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Synthesis of a new class of azathia crown macrocycles containing two 1,2,4-triazole or two 1,3,4-thiadiazole rings as subunits

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ABSTRACT

A series of new 1,2/1,3-bis[*o*-(*N*-methylidenamino-5-aryl-3-thiol-4*H*-1,2,4-triazole-4-yl)phenoxy]alkane derivatives **3a–d** and bis[*o*-(*N*-methylidenamino-2-thiol-1,3,4-thiadiazole-5-yl)phenoxy]alkanes **6a–c** were prepared by condensation of 4-amino-5-(aroyl)-4*H*-1,2,4-triazole-3-thiols **2a–b** or 2-amino-5-mercapto-1,3,4-thiadiazole with bis-aldehydes **1a–c**. Further reaction of compounds **3a–d** and **6a–c** with dibromoalkanes afforded the new macrocycles **5a–f** and **8a–d**. The cyclization does not require high dilution techniques and provides the expected azathia macrocycles in good yields, ranging from 55% to 68%.

1. Introduction

Recently, much attention has been focused on 1,2,4-triazole and 1,3,4-thiadiazole derivatives due to their broad-spectrum activities such as antitumor, analgesic, anticancer, anti-inflammatory, and antibacterial activities.[1–5] Schiff base derivatives of 1,2,4-triazoles and their reduced derivatives have also been found to possess pharmacological activities.[6–8]

Crown ethers were discovered by Pederson at DuPont.[9] Since then, various structural changes have been made to the basic crown ether structures in an attempt to enhance the selectivity of these ligands and the stability of the complexes formed with both metal and organic cations. These changes involve substitution of the polyether ligand-containing oxygen donor atoms by sulfur and/or nitrogen atoms.[10] The incorporation of oxygen, nitrogen, and sulfur donor atoms in the macrocycles will also markedly affect their complexing properties because of the hard (O, N) and soft (S) character of the donor atoms and the exodentate tendency of the sulfide linkages.[11] Other changes involve the insertion of aromatic and/or heterocyclic ring systems into the macrocycles;[12] heterocyclic groups provide rigidity, and in some cases are able to form complexes through their soft donor atoms.[13] The wide interest in the construction of synthetic macrocyclic compounds containing five- and six-membered heterocyclic rings as subunits has led to the preparation of a range of such compounds which have been shown to possess very interesting properties in a variety of fields.[12] These macrocycles were found to exhibit interesting host–guest complexation characteristics,[14] and have shown antibacterial activities,[15] in which the biological activity is highly dependent upon the side chain substitution pattern. These properties prompted us to synthesize some new bis-Schiff-base derivatives and a series of 20–24-membered macrocycles fused with two 1,2,4-triazole or two 1,3,4-thiadiazole rings.

Recently, Abbas[16] reported the synthesis of azathia crown ethers by reacting a bis-triazole with a bis-aldehyde in acetic acid under high dilution conditions (the high dilution technique is the most versatile procedure for the synthesis of macrocycles[17]). On the other hand, Sharghi[18] and others[19–22] reported the synthesis of macrocycles without the use of high dilution techniques. In this Letter, we demonstrate a new method to introduce 1,2,4-triazole or 1,3,4-thiadiazole rings into macrocycles employing novel precursors **3** and **6** (Schemes 1 and 2) without using high dilution conditions.

The macrocyclization step in this method involves the reaction of bis[*o*-(*N*-methylidenamino-5-aryl-3-thiol-4*H*-1,2,4-triazole-4-yl)phenoxy]alkane derivatives **3a–d** or bis[*o*-(*N*-methylidenamino-2-thiol-1,3,4-thiadiazole-5-yl)phenoxy]alkanes **6a–c** with the appropriate dibromoalkanes as shown in Schemes 1 and 2. Two strategies were attempted for the synthesis of macrocycles **5a–f**. In the first strategy, bis-triazoles were chosen as the starting material as described by Elwahy and coworkers.[23] During the *S*-alkylation, which gave 18–20% yields of the target bis-triazoles, we observed (TLC monitoring) the formation of oxadiazoles as secondary products. This may be attributed to reaction of the hydroxyl group with the aminotriazoles giving the oxadiazole compounds

