

Syntheses of diazadithiacrown ethers containing two 8-hydroxyquinoline side arms

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This paper is dedicated to Professor Miha Tišler to mark his 75th birthday and to acknowledge his dedication to synthetic heterocyclic chemistry
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Abstract

Ten new diazadithiacrown ethers containing two 8-hydroxyquinoline (HQ) sidearms attached through the HQ 7-positions and four new diazadithiacrown ethers containing two HQ sidearms attached through the HQ 2-positions have been prepared. Some of these new ligands also contain a hydroxymethyl substituent. The starting macrocyclic diazadithiacrown ethers were obtained by treatment of a bis(α -chloroamide) with the appropriate dimercaptan using K_2CO_3 as the base followed by reduction of the resulting macrocyclic dithiadamide by BH_3 -THF or by $NaBH_4$ in the presence of BF_3 -ether as a catalyst. HQ-containing ligands **23-32** were synthesized by a Mannich reaction of the secondary macrocyclic diamines with the substituted-8-hydroxyquinoline. HQ-containing ligands **33-36** were prepared by reductive amination of the secondary macrocyclic diamines with 8-hydroxyquinoline-2-carbaldehyde. The HQ-containing diazadithiacrown ethers which also contain a hydroxymethyl group on the macroring **23-29**, **33**, and **35** are more soluble in polar solvents than those without the hydroxymethyl group.

Keywords: Diazadithiacrown ethers, 8-hydroxyquinoline, Mannich reaction, hydroxymethyl substituents

Introduction

In general, the complexing ability and selectivity of lariat ethers for metal ions can be varied by changing certain parameters such as the acidity of the phenolic OH group; the size of the crown ether ring; type, number, and position of the complexing crown ether heteroatoms; the stereochemistry imposed by the arms which connect the phenolic group to the macro ring; and

the pH of media.¹ For example, diaza-18-crown-6 containing two 5-chloro-8-hydroxyquinoline (CHQ) groups attached through the CHQ 7-position (**1**, Figure 1) exhibits a stronger affinity for Mg^{2+} than for Ba^{2+} (log K value in MeOH for Mg^{2+} is 6.82, for Ba^{2+} 3.60) and its isomer, diaza-18-crown-6 bearing two CHQ groups attached through the CHQ 2-position **4**, has a stronger affinity for Ba^{2+} than for Mg^{2+} (log K value in MeOH for Ba^{2+} is 12.2).² Ligands **3** and **5**, the HQ analogs of **1** and **4**, respectively (**1** and **4** with the chlorine atoms removed), do not exhibit the same complexing properties as do **1** and **4**.³ Increasing the number of macroring nitrogen atoms and changing the size of macroring could change the affinity of the ligand toward the heavy metal ions. For example, for ligand **5**, the log K value in MeOH for Cu^{2+} is 4.39 while its tetraaza-15-crown-5 analog **6** has a log K value for Cu^{2+} of 15.5.⁴

Ligand **2**, which has a 5-nitro substituent on each 8-hydroxyquinoline, has a high affinity and selectivity for Hg^{2+} and has proven to be a chemosensor for Hg^{2+} .⁵ Diaza-18-crown-6 with two 4-methyl(or nitro)-6-aminophenol groups attached through the phenol 2-positions, **7** and **8** form dinuclear complexes with one Cu^{2+} complexed to the two 6-aminophenols and one Na^+ in the macroring cavity.⁶

