N-(quinolin-2-yl)-N-(pyridin-1-ium)aminomethyl]phenoxy methyl}benzene tetrabromide (**14b**).* See Ref. 3b.

*2.3.10. 1,3-Bis(3,5-bis{N-[5(4-hydroxymethylphenyl)pyridin-2-yl]-N-(pyridin-1-ium) aminomethyl}phenoxymethyl)benzene (**14c**).* From **10b** and 277 mg of the *N*-[(4-hydroxymethyl phenyl)pyridin-2-yl]pyridinium aminide,[3b] 248 mg of **14c** were obtained as a light brown solid (mp>195 °C dec, 70%). IR (KBr), ν_{max} (cm^{-1}): 3020, 1598, 1475, 1371, 1297, 1157, 1047, 811, 676. ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.41 (8H, br d, J=6.0 Hz, *H*2(6)), 8.75 (4H, br t, J=7.8 Hz, *H*4), 8.49 (4H, d, J=2.6 Hz, *H*6′), 8.27 (8H, m, *H*3(5)), 8.17 (4H, dd, J=8.7 and 2.6 Hz, *H*4′), 7.62 (8H, d, J=8.4 Hz, *H*2″(6″)), 7.48 (1H, br s, *H*2$_{xyl}$), 7.39 (11H, m, *H*3″(5″), *H*4$_{xyl}$(6$_{xyl}$) and *H*5$_{xyl}$), 7.22 (4H, d, J=8.7 Hz, *H*3′), 7.13 (2H, br s, *H*4$_{Ar}$), 7.10 (4H, br s, *H*2$_{Ar}$ (6$_{Ar}$)), 5.40 (8H, br s, C*H*$_2$N), 5.25 (4H, t, J=5.7 Hz, O*H*), 5.09 (4H, br s, C*H*$_2$O), 4.52 (8H, d, J=5.7 Hz, C*H*$_2$OH). ^{13}C NMR (125 MHz, CD_3OD), δ (ppm): 161.0 (*C*1$_{Ar}$), 157.3 (*C*2′), 149.6 (*C*2(6)), 149.1 (*C*4), 147.0 (*C*6′), 143.0 (*C*4″), 138.7 (*C*1$_{xyl}$(3$_{xyl}$)), 138.0 (*C*4′), 136.7 (*C*3$_{Ar}$(5$_{Ar}$)), 133.9 (*C*1″), 130.6 (*C*3(5)), 130.5 (*C*5′), 130.0 (*C*5$_{xyl}$), 128.8 (*C*3″(5″)), 128.3 (*C*4$_{xyl}$(6$_{xyl}$)), 127.9 (*C*2$_{xyl}$), 127.7 (*C*2″(6″)), 122.7 (*C*4$_{Ar}$), 117.0 (*C*2$_{Ar}$(6$_{Ar}$)), 111.1 (*C*3′), 70.9 (*C*H$_2$O), 64.7 (*C*H$_2$OH), 58.7 (*C*H$_2$N). Elemental Analysis: Calculated for $C_{92}H_{82}Br_4N_{12}O_6 \cdot 6H_2O$: C=58.79, H=5.04, N=8.94, Found C=58.80, H=4.99, N=8.54.

2.4. Reduction of tri- and tetra-aminopyridinium bromides. General procedure

A solution of the polyaminopyridinium bromide (**11**, **13** or **14**) in AcOH/MeOH (2:1, 30 mL) was prepared in a 50 mL round-bottomed flask. Zn dust (10 equiv per pyridinium group to be reduced) was added and the mixture was stirred at room temperature for 12 h. During this period a change in colour may be observed. Once the reaction was complete, the excess solid was filtered off and the solvent was removed from the filtrate. The residue was treated with a mixture of 15 mL NaOH (10%) and 30 mL AcOEt. The organic layer was separated and the aqueous layer extracted with AcOEt (3×10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by column chromatography with a suitable eluent, to give the

polyaminopyridine as a white to yellow solid or oil. When possible, the polyaminopyridine was crystallized from the indicated solvent.

