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Synthesis of new Bis- and Tetra-Acridines

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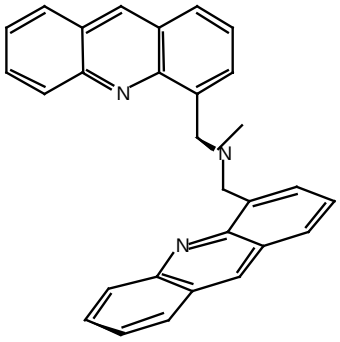
Abstract: A new series of bis- and tetra-acridines has been prepared from 4-(bromo-methyl)acridine; some of them exhibited encouraging *in vitro* cytotoxic activities against murine cell lines.

Keywords: Acridines, polycycles, amines, diamines, *N*-alkylation.

Introduction

Acridine derivatives are well known therapeutic agents whose mutagenic properties depend on their ability to interact with nucleic acids. One mechanism of this interaction is the intercalation between the acridine moiety and the base pairs of the DNA helix.[1] Moreover the pharmacological activity of these intercalating drugs derives from their ability to inhibit the synthesis of nucleic acids by blocking the action of DNA metabolizing proteins.[2] To develop more effective antagonists of DNA metabolism, many chemists have made molecules combining two or more intercalating ligands. For instance, Denny and co-workers prepared tetra-acridinic derivatives [3] and demonstrated that the higher order structure of DNA can be controlled by a complexation using ligands with multiple binding sites. The biological response of such compounds could be of interest because the higher order DNA structure plays an essential part in the regulation of gene expression by the cooperative binding proteins.

We prepared bis- and tetra-acridine compounds linked by a short nitrogen chain, with acridine moities closed enough to avoid the self-stacking of the aromatic planes; consequently all the synthesized compounds include a specific fragment like the *N*-bisacridine represented in Scheme 1.

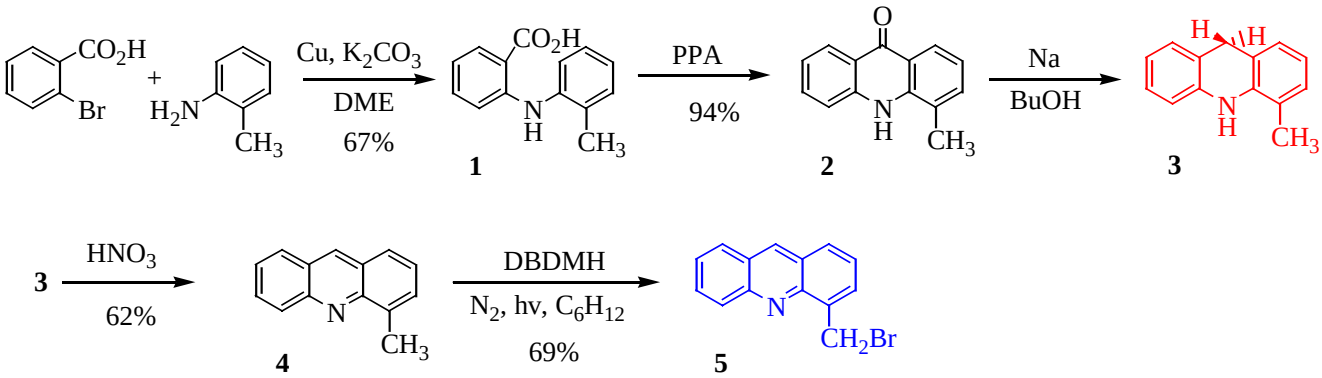


Scheme 1

Results and Discussion

Our synthetic pathway was based first on the preparation in 5 steps of the 4-(bromomethyl)acridine **5**, followed by N-alkylation with different amines. First, the condensation of *ortho*-toluidine and 2-bromobenzoic acid by Ullmann condensation in ethylene glycol dimethyl ether with copper and anhydrous potassium carbonate gave the 2-[(2-methylphenyl)amino]benzoic acid (**1**) [4]. The cyclization of **1** in refluxing polyphosphoric acid (PPA) led finally to the 4-methyl-9(10*H*)-acridinone **2** by an intra-molecular Friedel-Crafts acylation [5]. The acridinone can be prepared alternatively with sulfuric acid or phosphorus oxychloride, but PPA is better because it induces less degradation of the anthranilic acid.

4-Methylacridine (**4**) was obtained in one pot after direct acidic oxidation of 4-methyl-acridane (**3**) (62%). Then, benzylic bromination of **4** was performed by a photochemical reaction. The use of N-bromosuccinimide (NBS) was described by Ledochowski [6] (50% yield), but we obtained better results (69% yield) with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, 0.5 equiv.) [7] in cyclohexane and 6 hours reaction time (Scheme 2).