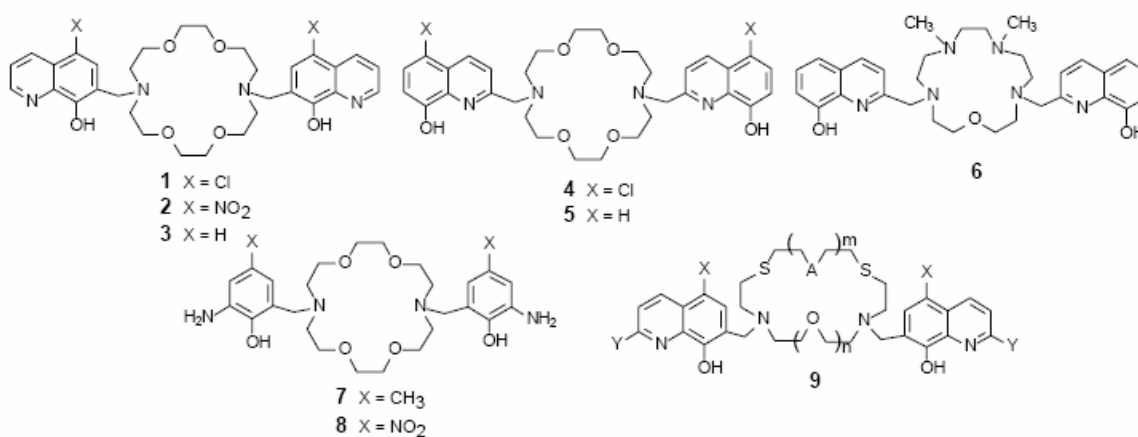


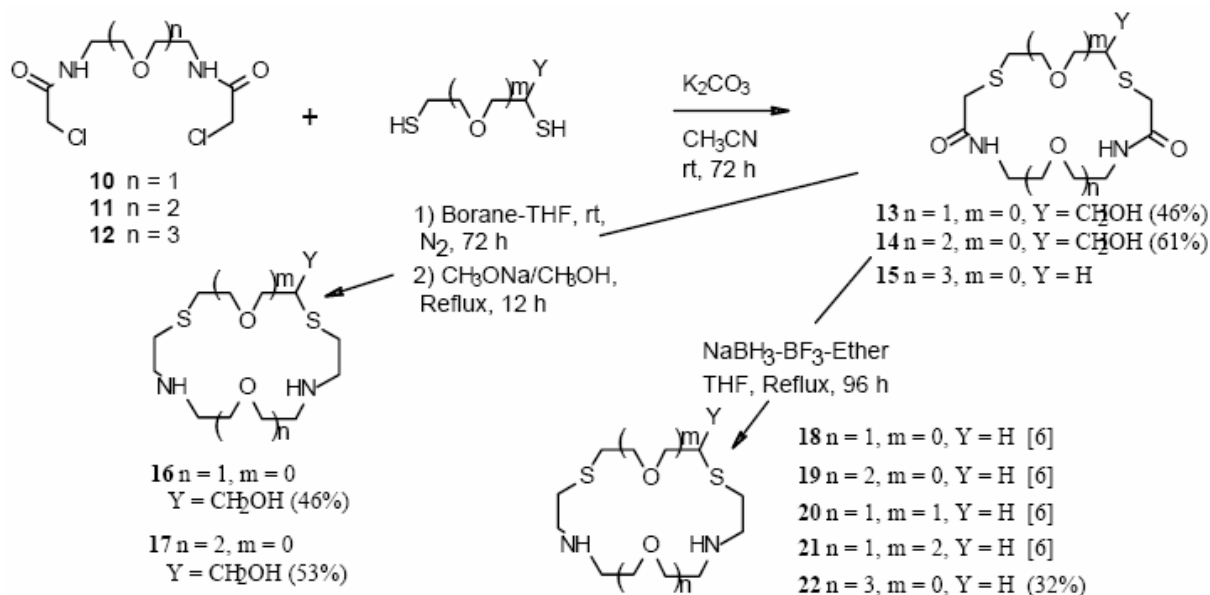
Figure 1. Compounds mentioned in the introduction.

Diazadithia (or trithia) crown ethers **9** containing two HQ side arms have also been synthesized.^{7,8} These new azathia ligands have poor solubilities in MeOH and, therefore, their complexing properties with metal ions cannot be conveniently studied. A few of ligands **9** have a hydroxymethyl substituent attached to the macro ring and are thereby more soluble in methanol. Herein, we report the synthesis of a series of new diazadithiacrown ethers bearing 5-substituent (or 2-methyl)-HQ side-arms. Some of these new ligands contain a hydroxymethyl group on the macroring. A report on the affinities of some of these new ligands for metal ions and their possible use as sensors for metal ions will be reported in due course.

Results and Discussion

The CHQ and HQ side arms are best attached to the diazadithiacrown ethers through macroring NH groups. Macrocyclic ligands containing two secondary amine functions have conveniently been prepared by treating diamines and dimercaptans with various bis(α -chloroamide)s.^{4,7,9-11} The NH functions of the secondary bis(α -chloroamide)s are unreactive toward alkylating agents including thiols.^{7,12} In the present case, bis(α -chloroamide)s **10-12** were treated with the appropriate dimercaptans using K₂CO₃ as the base to form macrocyclic diamides **13-15** in yields of 46%-61% as shown in Scheme 1. The macrocyclic diamides were in turn reduced to the desired diazadithiacrown ethers **16, 17**, and **22** by either B₂H₆-THF or the NaBH₄-BF₃-THF complex (Scheme 1). Ligands **18-21** shown in Scheme 1 were prepared as reported.⁷ Satisfactory elemental analyses were obtained for the new macrocyclic diamides or for new HQ and CHQ armed ligands **23-36** prepared from them.