*2.4.1. 1,3,5-Tris{[5-(4-hydroxymethylphenyl)pyridin-2-yl]aminomethyl}benzene (**12a**).* From 297 mg (0.25 mmol) of **11a** and following the general procedure, after chromatography with AcOEt/EtOH (1:1), 143 mg of **12a** were obtained as a white solid (mp=186–190 °C, acetone/*i*PrOH, 79%). IR (KBr), ν_{max} (cm^{-1}): 3317, 3217, 2920, 2851, 1737, 1606, 1547, 1496, 1384, 1000, 806. ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 8.24 (3H, d, J=2.3 Hz, *H*6), 7.63 (3H, dd, J=8.8 and 2.3 Hz, *H*4), 7.46 (6H, ap d, J=8.2 Hz, *H*2′(6′)), 7.30 (6H, ap d, J=8.2 Hz, *H*3′(5′)), 7.21 (3H, br s, H_{Ar}), 7.15 (3H, br t, J=5.9 Hz, N*H*), 6.53 (3H, d, J=8.8 Hz, *H*3), 5.13 (3H, t, J=5.9 Hz, O*H*), 4.48 (12H, m, CH_2N and CH_2O). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 157.4, 144.8, 140.1, 140.0, 136.0, 134.4, 126.6, 124.5, 124.0, 123.2, 107.6, 62.2, 43.8. HRMS (ESI-TOF, MeOH): calculated for $C_{45}H_{43}N_6O_3$ $[M+H]^+$ 715.33912, found 715.33667.

*2.4.2. 1,3,5-Tris{[3,5-bis(4-hydroxymethylphenyl)pyridin-2-yl]aminomethyl}benzene (**12b**).* From 377 mg (0.25 mmol) of **11b** and following the general procedure, after chromatography with AcOEt/EtOH (1:1), 195 mg of **12b** were obtained as a white solid (mp>80 °C dec, *i*PrOH, 71%). IR (KBr), ν_{max} (cm^{-1}): 3350, 2924, 1712, 1603, 1497, 1403, 1246, 1015, 819, 668. ^1H NMR (200 MHz, CD_3OD), δ (ppm): 8.11 (3H, d, J=1.9 Hz, *H*6), 7.34 (27H, m, *H*4, *H*2′(6′), *H*3′(5′), *H*2″(6″) and *H*3″(5″)), 7.15 (3H, br s, H_{Ar}), 4.64 (6H, s, CH_2N), 4.60 (12H, m, CH_2O). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 156.1, 145.2, 142.6, 142.0, 141.2, 138.2, 137.8, 137.2, 130.9, 128.8, 128.6, 126.8, 126.7, 124.7, 123.8, 64.9, 64.8, 45.6. HRMS (ESI-TOF, MeOH): calculated for $C_{66}H_{61}N_6O_6$ $[M+H]^+$ 1033.46471, found 1033.45614.

*2.4.3. 1,3,5-Tris{[3,5-bis(3-chlorophenyl)pyridin-2-yl]aminomethyl}benzene (**12c**).* From 383 mg (0.25 mmol) of **11c** and following the general procedure, after chromatography with hexane/CH_2Cl_2 (8:2), 181 mg of **12c** were obtained as a white solid (mp=94–97 °C, hexane, 79%). IR (NaCl), ν_{max} (cm^{-1}): 3441, 3060, 2924, 1604, 1574, 1508, 1475, 1401, 1244, 1100, 1081, 907, 786, 733, 703. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.27 (3H, d, J=2.3 Hz, *H*6), 7.33 (27H, m, *H*4, *H*2′, *H*4′, *H*5′, *H*6′, *H*2″, *H*4″, *H*5″ and *H*6″), 7.15 (3H, br s, H_{Ar}), 4.97 (3H, br t, J=5.9 Hz, N*H*), 4.65 (6H, d, J=5.6 Hz CH_2N). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 154.6, 145.7, 140.4, 139.8, 139.2, 135.7, 135.2, 134.8, 130.5, 130.1, 129.1, 128.2, 126.9, 126.7, 125.9, 124.9, 124.7, 124.0, 120.6, 45.2. HRMS (ESI-TOF, CH_3OH): calculated for $C_{60}H_{43}{}^{35}Cl_6N_6$ $[M+H]^+$ 1057.1680, found 1057.1580.