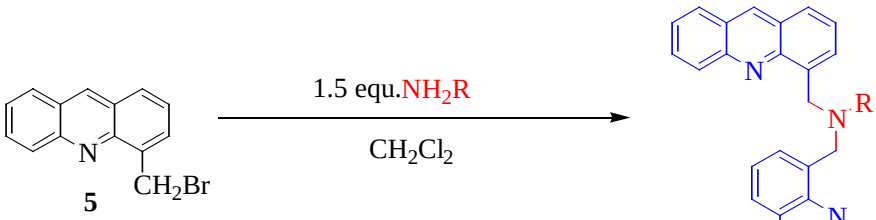
Scheme 2.

The dimeric and tetrameric polyacridine derivatives were obtained from the reaction of 4-(bromomethyl)acridine (**5**) in dichloromethane or acetonitrile with different arylamines or aliphatic primary amines. Moreover, dimers and tetramers can be obtained selectively using a specific reactant ratio as described in Table 1.

Table 1: Proportions of amines and diamines used to prepared **6a-g**, **7**, **8a-b** and **9a-e**.

Amine equivalent	0.5 equ.	1 equ.	1.5 equ.
primary amine	-	-	dimer
primary diamine	tetramer	dimer	-
secondary diamine	-	-	dimer

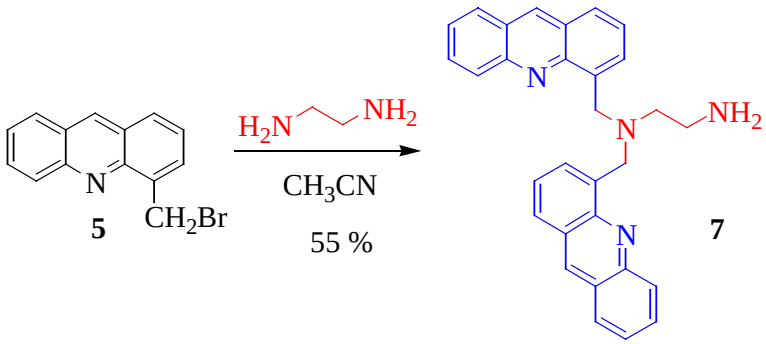
To obtain the dimeric acridine derivatives **6a-g** we used aliphatic and aromatic primary amines (1.5 equivalent of amine) in dichloromethane; the yields are 41-97 % after purification, except for the *N*,*N*-bis[methyl(4'-acridinyl)]-*p*-chlorophenyl **6c** preparation (26 %) (Scheme 3).



6a, R = n-propyl 92%
6b, R = phenyl 41%
6c, R = *p*-chlorophenyl 26%
6d, R = *p*-methoxyphenyl 66%
6e, R = *p*-fluorophenyl 58%
6f, R = (*m*,*p*)-dimethoxyphenyl 97%
6g, R =*N*-(*m*-methoxyphenyl)methanesulfonamide 82%

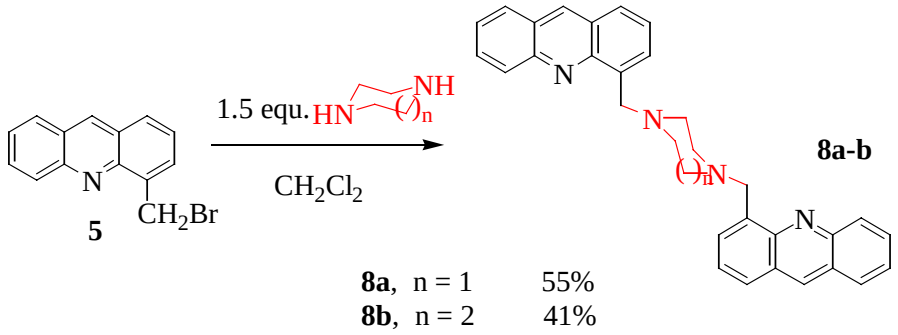
Scheme 3.

Using only one equivalent of the ethylene diamine with **5** in acetonitrile we obtained only one polycycle, the *N*,*N*-bis[methyl(4'-acridinyl)]-aminoethylamine **7** in 55 % yield (Scheme 4).



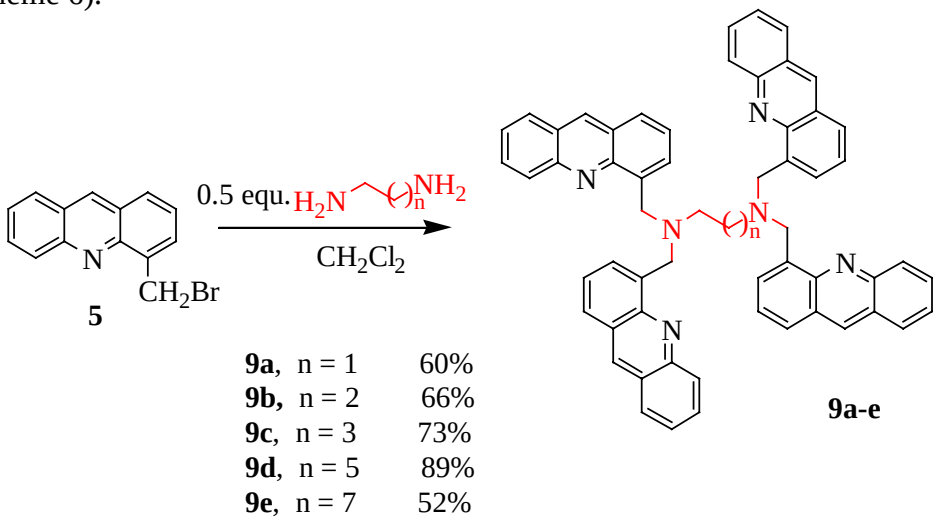
Scheme 4.