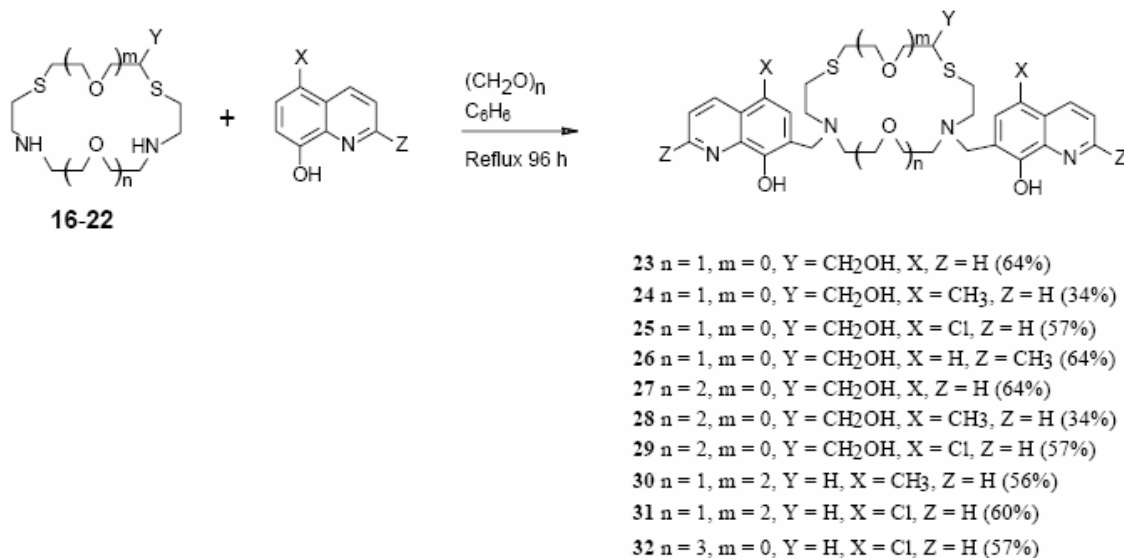
Mannich aminomethylation has been used to attach HQ and CHQ groups to the azacrown ethers through HQ and CHQ 7-positions.^{3,7,13-15} In the present case, the appropriate diazadithiacrown ether **16-22** and the appropriate HQ derivative were treated with paraformaldehyde in refluxing benzene in the one-step aminomethylation reaction^{3,7,16,17} to give the bis(2-or 5-substituted-8-quinolin-7-ylmethyl)-substituted ligands **23-32** (Scheme 2).



Scheme 1

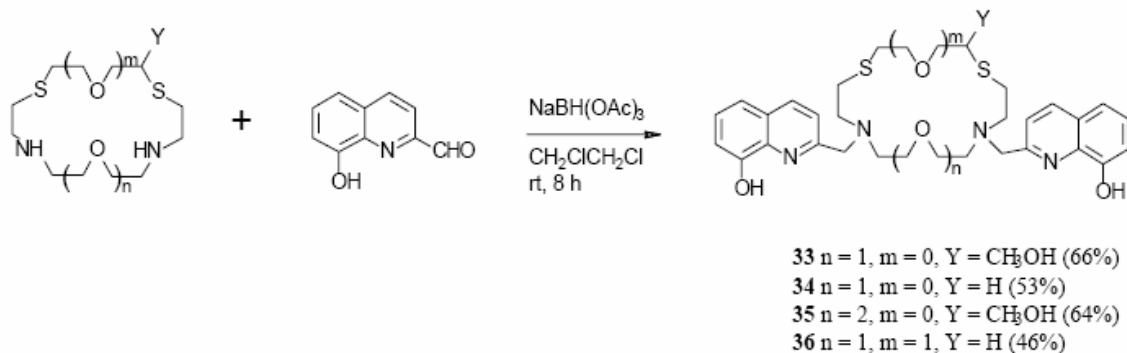
The products of the Mannich reaction of the diazadithiacrown ethers with HQ (**23** and **27**) and 8hydroxyquinaldine (**26**) were mixtures. Each of these two starting materials has no substituent on the quinoline 5-position. Thus, both the 5 and 7 positions could be aminomethylated under these reaction conditions. Although we did not look for the side products

in these reactions, we recently showed by a careful ^1H NMR analysis that when diazatrithiacrown ether **18** was treated with 8-hydroxyquinoline, the product mixture proved to be about 90% of the desired product where both quinoline substituents were attached through the 8-hydroxyquinoline 7-position, about 9% of the product with one 8-hydroxyquinoline attached through its 7-position and the other through its 5-position and the remaining product had both 8-hydroxyquinoline groups attached through their 5-positions. Thus, we suspect that products **23**, **26** and **27** are mixtures where the HQ groups are attached through their 7-and 5-positions.



Scheme 2

HQ has been attached to diaza-18-crown-6³ and a series of tetraaza-15 (and 16)-crown-5 ligands⁴ through the HQ 2-position by a reductive amination process using $\text{NaBH}(\text{OAc})_3$.¹⁸ In the present case, 8-hydroxyquinoline-2-carbaldehyde and the appropriate ligand (**16-18** or **20**) were treated with $\text{NaBH}(\text{OAc})_3$ to form the bis(8-hydroxyquinolin-2-ylmethyl)-substituted ligands **33-36** in yields of 46% -66% (Scheme 3). It is important to note that the hydroxy group of HQ did not have to be protected for this reaction as previously reported.⁴



Scheme 3

Experimental Section

General Procedures. The ^1H and ^{13}C NMR spectra were recorded on 200 or 300 MHz in deuteriochloroform. Solvents and starting materials were purchased from commercial sources where available. Bis (α -chloroamides) **10-12**⁴ and diazadithiacrown ethers **18-21**⁷ were prepared as reported.