*2.4.4. 1,3,5-Tris{[3,5-bis(3,5-dimethylphenyl)pyridin-2-yl]aminomethyl}benzene (**12d**).* From 374 mg (0.25 mmol) of **11d** and following the general procedure, after chromatography with AcOEt/hexane (8:2), 167 mg of **12d** were obtained as a yellow oil (70%). IR (NaCl), ν_{max} (cm^{-1}): 3436, 3020, 2917, 2859, 1603, 1570, 1503, 1405, 1325, 909, 848, 733. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.28 (3H, d, J=2.3 Hz, *H*6), 7.43 (3H, d, J=2.3 Hz, *H*4), 7.16 (3H, br s, H_{Ar}), 7.06 (6H, br s, *H*2′(6″) or *H*2′(6′)), 7.00 (6H, br s, *H*2′(6′) or *H*2″(6″)), 6.95 (3H, br s, *H*4″ or *H*4′), 6.91 (3H, br s, *H*4′ or *H*4″), 4.97 (3H, t, J=5.6 Hz, N*H*), 4.64 (6H, d, J=5.6 Hz, CH_2N), 2.31 (18H, s, CH_3), 2.28 (18H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 154.6, 144.9, 147.7, 138.8, 138.5, 138.2, 137.7, 135.8, 129.5, 128.2, 126.6, 126.2, 125.0, 124.1, 122.2, 45.4, 21.4, 21.3. HRMS (ESI-TOF, CH_3OH): calculated for $C_{72}H_{73}N_6$ $[M+H]^+$ 1021.5897, found 1021.5916.

*2.4.5. 1,6-Bis{3,5-bis[N-(pyridin-2-yl)aminomethyl]phenoxy}hexane (**15a**).* See Ref. 3b.

*2.4.6. 1,6-Bis{3,5-bis[N-(benzothiazol-2-yl)aminomethyl]phenoxy}hexane (**15b**).* From 100 mg ($6.44\cdot10^{-5}$ mol) of **13b** and following the general procedure, after chromatography with AcOEt, 40 mg of **15b** were obtained as a white solid (mp=249–252 °C, acetone, 68%). IR (NaCl): ν_{max} (cm^{-1}): 3353, 2926, 1655, 1614, 1547, 1446, 1154, 1020, 751, 723, 668. ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 8.48 (4H, br t, J=5.3 Hz, N*H*), 7.63 (4H, dd, J=7.9 and 1.0 Hz, *H*4), 7.35 (4H, d, J=7.9 Hz, *H*7), 7.19 (4H, ddd, J=8.2, 7.2 and 1.0 Hz, *H*6), 6.99 (4H, ddd, J=8.2, 7.9 and 1.3 Hz, *H*5), 6.95 (2H, br s, $H4_{Ar}$), 6.83 (4H, br s, $H2_{Ar}(6_{Ar})$), 4.53 (8H, d, J=5.3 Hz, CH_2N), 3.89 (4H, t, J=6.3 Hz, CH_2O), 1.64 (4H, m, C$H_2\beta$), 1.36 (4H, m, C$H_2\gamma$). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 165.7 (*C*2), 158.3 ($C1_{Ar}$), 151.8 (*C*3a), 140.0 ($C3_{Ar}(5_{Ar})$), 129.8 (*C*7a), 125.0 (*C*4), 120.5 (*C*5 or *C*6), 120.4 (*C*6 or *C*5), 117.9 ($C4_{Ar}$), 117.5 (*C*7), 111.5 ($C2_{Ar}(6_{Ar})$), 66.8 (*C*H$_2$O), 46.7 (*C*H$_2$N), 28.1 (*C*H$_2\beta$), 24.7 (*C*H$_2\gamma$). HRMS (ESI-TOF): Calculated for $C_{50}H_{47}N_8O_2S_4$ $[M+H]^+$, 919.2705, found 919.2694.

