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Synthesis of Diazadi(and tri)thiacrown Ethers Containing Two 5-Substituent(or 2-methyl)-8-hydroxyquinoline Side Arms

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Sixteen new diazadi(or tri)thiacrown ethers containing two 5-substituent(or 2-methyl)-8-hydroxyquinolin-2-ylmethyl side arms have been prepared by a three-step process. First, the appropriate bis(α-chloroamide)s were treated with five dimercaptans in base to form macrocyclic di(or tri)thiadiamides. The macrocyclic diamides were reduced by BH_3-THF to form 1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (11); 1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecane (12); 1,7-diaza-4-oxa-10,13,16-trithiacyclooctadecane (13); 1,7-diaza-4,13,16-trioxa-10,19-dithiacycloheneicosane (14); and 1,10-diaza-4,7-dioxa-13,16-dithiacyclooctadecane (15). The diazadi(or tri)thiacrown ethers were then treated with 8-hydroxyquinoline, 8-hydroxy-5-methylquinoline, 5-chloro-8-hydroxyquinoline, and 8-hydroxyquinaldine in the presence of paraformaldelyde in refluxing benzene to form the bis(8-hydroxy-5-substituent(or 2-methyl)quinolin-7-ymethyl)-substituted diazadi(or tri)thiacrown ethers 16–31. The crown ethers containing two 8-hydroxyquinoline or 8-hydroxyquinaldine side arms proved to be mixtures of about 90% bis(8-hydroxyquinolin-7-ylmethyl)-substituted crown ethers; 9% mixed (8-hydroxyquinolin-7-ymethyl)-substituted and (8-hydroxyquinolin-5-ylmethyl)-substituted crown ethers; and 1% bis(8-hydroxyquinolin-5-ylmethyl)-substituted crown ethers.

Keywords: Hydroxyquinoline; Benzene; NMR spectrum; Crown ethers

INTRODUCTION

8-Hydroxyquinoline (HQ) has been used extensively as a chromogenic, extraction, and precipitation reagent in analysis and as a fluorescence reagent [1]. 1-(2-Pyridylazo)-2-naphthol, 4-(2-pyridylazo)resorcinol, 2-(5-bromo-2-pyridylazo)-5-(diethylamino)phenol, and 1-nitroso-2-naphthol, which contain active phenolic OH groups, are also good open-chain analytical reagents [2]. Introducing HQ fragments into the macrocycle framework can increase the rigidity of those ligands and improve their complexation ability and selectivity for metal ions or organic molecules [3–6]. In the macrocyclic ligands containing HQ side-arms, ion coordination with the HQ fragments and the macrocyclic ether can cause interesting

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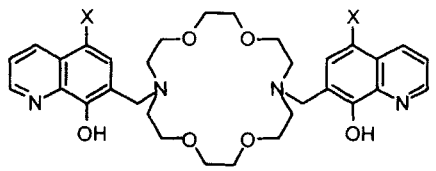
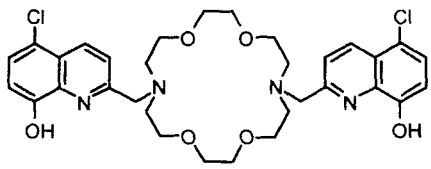
and important metal ion complexation. For example, *N,N'*-bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-substituted diaza-18-crown-6 (**1**, Fig. 1), in which HQ was attached to the macroring through position 7 of the quinoline ring (next to the OH group), has a stronger complexing ability for Mg^{2+} than for Ba^{2+} ($\log K$ value in methanol for Ba^{2+} is 3.60, for Mg^{2+} is 6.82) [4,5], while **3**, which has the HQ group attached to the macroring through position 2 of the quinoline ring (next to the quinoline nitrogen), has a stronger complexing ability for Ba^{2+} than for Mg^{2+} ($\log K$ value in methanol for Ba^{2+} is 12.2) [5,6]. Ligand **1** has high affinity and high selection for Mg^{2+} and its complex with Mg^{2+} has a greatly improved fluorescence, even in the presence of other alkali metal and alkaline earth metal ions [7a]. Thus, **1** is a chemosensor for Mg^{2+} ions. Ligand **2**, which has a 5-nitro substituent, has a high affinity and selectivity for Hg^{2+} ions and has proven to be a chemosensor for Hg^{2+} ions [7b].



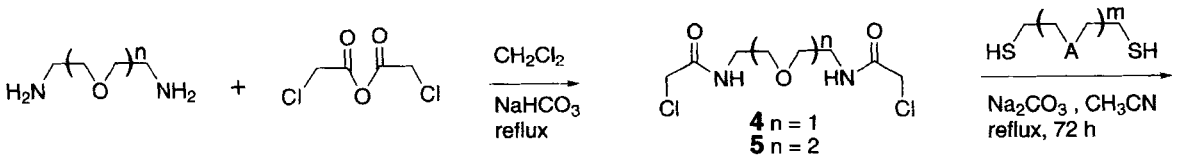
1 X = Cl
2 X = NO_2



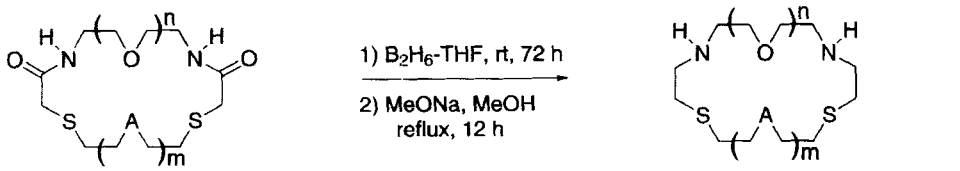
3

FIGURE 1 5-chloro-8-hydroxyquinoline (CHQ)-substituted diaza-18-crown-6 ligands **1**–**3**.