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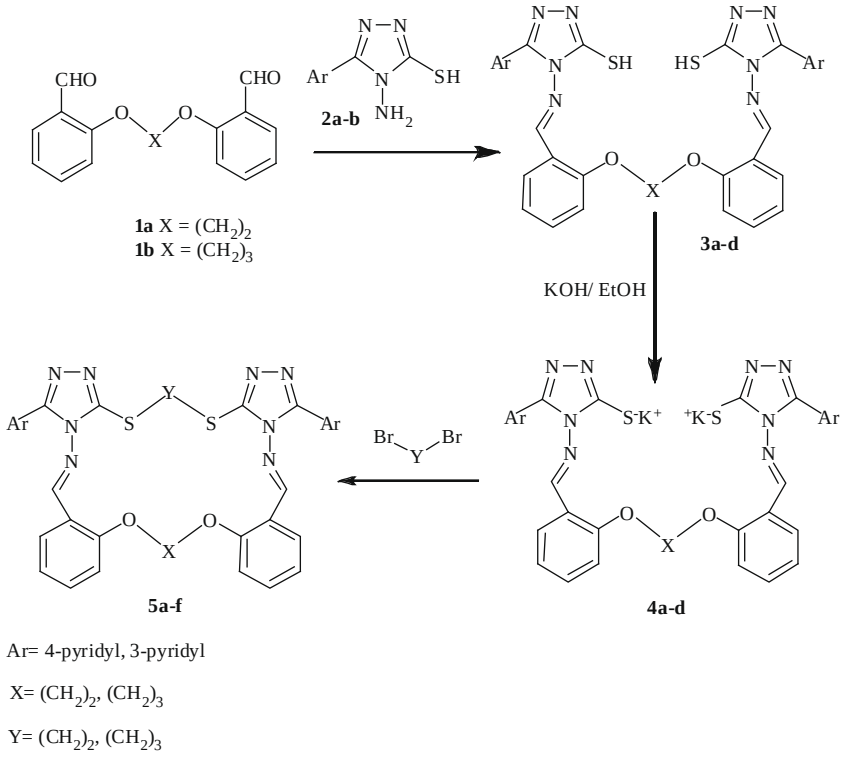
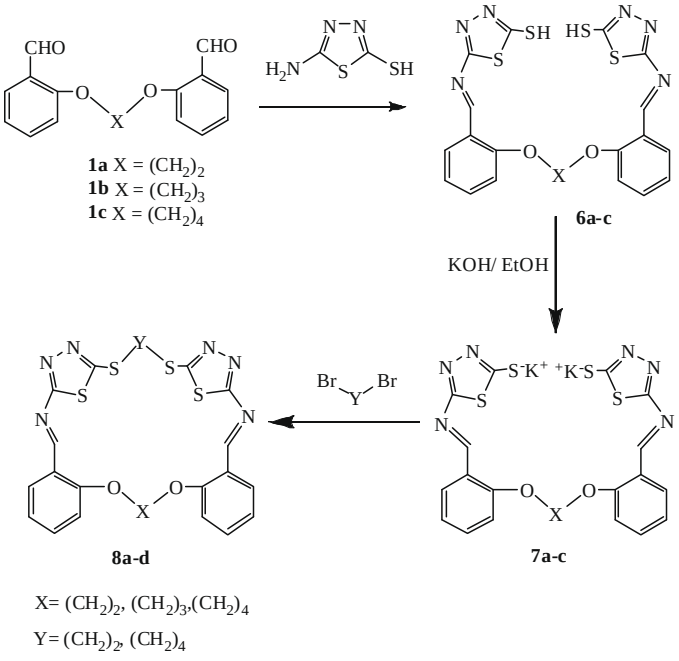


Scheme 1.



Scheme 2.

(as by-products) as reported in the literature.[24] We next applied the second strategy as outlined in Scheme 1.

Reaction of bis-aldehydes **1a–b**[25] with 4-amino-5-(aroyl)-4*H*-1,2,4-triazole-3-thiols **2a–b**[26] in acetic acid under reflux for 3 h afforded the corresponding 1,2/1,3-bis[*o*-(*N*-methylidenamino-5-aryl-3-thiol-4*H*-1,2,4-triazole-4-yl) phenoxy]alkanes **3a–d** as reported in Table 1. The products were obtained in reasonable yields. Next, potassium salts **4a-d** (obtained upon treatment of compounds **3a–d** with hot ethanolic potassium hydroxide solution) were reacted with the appropriate dibromoalkanes in DMF under reflux to give the azathia macrocycles **5a–f** in good yields as reported in Table 2.