General procedure A to prepare macrocyclic diamides **13-15** (Scheme 1)^{4,7}

A mixture of bis(α -chloroamide), an equivalent of the dithiol, a 4 fold excess of anhydrous K_2CO_3 and CH_3CN [350 mL/ 0.1 mol of the bis(α -chloroamide)] 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, $\text{C}_2\text{H}_4\text{Cl}_2 : \text{MeOH} : \text{NH}_4\text{OH} = 80 : 10 : 1$).

11-Hydroxymethyl-1,7-diaza-4-oxa-10,13-dithiacyclopentadecan-8,15-dione (13). Macrocyclic diamide **13** (2.78 g, 46%) was synthesized from 2.42 g (1.95 mmol) of 1,2-dimercapto-3-propanol and 5.01 g (1.95 mmol) of bis (α -chloroamide) **10** according to general procedure A; mp 132-133.5 °C; ^1H NMR: δ 2.82-3.00 (m, 3H), 3.28 (m, 2H), 3.36 (s, 2H), 3.47-3.61 (m, 8H), 3.71-3.91 (m, 2H); ^{13}C NMR: 34.55, 35.55, 37.31, 39.59, 49.32, 61.69, 69.93, 70.13, 70.54, 169.19; HRMS calcd for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_2(\text{M}+\text{H})^+$ 309.0944, found 309.0938.

14-Hydroxymethyl-1,10-diaza-4,7-dioxa-13,16-dithiacloctadecan-11,18-dione (14). Macrocyclic diamide **14** (8.65 g, 61%) was obtained from 4.96 g (40.0 mmol) of 1,2-dimercapto-3-propanol and 12.04 g (40.0 mmol) of bis(α -chloroamide) **11** according to general procedure A; mp 98.5-99.5 °C; ^1H NMR: δ 2.86 (s, 3H), 3.31 (m, 4H), 3.73 (m, 12H), 3.92 (m, 2H); ^{13}C NMR: δ 34.50, 35.49, 37.24, 39.51, 49.22, 61.67, 69.80, 70.00, 70.34, 70.43, 168.77, 168.96; HRMS calcd for $\text{C}_{13}\text{H}_{25}\text{N}_2\text{O}_5\text{S}_2(\text{M}+\text{H})^+$ 353.1207, found 353.1216.

1,13-Diaza-4,7,10-trioxa-16,19-dithiacycloheneicosan-14,21-dione (15). Macrocyclic dithiadiamide **15** (8.76g, 60%) was synthesized from 3.77 g (40.0 mmol) of 1,2-ethanedithiol and 13.80 g (40.0 mmol) of bis(α -chloroamide) **12**; mp 106-106.5 °C; ^1H NMR: δ 2.81 (s, 4H), 3.27

(s, 4H), 3.49-3.66 (m, 16H); ^{13}C NMR: δ 32.71, 36.30, 39.57, 69.65, 70.63, 70.82, 168.68; HRMS calcd for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5\text{S}_2\text{Na}(\text{M})^+$ 389.1147, found 389.1186; Anal. Calcd. for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5\text{S}_2$: C, 45.88; H, 7.15. Found C, 45.62; H, 7.03.

General procedure B to synthesize crown ethers (16) and (17)^{4,7} (Scheme 1)

To a solution of 10.0 mmol of macrocyclic diamide in 30 mL of dry THF was added 80 mL of a solution of borane in THF (1 mol per liter of THF). The mixture was stirred for 72 h at room temperature and the solvent was evaporated under reduced pressure. To this residue was added a dilute solution of NaOMe in MeOH, and the mixture was refluxed overnight. After the MeOH was evaporated, some water was added and the mixture was extracted several times by portions of CHCl_3 until all the product was extracted from the water. The combined CHCl_3 extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product which was purified by chromatography on silica gel (eluent: CH_2Cl_2 : MeOH: NH_4OH = 50 : 5 : 1).

11-Hydroxymethyl-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (16). Ligand **16** (2.33 g, 46%) was obtained as a low melting solid by the reduction of 2.96 g (9.6 mmol) of **13** with 38 mL of borane-THF complex in 30 mL of THF according to general procedure B; ^1H NMR: δ 2.79-2.89 (m, 15H), 3.59-3.65 (m, 6H); HRMS calcd for $\text{C}_{11}\text{H}_{25}\text{N}_2\text{O}_2\text{S}_2(\text{M}+\text{H})^+$ 281.1357, found 281.1352. Anal. calcd for $\text{C}_{11}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2$: C, 47.11; H, 8.63. Found C, 47.27; H, 8.73.

14-Hydroxymethyl-1,10-diaz-4,7-dioxa-13,16-dithiacyclootadecane (17). Macrocyclic ether **17** (0.51 g, 53%) was obtained as an oil by the reduction of 1.05 g (3.0 mmol) of **14** with 10 mL of borane-THF in 10 mL of THF according to general procedure B; ^1H NMR: δ 2.83 (m, 15H), 3.64 (m, 8H), 3.78 (m, 2H); ^{13}C NMR: δ 31.85, 33.37, 35.08, 48.37, 49.06, 49.23, 49.31, 64.46, 70.02, 70.15, 70.34, 70.40; HRMS Calcd. for $\text{C}_{13}\text{H}_{28}\text{N}_2\text{O}_3\text{S}_2\text{Na}^+$ 347.2173, found 347.2178.