With two cyclic diamines, such as piperazine and homopiperazine, we obtained two dimers **8a-b**, in yields of 55 and 41% respectively (Scheme 5).



Scheme 5.

Tetrameric *N*,*N*,*N'*,*N'*-tetra[methyl(4'-acridinyl)]-diaminoalcanes **9a-e** were obtained using different diamines. With only 0.5 equivalent of amine, only tetrameric acridines were recovered, in 52 – 89% yields (Scheme 6).



Scheme 6.

Biological Activity

The cytotoxicities of ten compounds (**6a**, **6d-g**, **7**, **9a**, **9c-e**) were determined in a panel of cell lines. The murine L1210 leukemia and A549 cell lines were used as a straightforward comparison of antiproliferative properties. Dimers **6e** and **6f** and tetramer **9a** had the best results against DNA reparation, while polyacridine **9c** had the least action against the L1210 leukemia cell line.

Conclusions

We propose an easy way to prepare a new class of polyacridinic derivatives using 4-(bromomethyl)acridines. Most of them display some biological activity and we are now expanding the scope of this approach to the synthesis of other polyacridines.

Experimental

General

The NMR spectra were recorded on a Bruker AM 200 spectrometer working at 200.13 MHz; Homonuclear (COSY) and heteronuclear (HMBC, HMQC) bidimensional spectra were performed on a Bruker AMX 400. The chemical shifts are reported in δ values for $CDCl_3$ or DMSO-d_6 solutions. Melting points were measured on an Electrothermal apparatus and are uncorrected. Reagents and solvents were purchased from commercial suppliers.

2-[(2-Methylphenyl)amino]benzoic acid (**1**). Compound **1** was obtained from the condensation of 2-bromobenzoic acid (15 g, 74 mmol) and *o*-toluidine (11 g, 0.102 mol), in the presence of copper catalyst (0.26 g, 4.09 mmol) and anhydrous potassium carbonate (13.95 g, 0.1 mol), all in ethylene glycol dimethyl ether (80 mL). After work-up a white powder was obtained (13.5 g, 67%); mp 185°C; lit. [8] mp 185°C; ^{1}H-NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 6.72 (dd, 1H, J = 8.0, 7.2 Hz), 6.85 (dd, 1H, J = 8.1, 1.3 Hz), 7.05 (ddd, 1H, J = 8.2, 7.4, 1.4 Hz), 7.28 (m, 4H), 7.88 (dd, 1H, J = 8.0, 1.3 Hz), 9.49 (s, 1H), 13.00 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ: 18.04, 109.71, 113.74, 116.52, 124.89, 125.20, 126.73, 131.13, 132.53, 133.49, 135.78, 138.54, 149.74, 174.23; Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; Found: C, 74.25; H, 5.50; N, 6.49.

4-Methyl-9(10H)]acridinone (**2**). A mixture of **1** (4 g, 17 mmol) and PPA (50 g) was refluxed for 3 hours at 120°C. Next the solution was poured into cold water (400 mL). After treatment with an ammonia solution (36%) and filtration of the suspension, the precipitate was dried and refluxed for 1 hour in DMF (150 mL). After filtration, the acridinone was precipitated in cold water (400 mL), and filtered to yield a yellow powder (4.41 g, 94%); mp 346°C; lit. [9] mp 346°C; ^{1}H-NMR (DMSO-d_6) δ: 2.59 (s, 3H, CH_3), 7.16 (dd, 1H, J = 8.1, 7.5 Hz), 7.28 (ddd, 1H, J = 8.0, 7.2, 1.3 Hz), 7.58 (dd, 1H, J = 7.5, 1.2 Hz), 7.71 (ddd, 1H, J = 8.1, 7.4, 1.1 Hz), 7.92 (dd, 1H, J = 8.1, 1.2 Hz), 8.12 (dd, 1H, J = 8.0, 1.3 Hz), 8.21 (dd, 1H, J = 8.1, 1.4 Hz), 10.6 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ: 17.82, 118.14, 120.33, 120.69, 120.69, 121.24, 123.93, 125.28, 125.73, 133.20, 134.08, 139.51, 141.07, 177.02; Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69; Found: C, 74.25; H, 5.50; N, 6.49.