Some monoazacrown ethers [6,8,9], diazacrown ethers [6,10], and tetraazacrown ethers [11], which bear HQ side arms, have been synthesized and studied in our laboratory. Some of the lariat ethers have strong complexation abilities and some have high selectivities for certain metal ions. In general the affinity and selectivity of the lariat ethers for metal ions can be varied by changing certain parameters such as the pH of the media; acidity of the phenolic OH group; the size of the crown ether ring; type, number, and position of the complexing heteroatoms; and the stereochemistry imposed by



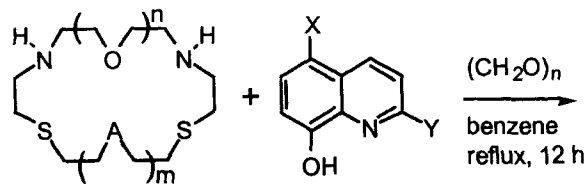
4 n = 1
5 n = 2



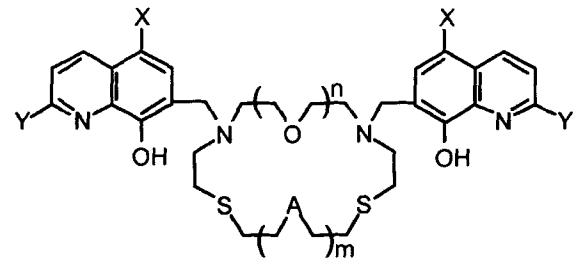
6 n = 1, m = 0 (58%)
7 n = 1, m = 1, A = O (57%)
8 n = 1, m = 1, A = S (55%)
9 n = 1, m = 2, A = O (53%)
10 n = 2, m = 0 (57%)

11 n = 1, m = 0 (55%)
12 n = 1, m = 1, A = O (62%)
13 n = 1, m = 1, A = S (70%)
14 n = 1, m = 2, A = O (27%)
15 n = 2, m = 0 (82%)

SCHEME 1 Syntheses of diazadithiacrown ethers **11**–**15**.



11-15



16 n = 1, m = 0, X, Y = H (74%)
17 n = 1, m = 0, X = Me, Y = H (94%)
18 n = 1, m = 0, X = Cl, Y = H (83%)
19 n = 1, m = 0, X = H, Y = Me (59%)
20 n = 1, m = 1, A = O, X, Y = H (74%)
21 n = 1, m = 1, A = O, X = Me, Y = H (31%)
22 n = 1, m = 1, A = O, X = Cl, Y = H (82%)
23 n = 1, m = 1, A = O, X = H, Y = Me (36%)
24 n = 1, m = 1, A = S, X, Y = H (78%)
25 n = 1, m = 1, A = S, X = Me, Y = H (43%)
26 n = 1, m = 1, A = S, X = Cl, Y = H (91%)
27 n = 1, m = 1, A = S, X = H, Y = Me (36%)
28 n = 2, m = 0, X, Y, = H (58%)
29 n = 2, m = 0, X = Me, Y, = H (63%)
30 n = 2, m = 0, X = Cl, Y, = H (58%)
31 n = 2, m = 0, X = H, Y, = Me (35%)

SCHEME 2 Syntheses of 8-hydroxyquinoline-substituted diazadi-(and tri)thia crown ethers **16**–**31**.

the arms which connect the phenolic group to the macrocycle. An example of how these changes can affect the log K values for metal ion complexation includes a substantial decrease in the log K value for the interaction of the 5-hydro analogue of **3** with Ba^{2+} [10]. In this case, exchanging the C-5 chlorine in **3** with hydrogen causes the phenolic group to be more acidic. In both of these complexes as well as that with the *N,N'*-bis(5,7-dichloro-8-hydroxyquinoline-2-ylmethyl)-substituted diaza-18-crown-6, upfield shifts for the peaks in the ^1H NMR spectrum attributed to the quinoline hydrogen atoms suggest that these complexes are in the form of cryptates with the two quinolines juxtaposed with one another [6, 10]. Changing the size of the macrocyclic ring and increasing the number of ring nitrogen atoms greatly changes the affinity of the ligand as shown by the great increase in log K values for the interaction of **3** with Cu^{2+} (log $K = 4.7$) verses *N,N'*-bis(5-chloro-8-hydroxyquinolin-2-ylmethyl)-substituted tetraza-15-crown-5 (log $K = 15.5$) [11].

In this paper, we report a new family of diazadithiacrown ethers containing two 5-substituent(or 2-methyl)-8-hydroxyquinolin-7-ylmethyl sidearms. The macrocycles include diazadithia-15-crown-5, diazadithia-18-crown-6, diazadithia-21-crown-7, and diazatrithia-18-crown-6 ligands. The HQ-armed macrocycles were prepared in 4 steps: preparation of a bis(α-chloroamide) by treatment of a diamine with chloroacetic anhydride, cyclization of the bis(α-chloroamide) with a dithiol, reduction of the macrocyclic diamide, and a modified Mannich reaction of the disecondary amine-containing crown ether with various HQ compounds as shown in Schemes 1 and 2.