1,13-Diaza-4,7,10-trioxa-16,19-dithiacycloheicosane (22). A solution of 2.56 g (7.0 mmol) of **15** and 2.64 g (70 mmol) of NaBH_4 in 100 mL of THF was stirred at 0-5 °C and 13.2 g (93 mmol) of $\text{BF}_3\text{-Et}_2\text{O}$ was added over a 3-hour period. The mixture was allowed to warm to room temperature and water was slowly added until H_2 stopped evolving. The mixture was neutralized with aqueous 20% NaOH to pH of 8 or 9. The THF was evaporated and the aqueous solution was extracted 3 times with 20 mL portions of CH_2Cl_2 . The combined extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by chromatography on silica gel (CH_2Cl_2 : MeOH: NH_4OH = 50 : 5 : 1) to give 0.76 g (32%) of **22**; ^1H NMR: δ 2.76-2.82 (m, 16H), 3.60-3.70 (m, 12H); ^{13}C NMR: δ 32.19, 32.47, 48.99, 49.03, 70.37, 70.41, 70.79; HRMS calcd for $\text{C}_{14}\text{H}_{30}\text{N}_2\text{O}_3\text{S}_2(\text{M})^+$ 338.1699, found 338.1691; Anal. Calcd. for $\text{C}_{14}\text{H}_{30}\text{N}_2\text{O}_3\text{S}_2$ 1/2 CH_2Cl_2 : C, 45.71; H, 8.20; found C, 45.82; H, 8.23.

General procedure C for the synthesis of diazadithiacrown ethers with two 5-substituent-8-hydroxyquinoline(or 8-hydroxyquinaldine) sidearms 23-32 (Scheme 2)

A solution of 45 mL of anhydrous benzene, 2.0 mmol of the macrocyclic ether, 4.2 mmol of the 5-substituent-8-hydroxyquinoline(or 8-hydroxyquinaldine) and paraformaldehyde (0.135 g, 4.5 mmol) was refluxed for 15 h. The solvent was evaporated under reduced pressure and the

mixture was separated by silica gel chromatography (CH₂Cl₂: MeOH: NH₄OH = 50 : 5 : 1).

1,7-Bis(8-hydroxyquinolin-7-ylmethyl)-11-hydroxymethyl-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (23). Ligand **23** (1.01 g, 65%) was isolated as a viscous liquid from 0.73 g (2.6 mmol) of **16** and 0.83 g (5.7 mmol) of 8-hydroxyquinoline. A small amount of hexane was added to the product and the mixture was ultrasonicated for 3 h. After most of hexane was decanted, the remaining hexane was evaporated under reduced pressure to give a low melting solid; ¹H NMR: δ 2.56-2.85(m, 15H), 3.67 (t, *J*=4.6 Hz, 4H), 3.90-4.08 (m, 6H), 7.28 (s, 4H), 7.38 (q, *J*=4.0 Hz, 2H), 8.08 (dd, *J*=1.6, 1.4 Hz, 2H), 8.87 (dd, *J*=1.4, 1.6 Hz, 2H); ¹³C NMR: δ 28.87, 29.87, 34.82, 49.01, 53.42, 53.52, 54.84, 55.60, 56.12, 56.54, 64.47, 69.66, 70.01, 119.58, 120.27, 122.28, 126.24, 127.74, 127.84, 133.14, 139.76, 149.51, 151.95, 152.09; HRMS Calcd. for C₃₁H₃₉N₄O₄S₂(M+H)⁺ 595.2415, found 595.2411; Anal. calcd for C₃₁H₃₈N₄O₄S₂: C, 62.60; H, 6.44. Found: C, 62.35; H, 6.27.

1,7-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-11-hydroxymethyl-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (24). Ligand **24** (0.32 g, 34%) was obtained from 0.42 g (1.5 mmol) of **16** and 0.51 g (3.2 mmol) of 5-methyl-8-hydroxyquinoline. The product was purified as **23** above to give a low melting solid; ¹H NMR: δ 2.56 (s, 6H), 2.78-2.96 (m, 15H), 3.63 (t, *J*=3.6 Hz, 6H), 3.94 (m, 4H), 7.11 (d, *J*=4.4 Hz, 2H), 7.40 (q, *J*=4.2 Hz, 2H), 8.21 (dd, *J*=1.2, 1.6 Hz, 2H), 8.85 (dd, *J*=1.2, 1.2 Hz, 2H); ¹³C NMR: δ 18.06, 28.90, 29.73, 34.83, 48.96, 53.31, 54.46, 54.82, 55.64, 56.53, 56.95, 64.49, 69.88, 70.28, 118.43, 121.01, 123.99, 127.58, 128.28, 128.39, 132.70, 139.54, 148.44, 150.90, 150.99; HRMS calcd for C₃₃H₄₃N₄O₄S₂(M+H)⁺ 623.2726, found 623.2740; Anal. Calcd. for C₃₃H₄₂N₄O₄S₂: C, 63.64; H, 6.80. Found C, 65.03; H, 6.86.