*2.4.7. 1,6-Bis{3,5-bis[N-(5-phenylpyridin-2-yl)aminomethyl]phenoxy}hexane (**15c**).* From 100 mg (6.13×10^{-5} mol) of **13c** and following the general procedure, after chromatography with AcOEt/hexane (1:1), 45 mg of **15c** were obtained as a white solid (mp=102–105 °C, hexane, 74%). IR (NaCl): ν_{max} (cm^{-1}) 3234, 3024, 2922, 2851, 1606, 1519, 1488, 1455, 1389, 1293, 1158, 818, 769, 696. ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 8.27 (4H, br s, *H*6), 7.67 (4H, dd, J=8.7 and 2.4 Hz, *H*4), 7.52 (8H, dd, J=8.4, 1.1 Hz, *H*2′(6′)), 7.36 (8H, ap t, J=7.6 Hz, *H*3′(5′)), 7.21 (8H, m, *H*4′ and N*H*), 6.90 (2H, br s, $H4_{Ar}$), 6.74 (4H, br s, $H2_{Ar}(6_{Ar})$), 6.56 (4H, d, J=8.7 Hz, *H*3), 4.44 (8H, d, J=6.0 Hz, CH_2N), 3.85 (4H, t, J=6.3 Hz, CH_2O), 1.63 (4H, m, C$H_2\beta$), 1.36 (4H, m, C$H_2\gamma$). ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 158.2 ($C1_{Ar}$), 157.5 (*C*2), 144.9 (*C*6), 141.5 ($C3_{Ar}(5_{Ar})$), 137.5 (*C*1′), 134.5 (*C*4), 128.3 (*C*2′(6′)), 125.7 (*C*4′), 124.8 (*C*3′(5′)), 123.3 (*C*5), 117.6 ($C4_{Ar}$), 110.9 ($C2_{Ar}(6_{Ar})$), 107.6 (*C*3), 66.6 (*C*H$_2$O), 43.7 (*C*H$_2$N), 28.1 (*C*H$_2\beta$), 24.8 (*C*H$_2\gamma$). HRMS (ESI-TOF, MeOH): Calculated for $C_{66}H_{63}N_8O_2$ $[M+H]^+$, 999.5074, found 999.5146.

*2.4.8. 1,3-Bis{3,5-bis[N-(pyridin-2-yl)aminomethyl]phenoxymethyl}benzene (**16a**).* From 100 mg (6.13×10^{-5} mol) of **14a** and following the general procedure, after chromatography with CH_2Cl_2/MeOH (95:5), 42 mg of **16a** were obtained as a white solid (mp=101–102 °C, hexane/AcOEt, 79%). IR (NaCl), ν_{max} (cm^{-1}): 3271, 2923, 2853, 1600, 1505, 1455, 1291, 1153, 711. ^1H NMR (300 MHz, $(CD_3)_2CO$), δ (ppm): 7.97 (4H, dd, J=4.9 and 1.0 Hz, *H*6), 7.48 (1H, br s, $H2_{xyl}$), 7.34 (7H, m, *H*4, $H4_{xyl}(6_{xyl})$ and $H5_{xyl}$), 6.98 (2H, br s, $H4_{Ar}$), 6.91 (4H, br s, $H2_{Ar}(6_{Ar})$), 6.48 (8H, m, *H*3 and *H*5), 6.15 (4H, m, N*H*), 5.03 (4H, s, CH_2O), 4.50 (8H, br s, CH_2N). ^{13}C NMR (75 MHz, $(CD_3)_2CO$), δ (ppm): 160.0 ($C1_{Ar}$), 159.9 (*C*2), 148.7 (*C*6), 143.3 ($C3_{Ar}(5_{Ar})$), 138.7 ($C1_{xyl}(3_{xyl})$), 137.5 (*C*4), 129.3 ($C2_{xyl}$), 127.8 ($C4_{xyl}(6_{xyl})$), 127.6 ($C5_{xyl}$), 119.8 ($C4_{Ar}$), 113.0 ($C2_{Ar}(6_{Ar})$ and *C*5), 108.7 (*C*3), 70.2 (*C*H$_2$O), 45.7 (*C*H$_2$N). HRMS (ESI-TOF, MeOH): Calculated for $C_{44}H_{43}N_8O_2$ $[M+H]^+$, 715.3509, found 715.3483.