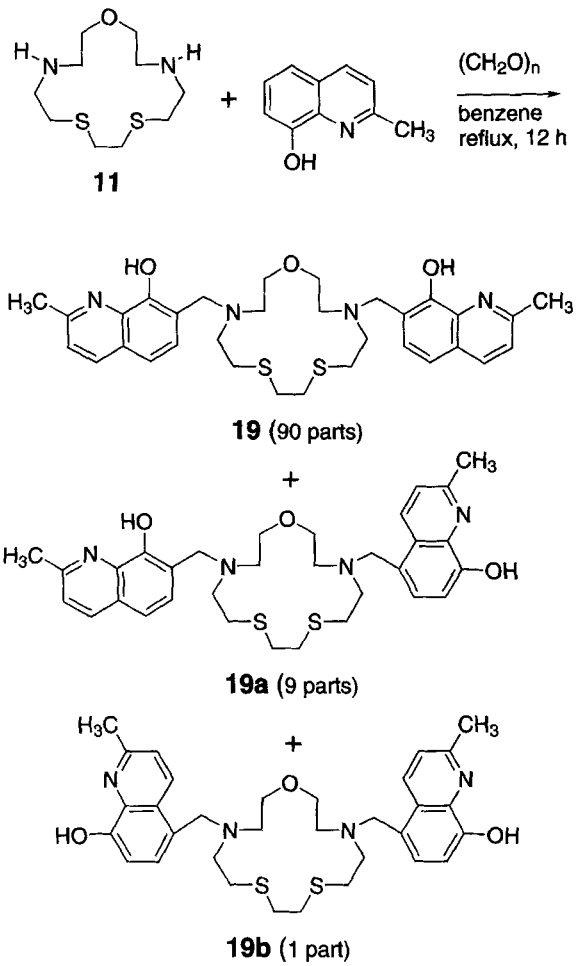
RESULTS AND DISCUSSION

A convenient method to attach the HQ sidearms to the diazadithiacrown ether is through attachment to the macroring ring NH groups. Thus, the relevant diazadithiacrown ethers containing two secondary amine groups had to be prepared. A crab-like synthesis of diazacrown ethers having one or two secondary amine functions using bis(α-chloroamide)s has been reported [11–14]. In the present case, two bis(α-chloroamide)s **4** and **5** were prepared by treating two diprimary amines with chloroacetic anhydride as shown in Scheme 1. Bis(α-chloroamide)s **4** and **5** each have two secondary amide NH functions which are unreactive toward alkylating agents. On the other hand, the

chloride groups of the α-chloramides are very reactive toward nucleophiles including thiols [15]. Thus, dichlorides **4** and **5** were treated with five dimercaptan compounds in acetonitrile using high dilution techniques with potassium carbonate as the base to form macrocyclic diazadithia(or trithia)crown ether diamides **6**–**10** in yields of 53%–58% as shown in Scheme 1. The macrocyclic diamides were reduced to the macrocyclic disecondary amines in 27%–82% yields using diborane-tetrahydrofuran followed by methanolic base to decompose any borane-ligand complex (Scheme 1) [11–15]. Satisfactory elemental analyses were obtained for macrocyclic diamides **6**–**10** but only diazadithia-18-crown-6 **12** gave a satisfactory elemental analysis. Ligands **11**, **13**–**15** gave satisfactory HRMS analyses and the elemental analyses for bis-HQ-substituted ligands prepared from these ligands as outlined below were satisfactory.

We have used a number of methods to attach HQ groups to the diazacrown ethers. Ligand **3** with the HQ groups attached through their positions 2 was prepared by a nucleophilic substitution by the secondary macroring amine functions on 2-bromomethyl-5-chloro-8-methoxyquinoline followed by removal of the methyl protecting groups [6]. Other bis(8-hydroxyquinolin-2-ylmethyl)-substituted crown ethers were prepared *via* a reductive amination process using the oligoazacrown ether, 8-acetoxyquinoline-2-carbaldehyde, and triacetoxyborohydride. The acetate protecting groups were removed in a second step [10, 11]. The latter reductive amination process was also used to prepare the bis(8-aminoquinolin-2-ylmethyl)-substituted tetraazacrown ethers using 8-nitroquinoline-2-carbaldehyde followed by reduction [11]. The bis(8-hydroxyquinolin-7-ylmethyl)-substituted diazacrown ethers (**1** for example) were generally prepared by the Mannich aminomethylation reaction either *via* an intermediate bis (methoxymethyl)-substituted diazacrown ether [6, 8] or by the direct reaction of the diazacrown ether, 8-hydroxyquinoline derivative, and paraformaldehyde in refluxing toluene [10, 16, 17]. The bis(5-substituted(or 2-methyl)-8-hydroxyquinolin-7-ylmethyl)-substituted diazadithia(or trithia)-crown ethers reported in this paper were prepared by treating the appropriate crown ether (**11**–**15**) with the HQ derivative and paraformaldehyde in refluxing benzene as shown in Scheme 2. The aminomethylation reactions resulted in yields of 35%–94% for new bis-HQ-substituted ligands **16**–**31**. The ^{1}H and ^{13}C NMR spectra of all new bis-HQ-substituted ligands were consistent with the structures shown in Scheme 2.

The products of the Mannich reaction with 8-hydroxyquinoline (**16**, **20**, **24**, and **28**) and with 8-hydroxyquinaldine (**19**, **23**, **27**, and **31**) (see Scheme 2) proved to be mixtures of HQ-substituted diazacrown products. The unsubstituted 5 positions on these reacting quinolines are also reactive toward aminomethylation allowing for the formation of some (8-hydroxyquinolin-5-ylmethyl)-substituted diazacrown ethers. The possible reaction products in the synthesis of **19**, for example, are shown in Scheme 3. The mixture of products in these syntheses could not be separated. The three products were identified by a careful analysis of the ^{13}C and ^{1}H NMR spectra. The bis(8-hydroxyquinolin-7-ylmethyl)-substituted products form in the highest yields in every case. This fact is shown by the large peak at δ 53.5 $\pm$ 0.5 ppm in the ^{13}C NMR spectra of all bis(8-hydroxyquinoline)-substituted products. The signal at δ 53.5 is caused by the methylene carbon atom connecting the diazacrown with the 7 position of the 8-hydroxyquinoline group. Similar peaks at δ 53.5 $\pm$ 0.5 ppm were observed for other (8-hydroxyquinolin-7-ylmethyl)-substitute azacrown ligands [10] (or 2-hydroxylbenzyl-substituted azacrown ethers [17]) that have been prepared in our laboratory. Thus, the major Mannich reaction products using 5-hydro-8-hydroxyquinoline type starting materials are the bis(8-hydroxyquinolin-7-ymethyl)-substituted ligands as shown in Scheme 2.



SCHEME 3 Isomeric products in the synthesis of **19**.

The ^{13}C NMR spectrum of all products produced from the 8-hydroxyquinoline and 8-hydroxyquinaldine reactions also had a small peak at δ 56.6 ± 0.5 ppm. We suspect that this signal is caused by the methylene carbon atom connecting the azacrown to the 5 position of the 8-hydroxyquinoline. The ^{13}C NMR spectrum for **19** exhibited a large peak at δ 25.3 and two very small peaks of equal intensity at δ 25.2 and 25.1 ppm. These signals can be attributed to the carbon atoms of the methyl groups on the 2 position of the quinoline in ligands **19** and **19a**, respectively. These peaks integrated to a ratio of about 9 : 1. The ^1H NMR spectrum of the product mixture of **19** exhibited a large doublet at δ 7.96, a small doublet at δ 8.27 and a very small doublet at δ 8.08 ppm (all $J = 8.8$ Hz) with integrated ratios of about 90 : 9 : 1, respectively. These results suggest that the products shown in Scheme 3 were produced in a ratio of about 90 : 9 :1 of **19 : 19a : 19b**, respectively, as one would expect for a statistical ratio of products where the quinolin-7-ylmethyl-substituted product was favored over the quinolin-5-ylmethyl one by about 9 : 1.