4-Methylacridine (**4**). A mixture of **2** (3g, 14 mmol) in butan-1-ol (77 mL) was stirred at 110°C and a solution of sodium (6g, 0.26 mol) dissolved in butan-1-ol (10 mL) was added dropwise. The mixture was then concentrated and the residual solid was recrystallized from water to yield a pale yellow powder of acridane **3**. Compound **3** was stirred with nitric acid (69%, 83 mL) for 2 hours at room temperature. The mixture was diluted with water (120 mL) and stirred for an additional 1 hour. After filtration, the filtrate was made basic with ammonia to pH 8 and filtered. The precipitate was dried, dissolved in hot ethanol (60 mL), and filtered. The organic phase was poured into water (200 mL), acidified with HCl (10 mL), and filtered. Next the solution was made basic with an ammonia solution (16%) and filtered to yield a yellow powder (1.70 g, 62%); mp 89°C; lit. [10] mp 89°C; ^{1}H-NMR ($CDCl_3$) δ: 2.96 (s, 3H, CH_3), 7.43 (dd, 1H, J = 8.0, 7.5 Hz), 7.53 (ddbr, 1H, J = 8.1, 7.3 Hz), 7.63 (dd, 1H, J = 7.5, 1.4 Hz), 7.73 (ddd, 1H, J = 8.1, 7.2, 1.5 Hz), 7.86 (dd, 1H, J = 8.1, 1.4 Hz), 7.99 (dbr, 1H,

J = 8.1 Hz), 8.29 (dd, 1H, J = 8.1, 7.1 Hz), 8.73 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 18.40, 125.41, 125.41, 126.14, 126.28, 126.46, 127.87, 129.42, 129.62, 129.87, 135.79, 137.11, 148.29, 148.53; Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25; Found: C, 87.19; H, 5.61; N, 7.33.

4-Bromomethylacridine (**5**). A mixture of **4** (3.15 g, 16 mmol) and DBDMH, (1,3-dibromo-5,5-dimethylhydantoin), (2.5 g, 8.74 mmol) in cyclohexane (160 mL) was placed in a three-necked flask. The solution was then warmed with a 500-Watt tungsten lamp under a nitrogen atmosphere and stirred for 6 hours. After filtration, the solution was cooled and the obtained yellow needles were filtered to give **5** (3.1 g, 69%); mp 165°C; lit. [11] mp 165°C; ^{1}H-NMR ($CDCl_3$) δ : 5.41 (s, 2H, CH_2), 7.45 (dd, 1H, J = 8.0, 7.2 Hz), 7.53 (ddbr, 1H, J = 8.1, 7.4 Hz), 7.78 (ddd, 1H, J = 8.2, 7.3, 1.5 Hz), 7.90 (dd, 1H, J = 7.2, 1.3 Hz), 7.94 (dd, 1H, J = 7.2, 1.3 Hz), 7.96 (dbr, 1H, J = 8.0 Hz), 8.29 (dbr, 1H, J = 8.2 Hz), 8.70 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 30.21, 125.37, 126.03, 126.10, 126.79, 128.03, 129.26, 130.23, 130.35, 131.14, 136.15, 136.15, 146.48, 148.75; Anal. Calcd for $C_{14}H_{10}NBr$: C, 61.79; H, 3.70; N, 5.15; Found: C, 62.03; H, 3.58; N, 5.41.

N,N'-Bis[methyl(4'-acridinyl)]propylamine (**6a**). A mixture of **5** (0.2 g, 0.73 mmol) and propylamine (0.065 g, 1.1 mmol) in dichloromethane (8 mL) was stirred under reflux for 3 hours. The solvent was evaporated. The resulting oil was recovered and dissolved in dilute HCl (2%, 5 mL) to yield **6a** as a brown powder after filtration (0.15 g, 92%); mp 124°C; ^{1}H-NMR ($CDCl_3$) δ: 1.23 (t, 3H, CH_3, J = 6.9 Hz), 2.29 (m, 2H, CH_2), 3.91 (t, 2H, CH_2, J = 6.9 Hz), 5.39 (d, 2H, CH_2, J = 14.1 Hz), 5.69 (d, 2H, CH_2, J = 14.1 Hz), 7.21 (m, 2H), 7.22 (m, 2H), 7.24 (t, 2H, J = 7.7 Hz), 7.34 (m, 2H), 7.60 (dbr, 2H, J = 8.0 Hz), 7.67 (dbr, 2H, J = 8.1 Hz), 7.97 (dbr, 2H, J = 8.0 Hz), 8.30 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 11.46, 19.11, 57.02, 58.58, 125.28, 125.28, 126.00, 126.08, 127.47, 127.91, 128.03, 129.61, 130.58, 134.45, 136.70, 146.11, 147.12; Anal. Calcd for $C_{31}H_{27}N_3$: C, 84.32; H, 6.16; N, 9.52; Found: C, 83.97; H, 6.48; N, 9.44.