*2.4.9. 1,3-Bis{3,5-bis[N-(quinolin-2-yl)aminomethyl]-phenoxymethyl}benzene (**16b**).* See Ref. 3b.

*2.4.10. 1,3-Bis(3,5-bis{N-[5(4-hydroxymethylphenyl)pyridin-2-yl]aminomethyl}phenoxy methyl)benzene (**16c**).* From 100 mg ($5.64\cdot10^{-5}$ mol) of **14c** and following the general procedure, after chromatography with AcOEt/MeOH (4:1), 50 mg of **16b** were obtained as a yellow solid (mp>145 °C, acetone, 78%). IR (KBr), ν_{max} (cm^{-1}): 3414, 3021, 2926, 2861, 1607, 1530, 1504, 1455, 1385, 1293, 1154, 1044, 810. ^1H NMR (200 MHz, CD_3OD), δ (ppm): 8.15 (4H, br s, *H*6), 7.61 (4H, dd, J=8.7 and 2.4 Hz, *H*4), 7.44 (8H, d, J=8.2 Hz, *H*2′(6′)), 7.44 (1H, br s, $H2_{xyl}$), 7.40 (8H, d, J=8.2 Hz, *H*3′(5′)), 7.24 (3H, m, $H4_{xyl}(6_{xyl})$ and $H5_{xyl}$), 6.99 (2H, br s, $H4_{Ar}$), 6.87 (4H, d, J=1.0 Hz, $H2_{Ar}(6_{Ar})$), 6.51 (4H, d, J=8.7 Hz, *H*3), 5.03 (4H, s, CH_2O), 4.63 (8H, s, CH_2OH), 4.48 (8H, s, CH_2N). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 158.0 ($C1_{Ar}$), 157.2 (*C*2), 144.8 (*C*6), 141.7 ($C3_{Ar}(5_{Ar})$), 140.0 (*C*4′), 136.8 ($C1_{xyl}(3_{xyl})$), 135.9 (*C*1′), 134.5 (*C*4), 128.0 ($C2_{xyl}$), 126.5 (*C*3′(5′) and $C4_{xyl}(6_{xyl})$), 126.3 ($C5_{xyl}$),

124.5 (*C*2′(6′)), 123.3 (*C*5), 118.1 (*C*4$_{Ar}$), 111.3 (*C*2$_{Ar}$(6$_{Ar}$)), 107.6 (*C*3), 68.5 (CH_2O), 62.1 (CH_2OH), 43.7 (CH_2N). HRMS (ESI-TOF, MeOH): Calculated for $C_{72}H_{67}N_8O_6$ $[M+H]^+$ 1139.5184, found 1139.5209.