1,7-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-11-hydroxymethyl-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (25). Ligand **25** (0.76 g, 57 %) was prepared from 0.56 g (2.0 mmol) of **16** and 0.75 g (4.2 mmol) of 5-chloro-8-hydroxyquinoline as **23** above; mp 133.5-134.5 °C; ¹H NMR: δ 2.77-3.08 (m, 15H), 3.61(t, *J*=3.4 Hz, 6H), 3.95 (s, 4H), 7.44 (d, *J*=10.2 Hz, 2H), 7.50 (q, *J*=3.8 Hz, 2H), 8.46 (dd, *J*=1.8, 1.8 Hz, 2H), 8.90 (dd, *J*=1.5, 1.5 Hz, 2H); HRMS calcd for C₃₁H₃₇Cl₂N₄O₄S₂(M+H)⁺ 663.1637, found 663.1615; Anal. calcd for C₃₁H₃₆Cl₂N₄O₄S₂: C, 56.10; H, 5.47. Found: C, 55.92; H, 5.61

1,7-Bis(2-methyl-8-hydroxyquinolin-7-ylmethyl)-11-hydroxymethyl-1,7-diaza-4-oxa-10,13-dithiacyclopentadecane (26). Compound **26** (0.26 g, 64%) was obtained as a low melting solid from 0.28 g (1.0 mmol) of **16** and 0.33 g (2.1 mmol) of 8-hydroxyquinaldine as **23** above; ¹H NMR: δ 2.78 (s, 6H), 2.85-3.10 (m, 15H), 3.61-3.80 (m, 6H), 3.86-3.98 (m, 4H), 7.23 (d, *J*=3.7 Hz, 4H), 7.28 (d, *J*=1.6 Hz, 2H), 8.00 (d, *J*=8.6 Hz, 2H); ¹³C NMR: δ 25.43, 25.50, 28.79, 29.61, 34.77, 48.81, 53.14, 53.36, 54.84, 55.82, 56.41, 56.85, 64.73, 69.92, 70.42, 117.53, 119.07, 122.53, 126.83, 127.24, 127.35, 136.23, 138.71, 152.22, 157.99; Anal. calcd for C₃₃H₄₂N₄O₄S₂: C, 63.64; H, 6.80. Found: C, 63.76; H, 6.68.

1,10-Bis(8-hydroxyquinolin-7-ylmethyl)-14-hydroxymethyl-1,10-diaza-4,7-dioxa-13,16-dithiacyclooctadecane (27). Ligand **27** (0.72 g, 64%) was obtained from 0.65 g (2.0 mmol) of **17** and 0.61 g (4.2 mmol) of 8hydroxyquinoline. It was purified as **23** above to give a low melting solid; ¹H NMR: δ 2.70-2.95 (s, 15H), 3.62-3.65 (m, 10H), 3.95 (d, 4H), 7.27 (s, 4H),

7.38 (q, $J=4.0$ Hz, 2H), 8.06 (dd, $J=1.6, 1.4$ Hz, 2H), 8.86 (dd, $J=1.4, 1.6$ Hz, 2H); HRMS for $C_{33}H_{43}N_4O_5S_2(M+H)^+$ 639.2675, found 639.2666; Anal. calcd for $C_{33}H_{42}N_4O_5S_2$: C, 62.04; H, 6.63. Found: C, 61.88; H, 6.45.

1,10-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-14-hydroxymethyl-1,10-diaza-4,7-dioxo-13,16-dithiacyclooctadecane (28). Ligand **28** (0.98 g, 94%) was synthesized from 0.51 g (1.57 mmol) of **17** and 0.52 g (3.30 mmol) of 5-methyl-8-hydroxyquinoline as a viscous liquid. The product was purified as **23** above to give a white powder; mp 59-60 °C; 1H NMR: δ 2.55 (s, 6H), 2.74-2.99 (m, 15H), 3.61-3.63 (m, 10H), 3.94 (d, 4H), 7.10 (d, $J=3.3$ Hz, 2H), 7.38 (q, $J=4.2$ Hz, 2H), 8.20 (d, $J=5.4$ Hz, 2H), 8.85 (t, $J=2.4$ Hz, 2H); HRMS calcd for $C_{35}H_{47}N_4O_5S_2(M+H)^+$ 667.2991, found 667.2997; Anal. Calcd. for $C_{35}H_{46}N_4O_5S_2$: C, 63.03; H, 6.95. Found: C, 62.89; H, 7.13.