Table 1
Schiff base compounds **3a–d**

Product	Ar	X	Yield (%)
3a	4-Pyridyl	$(CH_2)_2$	68
3b	3-Pyridyl	$(CH_2)_2$	68
3c	4-Pyridyl	$(CH_2)_3$	70
3d	3-Pyridyl	$(CH_2)_3$	66

As an extension of this study, we reacted 2-amino-5-mercapto-1,3,4-thiadiazole with bis-aldehydes **1a–c**[25] to give Schiff bases **6a–c**. The potassium salts **7a–c**, prepared as before, were reacted with dibromoalkanes of general formula $Br(CH_2)_nBr$ ($n = 2–4$) to give the macrocycles **8a–d** in reasonable yields as reported in Table 3.

The IR spectra of the 4-amino-5-(aroyl)-4*H*-1,2,4-triazole-3-thiols **2a–b** showed absorption bands at 3230 and 3400 cm^{-1} due to the NH_2 group, which were absent in the IR spectra of the bis [*o*-(*N*-methylidenamino-5-aryl-3-thiol-4*H*-1,2,4-triazole-4-yl)phenoxy]alkanes **3a–d**. Similarly, the ^1H NMR spectra of **2a–b** showed a

Table 2
Azathia crown ethers **5a–f**

Product	Ar	X	Y	Yield (%)
5a	4-Pyridyl	$(CH_2)_2$	$(CH_2)_2$	61
5b	3-Pyridyl	$(CH_2)_2$	$(CH_2)_2$	62
5c	4-Pyridyl	$(CH_2)_3$	$(CH_2)_3$	58
5d	3-Pyridyl	$(CH_2)_3$	$(CH_2)_3$	60
5e	4-Pyridyl	$(CH_2)_3$	$(CH_2)_2$	68
5f	3-Pyridyl	$(CH_2)_3$	$(CH_2)_2$	65

Table 3
Schiff bases **6a–c** and azathia crown ethers **8a–d**

Product	X	Y	Yield (%)
6a	$(CH_2)_2$	—	70
6b	$(CH_2)_3$	—	80
6c	$(CH_2)_4$	—	74
8a	$(CH_2)_2$	$(CH_2)_2$	56
8b	$(CH_2)_2$	$(CH_2)_4$	58
8c	$(CH_2)_3$	$(CH_2)_2$	62
8d	$(CH_2)_4$	$(CH_2)_2$	55

broad signal at $\delta = 5.90$ ppm attributed to the NH_2 group which was not present in the spectra of compounds **3a–d**. In addition, the absence of the IR absorptions and ^1H NMR signals due to the SH groups of compounds **3a–d** and **6a–c** further confirmed the formation of azathia crown macrocycles **5a–f** and **8a–d**.

In summary, we have reported a simple and efficient method for the preparation of azathia crown macrocycles containing two triazoles or thiadiazole subunits. This procedure offers several advantages such as good yields of cyclization products without the need for high dilution conditions, short reaction times, and simple purification.

2. General procedure for the synthesis of bis-Schiff bases 3a–d

A solution of bis-aldehydes **1a–b** (5 mmol) and 4-amino-5-(aroyl)-*4H*-1,2,4-triazole-3-thiols **2a–b** (10 mmol) in glacial acetic acid (20 ml) was heated under reflux for 3 h. After cooling, the mixture was poured into ice-water (50 ml). The precipitate that formed was filtered and recrystallized from an appropriate solvent to give the desired compounds **3a–d**.

3. General procedure for the synthesis of azathia crown macrocycles 5a–f

Compounds **3a–d** (0.15 mmol) were dissolved in hot ethanolic KOH [prepared by dissolving KOH (0.30 mmol) in 20 ml of absolute ethanol], and the solvent was then removed under vacuum. The residue was dissolved in DMF (7 ml) and the appropriate dibromoalkane (0.15 mmol) was added. The mixture was refluxed for 5 min, during which time KBr separated out. The KBr was removed by filtration, and the resulting solution was poured into water and a precipitate formed. The precipitate was filtered and recrystallized from H_2O/DMF (2:1) to give the pure azathia crown macrocycles **5a–f**.