Ligand **16** was found to have similar isomers as shown in Scheme 3 by a careful analysis of its ^{13}C and ^1H NMR spectra. The other products, **20**, **23**, **24**, **27**, **28**, and **31**, would be expected to have the three types of HQ-substituted ligand products as shown in Scheme 3 and probably in similar ratios.

EXPERIMENTAL

The ^1H NMR spectra (200 MHz or 300 MHz) and ^{13}C NMR spectra (50 MHz or 75 MHz) were recorded in $CDCl_3$. Melting points are uncorrected. HRMS spectra were determined using the fast atom bombardment (FAB) method. Solvents and starting materials were purchased from commercial source where available. Bis(α-chloroamide)s **4** and **5** were prepared as reported [11].

8-Hydroxy-5-methylquinoline [18] A mixture of 9.2 g (75 mmol) of 2-amino-4-methylphenol, 6.6 g (43 mmol) of 4-methyl-2-nitrophenol, 37.5 g of dry glycerol, 22.5 mL of 80% acetic acid and 15 mL of concentrated H_2SO_4 was gently refluxed for 16 h, after which the mixture was steam distillated for 5 h. The residue was filtered and the filtrate was cooled and carefully neutralized with dilute aqueous NH_3 to give the free base product. The product was purified by chromatography on silica gel using CH_2Cl_2-hexane as eluent to give 6.86 g (58%) of 8-hydroxy-5-methylquinoline; mp 121 – 122°C; ^1H NMR: δ 2.58 (s, 3H), 7.05 (d, $J = 7.8$ Hz, 1H), 7.26 (t, $J = 2.4$ Hz, 1H), 7.45 (q, $J = 4.2$, Hz, 1H), 8.27

(dd, $J = 1.8$, 1.6 Hz, 1H), 8.78 (dd, $J = 1.6$,1.4 Hz, 1H); ^{13}C NMR: δ 17.9, 109.6, 121.5, 124.6, 127.8, 233.2, 138.8, 147.6, 150.8; HRMS calcd. for $C_{10}H_{10}NO$ $(M+H)^+$: 160.0763, found: 160.0751.

General Procedure A to Prepare Macrocyclic Diamides 6–10 (Scheme 1) A mixture of equimolar amounts of dichlorodiamide and dithiol, a 4 fold excess of anhydrous K_2CO_3 and CH_3CN (350 mL/0.1 mol of dichlorodiamide) was stirred at room temperature for 72 h. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was separated by chromatography (silica gel, CH_2Cl_2: CH_3OH: $NH_4OH = 80:10:1$).

1,7-Diaza-4-oxa-10,13-dithiacyclopentadecan-8,15-dione (6) Macrocyclic diamide **6** (7.5 g, 58%) was obtained according to general procedure A from 10.3 g (40 mmol) of **4** and 3.8 g (40 mmol) of 1,2-dimercaptoethane; mp 178–180°C; ^1H NMR: δ 2.82 (s, 4H), 3.29 (s, 4H), 3.52 (t, $J = 6.0$ Hz, 4H), 3.59 (t, $J = 5.0$ Hz, 4H); ^{13}C NMR: δ 34.0, 37.3, 39.9, 69.5, 168.7; HRMS calcd. for $C_{10}H_{19}N_2O_3S_2$ $(M+H)^+$: 279.0839, found: 279.0839. *Anal.* Calcd for $C_{10}H_{18}N_2O_3S_2$: C, 43.14; H, 6.25. Found: C, 43.22; H, 6.33.

1,7-Diaza-4,13-dioxa-10,16-dithiacyclooctadecan-8,18-dione (7) Macrocyclic diamide **7** (6.5 g, 57%) was prepared from 10.5 g (35 mmol) of **4** and 3.3 g (35 mmol) of 2-mercaptoethyl ether according to general procedure A; mp 143–144°C; ^1H NMR: δ 2.81(t, $J = 5.4$ Hz, 4H), 3.36 (s, 4H), 3.51–3.60 (m, 8H), 3.74 (t, $J = 5.6$ Hz, 4H); ^{13}C NMR: δ 32.5, 36.6, 39.6, 69.4, 71.5, 169.1; HRMS calcd. for $C_{12}H_{23}N_2O_4S_2$ $(M+H)^+$: 323.1101, found: 323.1083. *Anal.* Calcd for $C_{12}H_{22}N_2O_4S_2$: C, 44.70; H, 6.88. Found: C, 44.59; H, 6.81.

1,7-Diaza-4-oxa-10,13,16-trithiacyclooctadecan-8,18-dione (8) Macrocyclic diamide **8** (7.2 g, 55%) was obtained according to general procedure A from 10.3 g (40 mmol) of **4** and 5.2 g (40 mmol) of mercaptoethyl sulfide; mp 153.5–154.5°C; ^1H NMR: δ 2.81 (t, $J = 5.4$ Hz, 8H), 3.36 (s, 4H), 3.51 (t, $J = 5.0$ Hz, 4H), 3.64 (t, $J = 5.0$ Hz, 4H); ^{13}C NMR: δ 31.8, 33.7, 36.8, 39.9, 69.6, 169.4; HRMS calcd. for $C_{12}H_{23}N_2O_3S_3$ $(M+H)^+$: 339.0873, found: 339.0866. *Anal.* Calcd. for $C_{12}H_{22}N_2O_3S_3$: C, 42.58; H, 6.55. Found: C, 42.73; H, 6.49.