N,N'-Bis[methyl(4'-acridinyl)]aniline (**6b**). A mixture of **5** (0.2 g, 0.73 mmol) and aniline (0.105 g, 1.1 mmol) in dichloromethane (8 mL) was refluxed and stirred for 3 hours. The mixture was filtered and the solvent evaporated. The resulting oil was dissolved in dilute HCl (2%, 5 mL) to yield a brown powder of **6b** (0.073 g, 41%); mp 139°C; ^{1}H-NMR (DMSO-d_6) δ: 5.60 (s, 4H, CH_2), 7.08 (d, 2H, J = 7.8 Hz), 7.58 (t, 1H, J = 7.8 Hz), 7.60 (dd, 2H, J = 8.8, 7.4 Hz), 7.73 (m, 4H), 7.76 (dbr, 2H, J = 8.0 Hz), 7.78 (ddd, 2H, J = 8.2, 7.1, 1.2 Hz), 8.13 (dbr, 2H, J = 8.1 Hz), 8.18 (dbr, 4H, J = 10.2 Hz), 9.16 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ: 51.78, 111.93, 116.04, 125.77, 126.09, 126.16, 126.46, 127.37, 127.58, 128.62, 128.95, 129.26, 130.90, 134.83, 137.13, 146.81, 147.40, 148.32; Anal. Calcd for $C_{34}H_{25}N_3$: C, 85.87; H, 5.30; N, 8.84; Found: C, 85.99; H, 5.03; N, 8.76.

N,N'-Bis[methyl(4'-acridinyl)]-p-chloroaniline (**6c**). Prepared as described for **6a** but with **5** (0.2 g, 0.73 mmol) and *p*-chlorophenylamine (0.140 g, 1.1 mmol). Work up yielded a brown powder which was dissolved in dichloromethane and precipitated with diethyl ether to afford the title compound (0.048 g, 26%); mp 120°C; ^{1}H-NMR (DMSO-d_6) δ: 5.59 (s, 4H, CH_2), 6.69 (d, 2H, J = 8.6 Hz), 7.08 (d, 2H, J = 8.5 Hz), 7.65 (m, 6H), 7.84 (ddd, 2H, J = 8.1, 7.2, 1.4 Hz), 8.09 (d, 2H, J = 8.2 Hz), 8.17 (d, 4H, J = 8.1 Hz), 9.14 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ: 51.68, 113.23, 115.29, 119.26, 125.61, 125.96,

126.08, 126.30, 126.99, 128.48, 128.72, 129.03, 130.67, 134.60, 136.76, 146.85, 147.21, 147.47; Anal. Calcd for $C_{34}H_{24}N_3Cl$: C, 80.07; H, 4.74; N, 8.24; Found: C, 80.34; H, 4.41; N, 8.01.

N,N'-Bis[methyl(4'-acridinyl)]-p-anisidine (**6d**). As described for **6a** but with **5** (0.2 g, 0.73 mmol) and *p*-anisidine (0.140 g, 1.1 mmol). After work up a brown powder of **6d** was recovered (0.122 g, 66%); mp 140°C; ^{1}H-NMR (DMSO-d_6) δ: 3.68 (s, 3H, OCH_3), 5.60 (s, 4H, CH_2), 6.95 (d, 2H, J = 8.8 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.55 (m, 8H), 7.80 (d, 2H, J = 8.2 Hz), 8.08 (m, 4H), 9.08 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ: 55.55, 60.24, 115.37, 122.67, 125.34, 125.51, 126.21, 126.25, 126.91, 127.78, 128.12, 130.02, 130.91, 134.16, 134.23, 137.29, 145.96, 147.19, 160.10; Anal. Calcd for $C_{35}H_{27}N_3O$: C, 83.14; H, 5.38; N, 8.31; Found: C, 83.33; H, 5.19; N, 8.24.

N,N'-Bis[methyl(4'-acridinyl)]-p-fluoroaniline (**6e**). A mixture of **5** (0.2 g, 0.73 mmol) and *p*-fluoro-phenylaniline (0.122 g, 1.1 mmol) in dichloromethane (8 mL) was stirred under reflux for 3 hours. The solvent was evaporated, and the resulting oil was dissolved in dichloromethane and washed with dilute HCl (2%, 10 mL). The oil recovered after evaporation was dissolved in dilute HCl (2%, 5 mL) to yield a brown powder of **6e** (0.105 g, 58%); mp 174°C; ^{1}H-NMR ($CDCl_3$) δ: 5.69 (s, 4H, CH_2), 6.85 (dd, 4H, J = 11.0, 8.1 Hz), 7.49 (ddd, 4H, J = 8.1, 7.2, 1.4 Hz), 7.69 (dd, 2H, J = 8.0, 7.3 Hz), 7.91 (m, 6H), 8.23 (d, 2H, J = 8.1 Hz), 8.73 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 54.14, 113.80, 116.18, 116.62, 126.32, 126.41, 127.00, 127.17, 128.09, 128.75, 129.12, 130.02, 130.85, 134.70, 136.96, 147.98, 148.29, 148.59; Anal. Calcd for $C_{34}H_{24}FN_3$: C, 82.74; H, 4.90; N, 8.51; Found: C, 82.98; H, 4.96; N, 3.40.