4. General procedure for the synthesis of bis-Schiff bases 6a–c

A solution of bis-aldehydes **1a–c** (5 mmol) and 2-amino-5-mercapto-1,3,4-thiadiazole (10 mmol) in glacial acetic acid (15 ml) was refluxed for 3 h. After cooling, the mixture was poured into ice-water (50 ml). The precipitate that formed was filtered and recrystallized from an appropriate solvent to give the desired compounds **6a–c**.

5. General procedure for the synthesis of azathia crown macrocycles 8a–d

Compounds **6a–c** (0.15 mmol) were dissolved in hot ethanolic KOH [prepared by dissolving KOH (0.3 mmol) in 10 ml of absolute ethanol] and the solvent was then removed under vacuum. The residue was dissolved in DMF (15 ml), and the appropriate dibromoalkane (0.15 mmol) was added. The mixture was refluxed for 15 min, during which time KBr separated out. The KBr was removed by filtration, and the resulting solution was poured into water and a precipitate formed. The precipitate was filtered and recrystallized from an appropriate solvent to give the pure azathia crown macrocycles **8a–d**.

References and notes

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1,2-*Bis*[*o*-(*N*-*methylidenamino*-5-(4-*pyridyl*)-3-*thiol*-*4H*-1,2,*4*-*triazole*-4-*yl*)*phenoxy*]*ethane* (Table 1, entry **3a**): IR (KBr): ν (cm^{-1}): 3070 (aromatic CH stretch.), 2698 (SH stretch.) 1599 (C=N), 1530, 1427 (C=C ring stretch.); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.28 (s, 2H, 2 SH), 10.03 (s, 2H, 2 CH=N), 8.68 (d, 4H, $H_{arom.}$, $J = 5.0$ Hz), 7.87 (d, 2H, $H_{arom.}$, $J = 7.7$ Hz), 7.79 (d, 4H, $H_{arom.}$, $J = 5.1$ Hz), 7.57 (t, 2H, $H_{arom.}$, $J = 7.7$ Hz), 7.30 (d, 2H, $H_{arom.}$, $J = 8.4$ Hz), 7.04 (t, 2H, $H_{arom.}$, $J = 7.5$ Hz), 4.53 (s, 4H, 2 OCH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 65.1, 113.7, 120.5, 121.6, 122.4, 126.9, 133.3, 135.1, 147.1, 150.7, 159.1, 161.6, 163.2. Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_2$: C, 58.05; H, 3.90; N, 22.57; S, 10.33. Found: C, 57.85; H, 3.89; N, 22.45; S, 10.26.
1,2-*Bis*[*o*-(*N*-*methylidenamino*-5-(3-*pyridyl*)-3-*thiol*-*4H*-1,2,*4*-*triazole*-4-*yl*)*phenoxy*]*ethane* (Table 1, entry **3b**):
IR (KBr): ν (cm^{-1}): 3070 (aromatic CH stretch.), 2728 (SH stretch.) 1600 (C=N), 1530, 1427 (C=C ring stretch.); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.25 (s, 2H, 2 SH), 10.15 (s, 2H, 2 CH=N), 9.03 (s, 2H, $H_{arom.}$), 8.70 (s, 2H, $H_{arom.}$), 8.23 (d, 2H, $H_{arom.}$, $J = 7.7$ Hz), 7.86 (d, 2H, $H_{arom.}$, $J = 7.5$ Hz), 7.56–7.60 (m, 4H, $H_{arom.}$), 7.22 (d, 2H, $H_{arom.}$, $J = 7.9$ Hz), 7.07 (t, 2H, $H_{arom.}$, $J = 7.5$ Hz), 4.52 (s, 4H, 2 OCH_2), ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 66.3, 113.7, 120.6, 121.6, 122.4, 127.1, 132.8, 133.2, 134.4 135.1, 148.8, 151.1, 159.3, 161.6, 163.2. Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_2$: C, 58.05; H, 3.90; N, 22.57; S, 10.33. Found: C, 57.72; H, 3.78; N, 22.38; S, 10.16.
1,2-*Bis*[*o*-(*N*-*methylidenamino*-5-(4-*pyridyl*)-3-*thiol*-*4H*-1,2,*4*-*triazole*-4-*yl*)*phenoxy*]*propane* (Table 1, entry **3c**): IR (KBr): υ (cm^{-1}): 3068 (aromatic CH stretch.), 2731 (SH stretch.) 1599 (C=N), 1530, 1430 (C=C ring stretch.); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.40 (s, 2H, 2 SH), 10.19 (s, 2H, 2CH=N), 8.73 (d, 4H, $H_{arom.}$, $J = 5.1$ Hz), 7.92 (d, 2H, $H_{arom.}$, $J = 7.8$ Hz), 7.85 (d, 4H, $H_{arom.}$, $J = 5.1$ Hz), 7.57 (t, 2H, $H_{arom.}$, $J = 7.8$ Hz), 7.23 (d, 2H, $H_{arom.}$, $J = 8.4$ Hz), 7.05 (t, 2H, $H_{arom.}$, $J = 7.5$ Hz), 4.38 (t, 4H, $2OCH_2$ $J = 5.5$ Hz), 2.24 (t, 2H, CH_2 $J = 5.5$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 28.9, 65.2, 113.7, 120.5, 121.6, 122.4,