1,7-Diaza-4,13,16-trioxa-10,19-dithiacycloheneicosan-8,21-dione (9) Macrocyclic diamide **9** (3.9 g, 53%) was obtained according to general procedure A from 5.1 g (20 mmol) of **4** and 3.6 g (20 mmol) of 2,2′-(ethylenedioxy)-diethanethiol; mp 100.5–101.5°C; ^1H NMR: δ 2.78 (s, 4H), 3.33 (s, 4H), 3.49 (t, $J = 5.2$, 4H), 3.55–3.63 (m, 8H), 3.73 (t, $J = 5.6$ Hz, 4H); ^{13}C NMR: δ 32.5, 36.7, 39.7, 69.5, 70.2, 71.3, 169.5; HRMS calcd. for $C_{14}H_{26}N_2O_5S_2Na^+$: 389.1182, found: 389.1184. *Anal.* Calcd. for $C_{14}H_{26}N_2O_5S_2$: C, 45.88; H, 7.15. Found: C, 45.79; H, 7.14.

1,10-Diaza-4,7-dioxa-13,16-dithiacyclooctadecan-11,18-dione (10) Macrocyclic diamide **10** (6.5 g, 57%) was obtained according to general procedure A from 10.5 g (35 mmol) of **5** and 3.3 g (35 mmol) of 1,2-dimercaptoethane; mp 153.5–154.5°C; ^1H NMR: δ 2.75 (s, 4H), 3.25 (s, 4H), 3.50 (t, $J = 5.6$ Hz, 4H), 3.60 (t, 8H); ^{13}C NMR: 32.8, 36.2, 39.6, 69.6, 70.6, 168.7; HRMS calcd. for $C_{12}H_{23}N_2O_4S_2$ $(M+H)^+$: 323.1101, found: 323.1088. *Anal.* Calcd. for $C_{12}H_{22}N_2O_4S_2$: C, 44.70; H, 6.88. Found: C, 44.84; H, 6.86.

General Procedure B to Prepare Diazadithiacrown Ethers 11–15 (Scheme 1) The macrocyclic diamide (10.0 mmol) was dissolved in 30 mL of dry THF and an 80 mL solution of 1MBH_3-THF was added to the solution. The mixture was stirred for 72 h at room temperature and the solvent was evaporated under reduced pressure. A dilute solution of $NaOCH_3$ in CH_3OH was added and the mixture was refluxed overnight. After the CH_3OH was evaporated, some water was added and the resulting mixture was extracted several times by portions of $CHCl_3$ until all the product was obtained. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and evaporated to give the crude product. The product was purified by chromatography on silica gel (eluent: CH_2Cl_2: CH_3OH: $NH_4OH = 50:5:1$).

1,7-Diaza-4-oxa-10,13-dithiacyclopentadecane (11) Diazadithiacrown ether **11** (3.3 g, 55%) was obtained as a viscous liquid according to general procedure B. The HRMS and NMR spectral data were idential to those reported [19].

1,7-Diaza-4,13-dioxa-10,16-dithiacyclooctadecane (12) Diazadithiacrown ether **12** (2.2 g, 62%) was isolated as a viscous liquid from **7** (4.0 g, 12.1 mmole) according to general procedure B; ^{1}H NMR: δ 2.29 (s, 2H), 2.71–2.83 (m, 16H), 2.58 (t, J = 4.8 Hz, 4H), 3.69 (t, J = 5.4 Hz, 4H); ^{13}C NMR: δ 32.1, 33.2, 48.5, 49.1, 70.1, 71.9; HRMS calcd. for $C_{12}H_{27}N_2O_2S_2$ $(M+H)^+$: 295.1566, found: 295.1515. *Anal.* Calcd. for $C_{12}H_{26}N_2O_2S_2 \cdot 1/5CH_2Cl_2$: C, 47.05; H, 8.54. Found: C, 47.36; H, 8.39.

1,7-Diaza-4-oxa-10,13,16-trithiacyclooctadecane (13) Diazatrithiacrown ether **13** (3.9 g, 70%) was isolated as a viscous liquid from **8** (6.1 g) according to general procedure B; ^{1}H NMR: δ 1.92 (s, 2H), 2.68–2.72 (m, 20H), 3.47 (t, J = 5.0 Hz, 4H); ^{13}C NMR: δ 32.4, 32.7, 48.4, 49.0, 70.3, 70.5; HRMS calcd. for $C_{12}H_{27}N_2OS_3$ $(M+H)^+$: 311.1288, found: 311.1267.

1,7-Diaza-4,13,16-trioxa-10,19-dithiacycloheneicosane (14) Macrocyclic diamide **9** (3.7 g, 10 mmol) was reduced by BH_3-THF according to general procedure B to give diazadithiacrown ether **14** (0.9 g, 27%) as a viscous oil; ^{1}H NMR: δ 2.61–2.77 (m, 16H), 3.53–3.73 (m, 12H); ^{13}C NMR: δ 32.1, 33.3, 48.8, 49.1, 70.5, 70.9, 71.8; HRMS calcd. for $C_{14}H_{31}N_2O_3S_2(M+H)^+$: 339.1778, found: 339.1782.

1,10-Diaza-4,7-dioxa-13,16-dithiacyclooctadecane (15) Diazadithiacrown ether **15** (3.8 g, 82%) was obtained as a viscous liquid from **9** (5.1 g, 5.8 mmol) according to general procedure B; ^{1}H NMR: δ 2.16 (s, 2H), 2.72–2.80 (m, 16H), 3.58 (m, 8H); HRMS calcd. for $C_{12}H_{27}N_2O_2S_2$ $(M+H)^+$: 295.1516, found: 295.1505.

General Procedure C for the Synthesis of Azathiacrown Ethers Containing Two 5-Substituted-8-hydroxyquinoline(or 8-hydroxyquinaldine) Sidearms (16–31) (Scheme 2) A solution of benzene (45 mL), 2.0 mmol of diazadi(or tri)thiacrown ether, 4.2 mmol of 5-substituted-8-hydroxyquinoline (or 8-hydroxyquinaldine) and paraformaldehyde (0.14 g, 4.5 mmol) was refluxed for 15 h. The solvent was evaporated under reduced pressure, the mixture was separated by chromatography on silica gel using CH_2Cl_2: CH_3OH: NH_4OH = 50:5:1 as eluent.