N,N'-Bis[methyl(4'-acridinyl)]-(m,p)-dimethoxyaniline (**6f**). As described for **6a** but with **5** (0.2 g, 0.73 mmol) and (*m,p*)-dimethoxyaniline (0.168 g, 1.1 mmol). A brown powder was recovered (0.192 g, 97%); mp 163°C; ^{1}H-NMR (DMSO-d_6) δ: 3.67 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.66 (s, 4H, CH_2), 6.89 (s 1H), 7.54 (m, 10H), 7.83 (dd, 2H, J = 7.4, 1.4 Hz), 8.06 (dd, 2H, J = 8.1, 1.5 Hz), 8.10 (d, 2H, J = 8.3 Hz), 9.08 (s, 2H); ^{13}C-NMR (DMSO-d_6) δ: 56.07, 56.23, 58.59, 103.65, 111.08, 112.52, 125.61, 125.84, 126.10, 126.25, 126.43, 127.84, 128.74, 129.24, 129.84, 131.43, 132.64, 138.34, 146.01, 146.93, 150.06; Anal. Calcd for $C_{36}H_{29}N_3O_2$: C, 80.72; H, 5.46; N, 7.84; Found: C, 81.08; H, 5.35; N, 7.78.

N,N'-Bis[methyl(4'-acridinyl)]-N-(4-amino-3-methoxyphenyl)methanesulfonamide (**6g**). Prepared as described for **6a** but using **5** (0.2 g, 0.73 mmol) and *N*-(4-amino-3-methoxyphenyl)methane-sulfonamide (0.238 g, 1.1 mmol). Work up yielded **6g** as a brown powder (0.18 g, 82%); mp 161°C; ^{1}H-NMR (DMSO-d_6/TFA) δ: 2.99 (s, 3H, CH_3), 3.02 (s, 3H, OCH_3), 5.57 (s, 4H, CH_2), 6.74 (d, 1H, J = 2.1 Hz), 7.01 (dd, 1H, J = 8.2, 2.0 Hz), 7.05 (d, 2H, J = 8.2 Hz), 7.46 (m, 6H), 7.77 (d, 2H, J = 8.1 Hz), 8.05 (dd, 2H, J = 7.3, 1.4 Hz), 8.09.(dd, 2H, J = 8.1, 1.2 Hz), 8.18 (d, 1H, J = 8.0 Hz), 9.03 (s, 2H); ^{13}C-NMR (DMSO-d_6/TFA) δ: 40.00, 55.88, 60.32, 102.84, 111.71, 124.28, 124.88, 125.47, 125.73, 126.53, 127.54, 127.89, 128.90, 130.85, 131.24, 134.31, 138.13, 141.18, 141.30, 146.24, 147.15, 152.42; Anal. Calcd for $C_{36}H_{30}N_4O_3S$: C, 72.22; H, 5.05; N, 9.36; Found: C, 72.07; H, 5.16; N, 9.43.

N,N'-Bis[methyl(4'-acridinyl)]aminoethylamine (**7**). A mixture of **5** (1 g, 3.67 mmol) and ethylene

diamine (0.22 g, 3.67 mmol) in acetonitrile (40 mL) was stirred and refluxed for 2 hours. After cooling the solution was filtered. The precipitate was washed with water (60 mL) and a beige powder of **7** was thus obtained (0.45 g, 55%); mp 182°C; ^{1}H-NMR ($CDCl_3$) δ: 2.95 (t, 2H, CH_2, J = 6.9 Hz), 3.17 (t, 2H, CH_2, J = 6.9 Hz), 4.62 (s, 4H, CH_2), 7.34 (dd, 2H, J = 8.1, 7.3 Hz), 7.43 (dd, 2H, J = 8.2, 7.3 Hz), 7.69 (dd, 2H, J = 8.1, 7.3 Hz), 7.77 (d, 2H, J = 8.1 Hz), 7.91 (dd, 2H, J = 7.4, 1.3 Hz), 7.92 (dd, 2H, J = 8.1, 1.3 Hz), 8.17 (d, 2H, J = 8.0 Hz), 8.65 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 39.77, 54.62, 56.63, 125.46, 125.66, 126.36, 126.62, 127.28, 128.04, 129.68, 130.13, 130.19, 136.18, 137.31, 147.91, 148.32; Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.42; H, 5.92; N, 12.66; Found: C, 81.51; H, 6.04; N, 12.61.