1,10-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-14-hydroxymethyl-1,10-diaza-4,7-dioxo-13,16-dithiacyclooctadecane (29). Ligand **29** (0.31 g, 28%) was prepared from 0.51 g (1.57 mmol) of **17** and 0.59 g (3.30 mmol) of 5-chloro-8-hydroxyquinoline as a viscous liquid. It was purified as **23** above; 1H NMR: δ 2.76-3.02 (m, 15H), 3.67-3.73 (m, 10H), 3.99 (d, 4H), 7.43 (d, $J=2.6$ Hz, 2H), 7.49 (q, $J=4.0$ Hz, 2H), 8.47 (dd, $J=2.0, 1.6$ Hz, 2H), 8.89 (dd, $J=1.4, 1.8$ Hz, 2H); HRMS calcd for $C_{33}H_{41}Cl_2N_4O_5S_2(M+H)^+$ 707.1899, found 707.1880; Anal. calcd for $C_{33}H_{40}Cl_2N_4O_5S_2$: C, 56.00; H, 5.70. Found: C, 56.12; H, 5.58.

1,7-Bis(5-methyl-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4,13,16-trioxo-10,19-dithiacycloheneicosane (30). According to general procedure C, ligand **30** (56%) was synthesized from **21** and 5-methyl-8-hydroxyquinoline as a viscous liquid. It was treated as **23** above; 1H NMR: δ 2.55 (s, 6H), 2.72 (t, $J=6.2$ Hz, 4H), 2.90 (m, 12H), 3.66 (m, 12H), 3.94 (s, 4H), 7.03 (s, 2H), 7.38 (q, $J=4.0$ Hz, 2H), 8.20 (dd, $J=1.4, 1.4$ Hz, 2H), 8.86 (dd, $J=1.4, 1.4$ Hz, 2H); ^{13}C NMR: δ 17.97, 29.47, 31.48, 53.06, 54.55, 56.43, 69.50, 70.67, 71.79, 118.36, 120.83, 123.81, 127.43, 128.22, 132.49, 139.52, 148.31, 150.98; Anal. calcd for $C_{36}H_{48}N_4O_5S_2$: C, 63.50, H, 7.11. Found: C, 63.32, H, 7.28.

1,7-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,7-diaza-4,13,16-trioxo-10,19-dithiacycloheneicosane (31). According to general procedure C, ligand **31** (60%) was synthesized from 0.51 g (1.5 mmol) of **21** and 5-chloro-8-hydroxyquinoline as a viscous liquid; 1H NMR: δ 2.73 (t, $J=6.2$ Hz, 4H), 2.92 (m, 12H), 3.67 (m, 12H), 3.98 (s, 4H), 7.41 (s, 2H), 7.48 (m, 2H), 8.45 (dd, $J=1.6, 1.4$ Hz, 2H), 8.90 (dd, $J=1.4, 1.4$ Hz, 2H); ^{13}C NMR: δ 29.44, 31.40, 52.98, 54.41, 55.99, 69.27, 70.58, 71.75, 119.37, 119.88, 121.93, 125.91, 127.51, 132.72, 139.57, 149.18, 151.92; Anal. calcd for $C_{34}H_{42}Cl_2N_4O_5S_2$: C, 56.58, H, 5.87. Found: C, 56.76, H, 5.69.

1,13-Bis(5-chloro-8-hydroxyquinolin-7-ylmethyl)-1,13-diaz-4,7,10-trioxo-16,19-dithiacycloheneicosane (32). Ligand **32** (57%) was isolated as a viscous liquid from macrocyclic diamine **22** and 5-chloro-8-hydroxyquinoline; 1H NMR: δ 2.77-2.99 (m, 16H), 3.67-3.71 (m, 12H), 3.97 (s, 4H), 7.41(s, 2H), 7.49 (q, $J=4.4$ Hz, 2H), 8.46 (dd, $J=1.4, 1.4$ Hz, 2H), 8.90 (dd, $J=1.4, 1.8$ Hz, 2H); ^{13}C NMR: δ 29.31, 31.76, 32.33, 53.17, 54.42, 56.53, 69.61, 70.89, 119.48, 120.19, 122.18, 126.17, 127.75, 133.00, 139.81, 149.41, 152.06; HRMS Calcd. for

$C_{34}H_{43}Cl_2N_4O_5S_2(M+H)^+$ 721.2056, found 721.2042; Anal. calcd for $C_{34}H_{42}Cl_2N_4O_5S_2$: C, 56.58, H, 5.87, found. C, 56.38, H, 6.00.

General procedure D for the reductive amination of azathiacrown ethers with 8-Hydroxyquinoline-2-carbaldehyde^{3,4} to form ligands 33-36 (Scheme 3)

The crown ether (3.0 mmol) and 1.08 g (6.3 mmol) of 8-hydroxyquinoline-2-carbaldehyde were added to 60 mL of 1,2-dichloroethane and the mixture was stirred at room temperature for 30 min. $NaBH(OAc)_3$ (1.92 g, 9.0 mmol) was added and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (50 mL) was then added to quench the reaction. The aqueous and organic layers were separated and the aqueous layer was extracted three times with 20 mL portions of CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 . The solvent was evaporated under reduced pressure and the product was separated by silica gel chromatography (CH_2Cl_2 : MeOH : NH_4OH = 80 : 5 : 1).