1,7-Bis(8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (16) According to general procedure C, 0.83 g (74%) of **16** was obtained as a viscous liquid from 0.50 g (2.0 mmol) of **11** and 0.61 g (0.42 mmol) of 8-hydroxyquinoline. A small amount of hexane was added to the flask and the mixture was ultrasonicated for 3 h. The hexane was decanted and evaporated under reduced pressure to give a solid product; mp 58–60°C; ^{1}H NMR: δ 2.77 (s, 4H), 2.83 (t, J = 1.8 Hz, 8H), 3.01(t, J = 4.6 Hz, 4H), 3.60 (t, J = 5.2 Hz, 4H), 3.95 (s, 4H), 7.24 (d, J = 3.4 Hz, 4H), 7.36 (q, J = 4.2 Hz, 2H), 8.04 (dd, J = 1.8, 2.2 Hz, 2H), 8.84 (dd, J = 1.6, 1.8 Hz, 2H); ^{13}C NMR: δ 28.8, 32.1, 53.3, 55.0, 57.1, 70.6, 117.8, 119.0, 121.5, 128.1, 128.6, 135.9, 139.4, 149.1, 153.0; HRMS calcd. for $C_{30}H_{37}N_4O_3S_2$ $(M+H)^+$: 565.2310, found: 565.2303. *Anal.* Calcd. for $C_{30}H_{36}N_4O_3S_2$: C, 63.80; H, 6.42. Found: C, 63.67; H, 6.62.

1,7-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (17) Ligand **17** (0.92 g, 94%) was obtained as a solid according to general procedure C from 0.56 g of **11** and 0.67 g of 5-methyl-8-hydroxyquinoline. The solid product was recrystallized from a mixture of CH_2Cl_2 and hexane; mp 144–145°C; ^{1}H NMR: δ 2.54 (s, 6H), 2.77 (d, 12H), 3.00 (d, 4H), 3.60 (s, 4H), 3.90 (s, 4H), 7.09 (s, 2H), 7.39 (q, J = 4.2 Hz, 2H), 8.24 (dd, J = 1.8, 1.6 Hz, 2H), 8.86 (t, J = 1.6 Hz, 2H); ^{13}C NMR: δ 17.9, 28.7, 32.0, 53.2, 55.0, 56.6, 70.6, 117.8, 121.0, 124.0, 127.5, 128.3, 132.6, 139.6, 148.4, 153.9; HRMS calcd. for $C_{32}H_{41}N_4O_3S_2$ $(M+H)^+$: 593.2623, found: 593.2618. *Anal.* Calcd. for $C_{32}H_{40}N_4O_3S_2$: C, 64.83; H, 6.80. Found: C, 65.03; H, 6.86.

1,7-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (18) Ligand **18** (1.05 g, 83%) was obtained from 0.56 g of **11** and 0.75 g of 5-chloro-8-hydroxyquinoline in the same way as **17** above; mp 153.5–154.5°C; ^{1}H NMR: δ 2.82–2.87 (m, 12H), 3.02–3.06 (m, 4H), 3.61 (t, J = 4.6 Hz, 4H), 3.94 (s, 4H), 7.42 (s, 2H), 7.49 (q, J = 4.2 Hz, 2H), 8.46 (dd, J = 1.6, 1.6 Hz, 2H), 8.90 (dd, J = 1.6, 1.4 Hz, 2H); ^{13}C NMR: δ 28.8, 29.7, 53.3, 55.6, 56.5, 70.3, 118.4, 121.1, 124.1, 127.7, 128.4, 132.8, 139.6, 148.5, 151.0; HRMS calcd. for $C_{30}H_{35}N_4O_3S_2Cl_2$ $(M+H)^+$: 633.1531, found: 633.1519. *Anal.* Calcd. for $C_{30}H_{34}N_4O_3S_2Cl_2$: C, 56.86; H, 5.41. Found: C, 56.78; H, 5.40.

1,7-Bis(2-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13-dithacyclopentadecane (19) This compound (59%) was obtained as a viscous liquid according to general procedure C; ^{1}H NMR: δ 2.72 (s, 6H), 2.81–2.92 (m, 12H), 3.06 (m, 4H), 3.59 (t, J = 4.4 Hz, 4H), 3.92 (m, 4H), 7.23–7.28 (m, 6H), 7.92 (dd, J = 3.8, 3.6 Hz, 2H); ^{13}C NMR: δ 25.5, 28.7, 32.0, 53.1, 55.1, 56.6, 70.8, 117.5, 119.0, 122.5, 126.7, 127.3, 136.1, 136.7, 152.2, 157.9; HRMS calcd. for $C_{32}H_{41}N_4O_3S_2$ $(M+H)^+$: 593.2623, found: 593.2625. *Anal.* Calcd. for $C_{32}H_{40}N_4O_3S_2$: C, 64.12; H, 6.96. Found: C, 64.28; H, 7.18.

1,7-Bis(8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecane (20) Ligand **20** (0.9 g, 74%) was obtained as a viscous liquid from 0.59 g (20.0 mmol) of **12** and 0.61 g (4.2 mmol) of 8-hydroxyquinoline according to general procedure C. **20** was isolated as was **17** to give a low melting solid; ^{1}H NMR: δ 2.74 (t, J = 6.0 Hz, 4H), 2.96 (d, J = 14.6 Hz, 12H), 3.69 (t, J = 6.0 Hz, 8H), 3.99 (s, 4H), 7.26 (d, J = 2.0 Hz, 4H), 7.36 (q, J = 4.0 Hz, 2H), 8.06 (dd, J = 4.0, 1.8 Hz, 2H), 8.83 (dd, J = 1.4, 1.0 Hz, 2H); ^{13}C NMR: δ 29.6, 31.4, 53.2, 54.5, 57.3, 69.6, 72.2, 117.8, 119.0, 121.5, 128.0, 135.9, 139.1, 149.2, 152.3; HRMS calcd. for $C_{32}H_{41}N_4O_4S_2$ $(M+H)^+$: 609.2572, found: 609.2569. *Anal.* Calcd. for $C_{32}H_{40}N_4O_4S_2$: C, 63.13; H, 6.62. Found: C, 63.41; H, 6.46.