*2.4.11. 1,3,5-Tris{pyridin-1-ium-[5-(4-bromomethylphenyl)pyridin-2-yl]aminomethyl}-benzene bromide (**17**).* The tris-aminopyridinium bromide **11a** (500 mg) was added portionwise to hydrobromic acid (48%, 25 mL) in a 100 mL flask. The mixture was stirred for 12 h at room temperature and the acid was evaporated under vacuum. The residue was dissolved in MeOH and eluted through a column filled with a solvated ion-exchange resin (Amberlite IRA-67) in order to remove excess acid from the product. Eluates from the column were evaporated, redissolved in DMF (approx. 1 mL) and precipitated by adding the solution dropwise to well stirred AcOEt (50 mL). The solid precipitate was collected by filtration, washed with AcOEt and crystallized from EtOH with a few drops of MeOH to give 620 mg of the halogenated tris-aminopyridinium bromide **17** as a yellow solid (mp>169 °C dec, EtOH/MeOH, 95%). IR (KBr), ν_{max} (cm^{-1}): 3400, 3018, 1615, 1598, 1475, 1372, 1229, 814, 678. ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 9.31 (6H, dd, *J*=6.7 and 1.4 Hz, *H*2(6)), 8.73 (3H, tt, *J*=7.8 and 1.4 Hz, *H*4), 8.45 (3H, d, *J*=2.5 Hz, *H*6′), 8.27 (6H, dd, *J*=7.8 and 6.7 Hz, *H*3(5)), 8.08 (3H, dd, *J*=8.7 and 2.5 Hz, *H*4′), 7.73 (3H, s, *H*$_{Ar}$), 7.58 (12H, m, *H*2″(6″) and *H*3″(5″)), 7.13 (3H, d, *J*=8.7 Hz, *H*3′), 5.50 (6H, s br, CH_2N), 4.64 (6H, s, CH_2Br). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 155.5, 147.9, 147.8, 145.2, 142.0, 137.2, 135.8, 134.2, 131.3, 129.4, 128.5, 127.3, 126.1, 109.4, 62.4, 56.6. Elemental Analysis: Calculated for $C_{60}H_{51}Br_6N_9\cdot 10H_2O$: C=46.26, H=4.59, N=8.09, Found C=46.13, H=4.45, N=8.47.

2.5. Alkylation of bromomethyl tris-aminopyridinium bromide 17 with pyridinium aminides. General procedure

A solution of tris-aminopyridinium bromide **17** (138 mg, 0.1 mmol) and the corresponding aminide[3b,10b] (0.4 mmol) in DMF (5 mL) was prepared in a dried 10 mL round-bottomed flask. The reaction mixture was stirred at room temperature for 72 h. Once the reaction was completed, purification of the aminopyridinium salts was performed as follows: the solvent was removed under vacuum, the residue was redissolved in the minimum amount of DMF (approx. 1–2 mL) and the solution was added dropwise to well stirred AcOEt (50 mL). The solid precipitate was collected by filtration, washed with AcOEt and crystallized from EtOH with a few drops of MeOH to give hexa-aminopyridinium bromides **18** as brown solids.

*2.5.1. 1,3,5-Tris{pyridin-1-ium-[5-(4-{pyridin-1-ium-[pyridin-2-yl] aminomethyl} phenyl)pyridin-2-yl]aminomethyl}benzene bromide (**18a**).* Brown solid (mp>189 °C dec, EtOH/MeOH, 155 mg, 82%). IR (KBr), ν_{max} (cm^{-1}): 3412, 3106, 3017, 1651, 1598, 1474, 1373, 816, 777, 680. ^{1}H NMR (500 MHz, CD_3OD), δ (ppm): 9.24 (6H, dd, *J*=6.8 and 1.3 Hz, *H*2$_{i/e}$(6$_{i/e}$)), 9.18 (6H, dd, *J*=6.8 and 1.5 Hz, *H*2$_{e/i}$ (6$_{e/i}$)), 8.71 (6H, m, *H*4$_{e+i}$), 8.68 (3H, d, *J*=1.2 Hz, *H*6′$_i$), 8.20 (15H, m, *H*3$_{e+i}$(5$_{e+i}$) and *H*6′$_e$), 8.05 (3H, dd, *J*=8.8 and 2.5 Hz, *H*4′$_i$), 7.89 (3H, ddd, *J*=8.4, 7.3 and 1.8 Hz, *H*4′$_e$), 7.68 (3H, s, *H*$_{Ar}$), 7.62 (6H, ap d, *J*=8.3 Hz, *H*2″(6″)), 7.52 (6H, ap d, *J*=8.3 Hz, *H*3″(5″)), 7.22 (6H, m, *H*3′$_{e+i}$), 7.16 (3H, dd, *J*=7.2 and 5.0 Hz, *H*5′$_e$), 5.47 (6H, s, CH_2N), 5.42 (6H, s, CH_2N). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 158.4, 157.6, 149.6, 149.2, 147.1, 140.7, 138.9, 138.5, 137.7, 135.0, 133.0, 131.0, 130.6, 130.5, 130.4, 129.7, 128.8, 128.5, 127.7, 120.9, 111.1, 110.9, 58.6, 58.6. Elemental Analysis: Calculated for $C_{90}H_{78}Br_6N_{18}\cdot 7H_2O$: C=53.59, H=4.60, N=12.50, Found C=53.57, H=4.77, N=12.16.