1,7-Bis(8-hydroxyquinolin-2-ylmethyl)-11-hydroxymethyl-1,7-diaza-4-oxa-10,13-

dithiacyclooctadecane (33). Ligand **33** (1.18 g, 66%) was prepared from **16** according to general procedure D. The crude product was purified by chromatography; mp 140.5-142.0 °C; 1H NMR: δ 2.80-3.08(m, 15H), 3.54 (m, 6H), 3.96 (s, 4H), 7.16 (d, $J=5.0$ Hz, 2H), 7.31 (s, 2H), 7.41 (t, $J=7.6$ Hz, 2H), 7.61(t, $J=8.4$ Hz, 2H), 8.12 (d, $J=8.4$ Hz, 2H); ^{13}C NMR: δ 29.29, 30.47, 35.42, 48.59, 54.26, 55.62, 55.96, 61.45, 64.25, 70.36, 70.57, 110.50, 117.72, 121.96, 127.45, 127.65, 136.58, 152.22, 152.46, 158.03; HRMS calcd for $C_{31}H_{39}N_4O_4S_2(M+H)^+$ 595.2415, found 595.2419; Anal. Calcd. for $C_{31}H_{38}N_4O_4S_2$: C, 62.60; H, 6.44. Found: C, 62.67; H, 6.30.

1,10-Bis(8-hydroxyquinolin-2-ylmethyl)-1,10-diaza-4,7-dioxa-13,16-dithia-cyclooctadecane

(34). Ligand **34** (53%) was synthesized from **18** as a viscous liquid according to procedure D. It was treated as **23** above to give a low melting solid; 1H NMR: δ 2.84 (m, 16H), 3.60 (s, 8H), 3.97 (s, 4H), 7.12 (d, $J=6$ Hz, 2H), 7.39 (m, 2H), 7.65 (m, 4H), 8.09 (m, 2H); HRMS Calcd. for $C_{32}H_{41}N_4O_4S_2(M+H)^+$ 609.2572, found 609.2560; Anal. calcd for $C_{32}H_{40}N_4O_4S_2$: C, 63.13; H, 6.62. Found: C, 62.92; H, 6.86.

1,10-Bis(8-hydroxyquinolin-2-ylmethyl)-14-Hydroxymethyl-1,10-diaza-4,7-dioxa-13,16-

dithiacyclooctadecane (35). Compound **35** (64%) was obtained as a viscous liquid from **17** according to general procedure D. CH_2Cl_2 (1 mL) was added to dissolve the crude product, then 15 mL of hexane was added and the product was purified as **23** above to obtain a low melting solid; 1H NMR: δ 2.84-3.00 (m, 15H), 3.61-3.66 (m, 8H), 3.96 (m, 6H), 7.17 (d, $J=6.8$ Hz, 2H), 7.30 (t, $J=1.8$ Hz, 2H), 7.41 (d, $J=7.8$ Hz, 2H), 7.53 (m, 2H), 8.08 (dd, $J=2.6, 2.2$ Hz, 2H); ^{13}C NMR: δ 29.22, 30.50, 35.35, 48.91, 54.21, 54.32, 55.40, 55.78, 61.71, 64.31, 65.02, 69.91, 70.05, 70.71, 110.42, 110.80, 117.67, 119.40, 121.85, 121.98, 127.41, 127.50, 127.74, 127.80, 136.61, 136.66, 137.67, 137.96, 152.39, 152.81, 157.37, 158.08; HRMS for $C_{33}H_{43}N_4O_5S_2(M+H)^+$ 639.2678, found 639.2682; Anal. Calcd. for $C_{33}H_{42}N_4O_5S_2$: C, 62.04; H, 6.63. Found: C, 61.88; H, 6.45.

1,7-Bis(8-hydroxyquinolin-2-ylmethyl)1,7-diaza-4,13-dioxa-10,16-dithiacyclootadecane

(**36**). Ligand **36** (46%) was synthesized from **20** according to procedure D; ^1H NMR: 2.73-2.92 (m, 16H), 3.47-3.55 (m, 4H), 3.66-3.72 (m, 4H), 3.96 (s, 4H), 7.12 (dd, $J=1.2, 1.4$ Hz, 2H), 7.27 (m, 2H), 7.37 (dd, $J=2.8, 2.6$ Hz, 2H), 7.64 (dd, $J=3.0, 2.6$ Hz, 2H), 8.06 (dd, $J=2.6, 2.6$ Hz, 2H); ^{13}C NMR: δ 30.37, 31.67, 53.81, 55.00, 61.51, 69.91, 71.87, 110.14, 117.68, 121.97, 127.28, 127.63, 136.51, 137.49, 152.19, 158.28; Anal. calcd for $\text{C}_{32}\text{H}_{40}\text{N}_4\text{O}_4\text{S}_2$: C, 63.13; H, 6.62. Found: C, 62.95; H, 6.61.

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