1,7-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecane (21) According to general procedure C, 0.39 g (31%) of ligand **21** was obtained as a viscous liquid from 0.59 g (20.0 mmol) of **12** and 0.67 g (4.2 mmol) of 5-methyl-8-hydroxyquinoline. Ligand **21** was recrystallized from CH_2Cl_2-hexane to give a solid product; mp 134–135°C; ^{1}H NMR: δ 2.55 (s, 6H), 2.73 (t, J = 6.0 Hz, 4H), 2.88 (m, 12H), 3.65 (m, 8H), 3.91 (s, 4H), 7.07 (s, 2H), 7.38 (q, J = 4.4 Hz, 2H), 8.19 (dd, J = 1.6, 1.4 Hz, 2H), 8.86 (dd, J = 1.6, 1.4 Hz, 2H); ^{13}C NMR: δ 18.0, 29.5, 31.3, 53.2, 54.5, 56.9, 69.7, 72.2, 118.4, 121.0, 124.0, 127.6, 128.3, 132.6, 139.8, 148.6, 151.2. *Anal.* Calcd. for $C_{34}H_{44}N_4O_4S_2$: C, 64.12; H, 6.96. Found: C, 64.26; H, 6.91.

1,7-Bis(5-chloro-8-hydroxyquinoline-7-ylmethyl)-1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecane (22) Ligand **22** (1.12 g, 82%) was prepared from **12** and 5-chloro-8-hydroxyquinoline according to general procedure C. Ligand **22** was recrystallized from a mixture of CH_2Cl_2 and hexane; mp 131–132°C; ^{1}H NMR: δ 2.75 (t, J = 6.0 Hz, 4H), 2.85–2.96 (m, 12H), 3.60–3.72 (m, 8H), 3.95 (s, 4H), 7.39 (s, 2H), 7.48 (dd, J = 4.2, 4.0 Hz, 2H), 8.45 (dd, J = 1.4, 1.6 Hz, 2H), 8.91 (dd, J = 1.6, 1.4 Hz, 2H); ^{13}C NMR: δ 29.7, 31.4, 53.2, 54.5, 56.5, 69.4, 72.2, 119.5, 120.2, 122.2, 126.2, 127.7, 133.0, 139.9, 149.5, 152.2; HRMS calcd. for $C_{32}H_{39}Cl_2N_4O_4S_2$ $(M+H)^+$: 677.1793; found: 677.1796. *Anal.* Calcd. for $C_{32}H_{38}Cl_2N_4O_4S_2$: C, 56.70; H, 5.66. Found: C, 57.00; H, 5.68.

1,7-Bis(2-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4,13-dioxa-10,16-dithiacyclooctadecane (23) According to general procedure C, ligand **23** (0.31 g, 36%) was isolated as a viscous liquid from **12** (0.40 g, 1.35 mmol) and 8-hydroxyquinaldine (0.45 g, 2.84 mmol). Ligand **23** was purified as 17; ^{1}H NMR: δ 2.73 (m, 10H), 2.83–3.01 (m, 12H), 3.58–3.70 (m, 8H), 3.94 (s, 4H), 7.19 (m, 4H), 7.27 (d, 2H), 7.93 (dd, J = 3.8, 3.8 Hz, 2H); ^{13}C NMR: δ 25.6, 29.4, 31.3, 53.1, 54.5, 56.9, 69.8, 72.2, 117.5, 119.1, 122.4, 126.8, 127.2, 136.1, 138.8, 152.4, 157.9; HRMS calcd. for $C_{34}H_{45}N_4O_4S_2$ $(M+H)^+$: 637.2885, found: 637.2896. *Anal.* Calcd. for

$C_{34}H_{44}N_4O_4S_2$: C, 64.12; H, 6.96. Found: C, 64.20; H, 7.04.

1,7-Bis(8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13,16-trithiacyclooctadecane (24) According to general procedure C, 0.64 g (78%) of **24** was obtained as a viscous liquid from 0.68 g (2.0 mmol) of **13** and 0.61 g (4.2 mmol) of 8-hydroxyquinoline; ^{1}H NMR: δ 2.75 (s, 8H), 2.88 (t, J = 2.6 Hz, 12H), 3.66 (s, 4H), 3.98 (s, 4H), 7.26 (m, 4H), 7.37 (m, 2H), 8.06 (dd, J = 1.6, 1.8 Hz, 2H), 8.87 (dd, J = 1.6, 1.6 Hz, 2H); HRMS calcd. for $C_{32}H_{38}N_4O_3S_3Na_3^+$: 691.1802, found: 691.1793. *Anal.* Calcd. for $C_{32}H_{40}N_4O_3S_3$: C, 61.51; H, 6.45. Found: C, 58.34; H, 6.02.

1,7-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13,16-trithiacyclooctadecane (25) Ligand **25** (0.56 g. 43%) was obtained from 0.68 g (2.0 mmol) of **13** and 0.67 g (4.2 mmol) of 5-methyl-8-hydroxyquinoline. Ligand **25** was recrystallized from CH_2Cl_2-hexane to give a pure product; mp 122.5–123.5°C; ^{1}H NMR: δ 2.55 (s, 6H), 2.75 (s, 8H), 2.87 (d, J = 4.0 Hz, 12H), 3.66 (t, J = 4.8 Hz, 4H), 3.93 (s, 4H), 7.08 (s, 2H), 7.40 (m, 2H), 8.21 (dd, J = 1.6, 1.6 Hz, 2H), 8.86 (dd, J = 1.6, 1.4 Hz, 2H); ^{13}C NMR: δ 18.0, 29.6, 32.3, 32.7, 53.8, 54.5, 56.7, 69.0, 118.4, 121.0, 124.0, 127.6, 128.3, 132.6, 139.6, 148.5, 151.0; HRMS calcd. for $C_{34}H_{45}N_4O_3S_3$ $(M+H)^+$: 653.2657, found: 653.2843. *Anal.* Calcd. for $C_{34}H_{44}N_4O_3S_3$: C, 62.54; H, 6.79. Found: C, 62.70; H, 6.87.