N,N'-Bis[methyl(4'-acridinyl)]piperazine (**8a**). A mixture of **5** (0.18 g, 0.66 mmol) and anhydrous piperazine (0.06 g, 0.68 mmol) in acetonitrile (30 mL) was stirred and refluxed for 3 hours. The solvent was evaporated, and the resulting oil was diluted in water (5 mL) to yield compound **8a** as a brown powder (0.085 g, 55%); mp 228°C; ^{1}H-NMR ($CDCl_3$) δ: 2.82 (s, 8H, CH_2), 4.49 (s, 4H, CH_2), 7.50 (dd, 2H, J = 8.1, 7.2 Hz), 7.51 (dd, 2H, J = 7.3, 1.2 Hz), 7.74 (ddd, 2H, J = 8.3, 7.0, 1.1 Hz), 7.89 (m, 4H), 7.96 (d, 2H, J = 8.1 Hz), 8.23 (d, 2H), 8.72 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 52.81, 56.13, 124.51, 124.51, 125.30, 125.55, 125.88, 126.94, 128.22, 128.75, 128.99, 134.85, 135.36, 147.10, 147.30; Anal. Calcd for $C_{32}H_{28}N_4$: C, 82.02; H, 6.02; N, 11.96; Found: C, 82.14; H, 6.18; N, 12.10.

N,N'-Bis[methyl(4'-acridinyl)]homopiperazine (**8b**). Prepared as described for **8a** but with **5** (0.2 g, 0.73 mmol) and homopiperazine (0.075 g, 0.75 mmol). Work up yielded **8b** as a brown powder (0.072 g, 41%); mp 170°C; ^{1}H-NMR ($CDCl_3$) δ: 2.64 (m, 2H, CH_2), 3.83 (t, 4H, CH_2, J = 6.8 Hz), 4.22 (s, 4H, CH_2), 5.22 (s, 4H, CH_2), 7.57 (m, 4H), 7.82 (ddd, 2H, J = 8.1, 7.2, 1.3 Hz), 7.98 (dd, 2H, J = 7.3, 1.5 Hz), 8.06 (dd, 2H, J = 8.2, 1.5 Hz), 8.40 (m, 4H), 8.80 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 20.23, 47.64, 53.73, 55.51, 125.28, 126.01, 126.40, 126.40, 127.31, 128.52, 129.20, 131.01, 131.20, 134.73, 137.54, 146.60, 147.89; Anal. Calcd for $C_{33}H_{30}N_4$: C, 82.13; H, 6.26; N, 11.61; Found: C, 82.20; H, 6.17; N, 11.73.

N,N,N',N'-Tetra[methyl(4'-acridinyl)]-1,2-diaminoethane (**9a**)**.** A mixture of **5** (1 g, 3.67 mmol) and 1,2-diaminoethane (0.11 g, 1.8 mmol) in dichloromethane (40 mL) was stirred and refluxed for 3 hours. After cooling at room temperature, the solution was filtered. The precipitate was washed with water (60 mL) to afford **9a** as a beige powder (0.45 g, 60%); mp 191°C; ^{1}H-NMR (DMSO-d_6) δ: 4.89 (s, 4H, CH_2), 5.42 (s, 8H, CH_2), 7.21 (dd, 4H, J = 7.5, 1.5 Hz), 7.31 (dd, 4H, J = 8.1, 7.3 Hz), 7.38 (dd, 4H, J = 8.2, 7.4 Hz), 7.48 (dd, 4H, J = 8.5, 7.4 Hz), 7.85 (m, 12H), 8.77 (s, 4H); ^{13}C-NMR (DMSO-d_6) δ: 51.48, 57.92, 124.97, 125.23, 125.78, 126.05, 127.66, 127.67, 128.31, 129.96, 130.66, 133.56, 137.42, 145.82, 146.65; Anal. Calcd for $C_{58}H_{44}N_6$: C, 84.44; H, 5.37; N, 10.19; Found: C, 84.67; H, 5.48; N, 9.85.

N,N,N',N'-Tetra[methyl(4'-acridinyl)]-1,3-diaminopropane (**9b**). Prepared as described for **9a** from **5** (0.2 g, 0.73 mmol) and 1,3-diaminopropane (0.027 g, 0.36 mmol). After filtration, the filtrate was evaporated. The resulting oil recovered was dissolved in water and the solution acidified (2 % HCl, 5 mL). A yellow powder of **9b** was obtained after filtration (0.101 g, 66%); mp 129°C; ^{1}H-NMR (DMSO-d_6) δ: 3.45 (s, 2H, CH_2), 4.33 (s, 4H, CH_2), 5.36 (s, 8H, CH_2), 7.02 (dd, 4H, J = 8.1, 7.4 Hz),

7.14 (dbr, 4H, J = 8.1 Hz), 7.25 (ddbr, 4H, J = 8.2, 7.2 Hz), 7.35 (ddbr, 4H, J = 8.2, 7.5 Hz), 7.70 (dd, 4H, J = 7.1, 1.4 Hz), 7.80 (d, 4H, J = 8.0 Hz), 7.82 (dd, 4H, J = 8.1, 1.4 Hz), 8.61 (s, 4H); ^{13}C-NMR (DMSO-d_6) δ: 19.57, 52.93, 56.88, 124.93, 125.14, 125.84, 126.03, 127.02, 127.42, 128.31, 130.00, 130.55, 133.76, 137.51, 145.64, 146.57; Anal. Calcd for $C_{59}H_{46}N_6$: C, 84.46; H, 5.52; N, 10.02; Found: C, 84.66; H, 5.52; N, 9.82.