126.9, 133.1, 135.3, 147.0, 150.8, 159.1, 161.5, 163.2. Anal. Calcd for $C_{31}H_{26}N_{10}O_2S_2$: C, 58.66; H, 4.13; N, 22.07; S, 10.10. Found: C, 58.41; H, 4.02; N, 22.25; S, 9.92.

1,2-*Bis*[*o*-(*N*-*methylidenamino*-5-(3-*pyridyl*)-3-*thiol*-4*H*-1,2,4-*triazole*-4-*yl*)*phenoxy*]*propane* (Table 1, entry **3d**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 2705 (SH stretch.) 1605 (C=N), 1547, 1427 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.45 (s, 2H, 2 SH), 10.19 (s, 2H, 2 CH=N), 9.02 (s, 2H, $H_{arom.}$) 8.70 (s, 2H, $H_{arom.}$), 8.22 (d, 2H, $H_{arom.}$, J = 7.8 Hz), 7.81 (d, 2H, $H_{arom.}$, J = 7.4 Hz), 7.55–7.59 (m, 4H, $H_{arom.}$), 7.21 (d, 2H, $H_{arom.}$, J = 8.0 Hz), 7.08 (t, 2H, $H_{arom.}$, J = 7.4 Hz), 4.38 (t, 4H, 2 OCH_2, J = 5.6 Hz), 2.25 (t, 2H, CH_2 J = 5.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 29.0, 65.1, 113.7, 120.5, 121.6, 122.5, 127.0, 132.9, 133.2, 134.6 135.2, 147.1, 150.7, 159.1, 161.6, 163.2. Anal. Calcd for $C_{31}H_{26}N_{10}O_2S_2$: C, 58.66; H, 4.13; N, 22.07; S, 10.10. Found: C, 58.39; H, 4.08; N, 21.91; S, 9.96.

2,3:16,17-*Dibenzo*-6,7:12,13-*bis*[5-(4-*pyridyl*)]-1,2,4-*triazolo*-[1,18,8,11,5,6,13,14]*dioxa dithia tetraaza cycloicosa*-4,14-*diene* (Table 2, entry **5a**): IR (KBr): ν (cm^{-1}): 3070 (aromatic CH stretch.), 1599 (C=N), 1525, 1437 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.18 (s, 2H, 2CH=N), 8.70 (d, 4H, $H_{arom.}$, J = 4.8 Hz), 7.92 (d, 2H, J = 7.6 Hz), 7.80 (d, 4H, $H_{arom.}$, J = 4.8 Hz), 7.60 (t, 2H, $H_{arom.}$, J = 8.0 Hz), 7.26 (d, 2H, $H_{arom.}$, J = 8.5 Hz), 7.05 (t, 2H, $H_{arom.}$, J = 7.5 Hz), 4.54 (s, 4H, 2OCH_2), 3.71 (s, 4H, 2SCH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 36.1, 67.8, 114.2, 120.0, 121.7, 122.5, 127.5, 134.0, 136.0, 147.1, 150.7, 159.2, 162.8, 164.7. MS (EI): m/z = 646 (M^+), 620, 618, 589, 578, 382, 264, 178, 146 (base peak), 119, 105. Anal. Calcd for $C_{32}H_{26}N_{10}O_2S_2$: C, 59.43; H, 4.05; N, 21.66; S, 9.92. Found: C, 59.15; H, 3.96; N, 21.50; S, 9.85.