*2.5.2. 1,3,5-Tris{pyridin-1-ium-[5-(4-{pyridin-1-ium-[5-(4-hydroxymethylphenyl) pyridin-2-yl]aminomethyl}phenyl)pyridin-2-yl]aminomethyl}benzene bromide (**18b**).* Brown solid (mp>193 °C dec, EtOH/MeOH, 111 mg, 85%,). IR (KBr), ν_{max} (cm^{-1}): 3400, 3022, 1598, 1475, 1371, 1215, 998, 813, 678. ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 9.36 (6H, d, *J*=6.2 Hz, *H*2(6)), 9.27 (6H, d, *J*=6.9 Hz, *H*2(6)), 8.76 (6H, m, *H*4 and *H*4), 8.52 (3H, d, *J*=2.1 Hz, *H*6′), 8.45 (3H, d, *J*=1.9 Hz, *H*6′), 8.26 (12H, m, *H*3(5) and *H*3(5)), 8.17 (6H, m, *H*4′ and *H*4′), 7.74 (3H, s, *H*$_{Ar}$), 7.61 (18H, m, *H*2″(6″), *H*2″(6″) and *H*3″(5″)), 7.34 (6H, m, *H*3″(5″)), 7.34 (3H, d, *J*=8.7 Hz, *H*3′), 7.24 (3H, d, *J*=8.7 Hz, *H*3′), 5.50 (12H, m, CH_2N), 4.79 (6H, s, CH_2OH). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 157.5, 157.4, 149.7, 149.1, 147.6, 147.1, 147.1, 138.8, 138.5, 137.8, 136.8, 134.9, 134.0, 133.0, 131.2, 130.8, 130.7, 130.2, 128.8, 128.5, 127.7, 127.3, 111.2, 111.1, 64.7, 58.8, 58.6. Elemental Analysis: Calculated for $C_{111}H_{96}Br_6N_{18}O_3\cdot 8H_2O$: C=56.50, H=5.04, N=10.68, Found C=56.78, H=4.93, N=11.01.

*2.5.3. 1,3,5-Tris-{[3-(4-{pyridin-2-ylaminomethyl}phenyl)2-pyridin-2-yl]amino methyl}benzene (**19**).* Reduction of 250 mg of **18a** was accomplished by dissolving the product in MeOH (15 mL) under an Ar atmosphere, followed by the addition of 100 mg of the catalyst Pd/C (10%, dry) and 500 mg of the reducing agent, NH_4HCO_2 (60 equiv).[9,10] After 24 h the same amounts of both catalyst and reducing agent were added again and the mixture was allowed to react for an additional 24 h period. After a total period of 48 h, removal of the catalyst and excess of reducing agent was achieved by evaporation of the solvent, addition of acetone and filtration of the suspension through Celite. The residue obtained by evaporation of the filtrate was purified by chromatography with acetone/methanol (95:5), but only an impure fraction of **19** as the main product was obtained. HRMS showed the peak for the calculated mass of **19**: $C_{60}H_{55}N_{12}$ $[M+H]^+$=943.4673, found: 943.9902.

Acknowledgements

The authors wish to thank the Ministerio de Ciencia y Tecnología (CTQ2005-08902 and CTQ2008-05027/BQU2) for financial support and the Ministerio de Educación y Ciencia (MEC) and Universidad de Alcalá (UAH) for fellowships (R.R.C. and M.C.)

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