N,N,N',N'-Tetra[methyl(4'-acridinyl)]-1,4-diaminobutane (**9c**). Prepared as described for **9a** but with **5** (0.2 g, 0.73 mmol) and 1,4-diaminobutane (0.032 g, 0.36 mmol). After filtration, the filtrate was evaporated. The resulting oil was dissolved in dilute HCl (2%, 5 mL) to yield **9c** as a brown powder (0.115 g, 73%); mp 129°C; ^{1}H-NMR (DMSO-d_6) δ: 2.71 (sbr, 4H), 4.09 (sbr, 4H), 5.14 (sbr, 4H, CH_2), 5.40 (sbr, 4H, CH_2), 7.26 (ddbr, 4H, J = 8.2, 7.3 Hz), 7.36 (dbr, 4H, J = 8.1 Hz), 7.38 (dd, 4H, J = 8.1, 7.2 Hz), 7.40 (ddbr, 4H, J = 8.2, 7.2 Hz), 7.77 (dd, 4H, J = 7.3, 1.5 Hz), 7.81 (d, 4H, J = 8.0 Hz), 7.85 (dd, 4H, J = 8.1, 1.5 Hz), 8.70 (s, 4H); ^{13}C-NMR (DMSO-d_6) δ: 22.25, 56.06, 57.17, 124.99, 125.09, 125.76, 125.98, 127.13, 127.52, 128.20, 130.01, 130.73, 133.68, 137.44, 145.50, 146.49; Anal. Calcd for $C_{60}H_{48}N_6$: C, 84.48; H, 5.67; N, 9.85; Found: C, 84.35; H, 5.77; N, 9.69.

N,N,N',N'-Tetra[methyl(4'-acridinyl)]-1,6-diaminohexane (**9d**). Prepared as described for **9a** but with **5** (0.2 g, 0.73 mmol) and 1,6-diaminohexane (0.042 g, 0.36 mmol). After filtration, the filtrate was evaporated. The resulting oil was dissolved in dilute HCl (2%, 5 mL) to yield a brown powder of **9d** (0.145 g, 89%); mp 145°C; ^{1}H-NMR (DMSO-d_6) δ: 1.84 (s, 4H, CH_2), 2.38 (sbr, 4H, CH_2), 3.72 (sbr, 4H, CH_2), 5.03 (sbr, 4H, CH_2), 5.37 (sbr, 4H, CH_2), 7.25 (m, 8H), 7.35 (dd, 4H, J = 8.1, 7.5 Hz), 7.37 (ddbr, 4H, J = 8.0, 7.3 Hz), 7.70 (d, 4H, J = 8.1 Hz), 7.80 (d, 4H, J = 8.0 Hz), 7.82 (dd, 4H, J = 8.0, 1.4 Hz), 8.60 (s, 4H); ^{13}C-NMR (DMSO-d_6) δ: 24.34, 25.92, 56.69, 57.26, 124.98, 125.03, 125.76, 125.96, 127.30, 127.36, 128.29, 129.94, 130.68, 133.57, 137.34, 145.54, 146.51; Anal. Calcd for $C_{62}H_{52}N_6$: C, 84.51; H, 5.95; N, 9.54; Found: C, 84.42; H, 6.01; N, 9.48.

N,N,N',N'-Tetra[methyl(4'-acridinyl)]-1,8-diaminooctane (**9e**). Prepared as described for **9a** but with **5** (0.2 g, 0.73 mmol) and 1,8-diaminooctane (0.053 g, 0.36 mmol). After filtration, the filtrate was evaporated. The resulting oil was dissolved in dilute HCl (2%, 5 mL) to yield **9e** as a brown powder (0.088 g, 52%); mp 136°C; ^{1}H-NMR (DMSO-d_6) δ: 1.42 (s, 4H), 1.66 (s, 4H), 2.25 (s, 4H), 3.82 (s, 4H), 4.91 (sbr, 4H, CH_2), 5.28 (sbr, 4H, CH_2), 7.24 (d, 4H, J = 8.3 Hz), 7.31 (dd, 4H, J = 8.1, 7.1 Hz), 7.33 (dd, 4H, J = 8.1, 7.5 Hz), 7.41 (ddbr, 4H, J = 8.1, 7.2 Hz), 7.62 (d, 4H, J = 7.5 Hz), 7.80 (d, 4H, J = 8.0 Hz), 7.82 (dd, 4H, J = 8.1, 1.4 Hz), 8.63 (s, 4H); ^{13}C-NMR (DMSO-d_6) δ: 24.57, 26.18, 28.65, 56.86, 57.37, 124.93, 125.02, 125.95, 127.34, 127.42, 127.79, 128.35, 129.91, 130.58, 133.39, 137.16, 145.62, 146.62; Anal. Calcd for $C_{64}H_{56}N_6$: C, 84.55; H, 6.21; N, 9.24; Found: C, 84.63; H, 6.03; N, 9.36.

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