1,7-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13,16-trithiacyclooctadecane (26) Ligand **26** was synthesized as **21** from 0.35 g (1.0 mmol) of **13** and 0.38 g (2.1 mmol) of 5-chloro-8-hydroxyquinoline to give 0.63 g (91%) of solid product; mp 122–123.5°C; ^{1}H NMR: δ 2.76 (s, 8H), 2.87 (m, 12H), 3.63 (t, J = 4.8 Hz, 4H), 3.94 (s, 4H), 7.41 (s, 2H), 7.47 (q, J = 4.2 Hz, 2H), 8.44 (dd, J = 1.4, 1.4 Hz, 2H), 8.89 (dd, J = 1.6, 1.8 Hz, 2H); HRMS calcd. for $C_{32}H_{39}Cl_2N_4O_3S_3$ $(M+H)^+$: 693.1565, found: 693.1547.

1,7-Bis(2-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4-oxa-10,13,16-trithiacyclooctadecane (27) According to general procedure C, ligand **27** (0.31 g, 36%) was synthesized from **13** and 8-hydroxyquinaldine as a viscous liquid. It was purified as **17** above; ^{1}H NMR: δ 2.72–2.90 (m, 26H), 3.60 (t, J = 4.8 Hz, 4H), 3.92 (s, 4H), 7.20 (t, 6H), 7.91 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ 25.6, 29.4, 32.4, 53.3, 54.5, 56.8, 69.7, 70.9, 117.4, 118.9, 113.4, 126.7, 127.2, 136.0, 138.4, 152.2, 157.7. *Anal.* Calcd. for $C_{34}H_{44}N_4O_3S_3$: C, 62.54; H, 6.79. Found: C, 62.46; H, 6.77.

1,10-Bis(8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7-dioxa-13,16-dithiacyclooctadecane (28) Ligand **28** (0.46 g, 58%) was synthesized from 0.38 g (1.3 mmol) of **15** and 0.43 g (2.7 mmol) of 8-hydroxyquinoline. It was isolated as **15** above to give a pure product with a low mp; ^{1}H NMR: δ 2.79 (m, 16H), 3.65 (m, 8H), 3.99 (s, 4H), 7.24 (m, 4H), 7.34 (q, J = 4.2 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 8.83 (dd, J = 1.4, 1.0 Hz, 2H); ^{13}C NMR: δ 29.1, 32.1, 53.2, 54.2, 57.0, 69.4, 70.7, 117.6, 118.9, 121.3, 128.0, 128.5, 135.8, 139.3, 148.9, 152.9; HRMS calcd. for $C_{32}H_{41}N_4O_4S_2$ $(M+H)^+$: 609.2572, found: 609.2559. *Anal.* Calcd. for $C_{32}H_{40}N_4O_4S_2$: C, 63.13; H, 6.62. Found: C, 62.91; H, 6.61.

1,10-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7-dioxa-13,16-dithiacyclooctadecane (29) Ligand **29** (0.56 g, 63%) was obtained from 0.41 g (1.4 mmol) of **15** and 0.47 g (2.9 mmol) of 5-methyl-8-hydroxyquinoline as a viscous liquid. A small amount of hexane was added and the mixture was ultrasonicated for 10 h. The product was collected as a white powder by filtration and dried; mp 59–60°C; ^{1}H NMR: δ 2.55 (s, 6H), 2.71–2.90 (m, 16H), 3.61–3.71 (m, 8H), 3.95 (s, 4H), 7.11 (s, 2H), 7.39 (q, J = 4.4 Hz, 2H), 8.20 (dd, J = 1.6, 1.6 Hz, 2H), 8.85 (dd, J = 1.4, 1.6 Hz, 2H); ^{13}C NMR: δ 18.0, 29.3, 32.4, 53.4, 54.5, 56.9, 69.7, 70.9, 121.1, 124.1, 127.7, 128.5, 132.7, 139.7, 148.6, 151.1, 179.4. *Anal.* Calcd. for $C_{34}H_{44}N_4O_4S_2$: C, 64.12; H, 6.96. Found: C, 63.88; H, 6.77.

1,10-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7-dioxa-13,16-dithiacyclooctadecane (30) Ligand **30** (0.64 g, 94%) was prepared from 0.41 g (1.4 mmol) of **15** and 0.53 g

(2.9 mmol) of 5-chloro-8-hydroxyquinoline. It was isolated as **29** above; mp 74–75°C; ^{1}H NMR: δ 2.73–2.89 (m, 16H), 3.63 (t, 8H), 3.97 (s, 4H), 7.39 (d, J = 2.8 Hz, 2H), 7.47 (q, J = 4.2 Hz, 2H), 8.43 (dd, J = 1.8, 1.4 Hz, 2H), 8.87 (d, J = 2.8 Hz, 2H); ^{13}C NMR: δ 29.4, 32.3, 53.4, 54.4, 56.5, 69.5, 70.9, 119.5, 120.2, 122.2, 126.2, 127.8, 133.0, 139.9, 149.5, 152.1. *Anal.* Calcd. for $C_{32}H_{38}Cl_2N_4O_4S_2$: C, 56.70; H, 5.66. Found: C, 56.53; H, 5.41.

1,10-Bis(2-methyl-8-hydroxyquinolin-7-ylmethyl)-1,10-diaza-4,7-dioxa-13,16-dithiacyclooctadecane (31) Ligand 31 (0.38 g, 35%) was prepared from 0.50 g (1.7 mmol) of **15** and 0.57 g (3.57 mmol) of 8-hydroxyquinaldine. It was isolated as **17** above to give a pure product with a low melting point; ^{1}H NMR: δ 2.75 (s, 6H), 2.78–2.90 (m, 16H), 3.59–3.71 (m, 8H), 3.99 (s, 4H), 7.22 (s, 4H), 7.27 (s, 2H), 7.94 (d, J = 8.6 Hz, 2H); ^{13}C NMR: δ 25.3, 29.1, 32.0, 53.0, 54.2, 56.5, 69.4, 70.5, 117.1, 118.7, 122.1, 126.4, 126.9, 135.7, 138.3, 151.8, 157.3. *Anal.* Calcd. for $C_{34}H_{44}N_4O_4S_2$: C, 64.12; H, 6.96. Found: C, 63.98; H, 6.79.

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