2,3:16,17-*Dibenzo*-6,7:12,13-*bis*[5-(3-*pyridyl*)]-1,2,4-*triazolo*-[1,18,8,11,5,6,13,14]-*dioxa dithia tetraaza cycloicosa*-4,14-*diene* (Table 2, entry **5b**): IR (KBr): ν (cm^{-1}): 3065 (aromatic CH stretch.), 1609 (C=N), 1530, 1445 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.24 (s, 2H, CH=N), 9.03 (s, 2H, $H_{arom.}$) 8.71 (s, 2H, $H_{arom.}$), 8.20 (d, 2H, $H_{arom.}$, J = 7.7 Hz), 7.85 (d, 2H, $H_{arom.}$, J = 7.0 Hz), 7.55-7.59 (m, 4H, $H_{arom.}$), 7.23 (d, 2H, $H_{arom.}$, J = 8.1 Hz), 7.08 (t, 2H, $H_{arom.}$, J = 7.3 Hz), 4.53 (s, 4H, 2OCH_2), 3.72 (s, 4H, 2SCH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 34.0 67.1, 113.7, 120.5, 121.5, 122.3, 127.1, 132.8, 133.2, 134.1 134.9, 148.9, 151.0, 159.5, 162.3, 163.9. MS (EI): m/z = 646 (M^+), 620, 618, 589, 578, 564, 264, 146 (base peak), 119, 105, 91. Anal. Calcd for $C_{32}H_{26}N_{10}O_2S_2$: C, 59.43; H, 4.05; N, 21.66; S, 9.92. Found: C, 59.61; H, 4.34; N, 21.95; S, 9.67.

2,3:17,18-*Dibenzo*-6,7:13,14-*bis*[5-(4-*pyridyl*)]-1,2,4-*triazolo*-[1,19,8,12,5,6,14,15]-*dioxa dithia tetraaza cyclodocosa*-4,15-*diene* (Table 2, entry **5c**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 1599 (C=N), 1530, 1445 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.29 (s, 2H, 2CH=N), 8.76 (d, 4H, $H_{arom.}$, J = 5.0 Hz), 7.77–7.98 (m, 6H, $H_{arom.}$), 7.64 (t, 2H, $H_{arom.}$, J = 7.8 Hz), 7.26 (d, 2H, $H_{arom.}$, J = 8.3 Hz), 7.13 (t, 2H, $H_{arom.}$, J = 7.5 Hz), 4.38 (t, 4H, 2 OCH_2 J = 5.6 Hz), 3.38 (t, 4H, 2SCH_2 J = 5.5 Hz), 2.29-2.35 (m, 4H, 2CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 28.2, 29.0, 33.8, 66.0, 113.7, 120.6, 121.6, 122.4, 127.0, 133.4, 135.0, 147.1, 151.0, 159.0, 161.5, 163.2. MS (EI): m/z = 674 (M^+), 646, 634, 618, 604, 578, 396, 278, 146 (base peak), 119, 105, 91. Anal. Calcd for $C_{34}H_{30}N_{10}O_2S_2$: C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.22; H, 4.33; N, 20.51; S, 9.41.

2,3:17,18-*Dibenzo*-6,7:13,14-*bis*[5-(3-*pyridyl*)]-1,2,4-*triazolo*-[1,19,8,12,5,6,14,15]-*dioxa dithia tetraaza cyclodocosa*-4,15-diene: (Table 2, entry **5d**): IR (KBr): ν (cm^{-1}): 3068 (aromatic CH stretch.), 1610 (C=N), 1527, 1440 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.23 (s, 2H, CH=N), 9.02 (s, 2H, $H_{arom.}$), 8.70 (s, 2H, $H_{arom.}$), 8.24 (d, 2H, H $_{arom.}$, J = 7.8 Hz), 7.85 (d, 2H, $H_{arom.}$, J = 7.2 Hz), 7.55–7.59 (m, 4H, $H_{arom.}$), 7.21 (d, 2H, $H_{arom.}$, J = 8.1 Hz), 7.07 (t, 2H, $H_{arom.}$, J = 7.5 Hz), 4.38 (t, 4H, 2OCH_2, J = 5.6 Hz), 3.85 (d, 4H, 2SCH_2 J = 5.6 Hz), 2.28–2.34 (m, 4H, 2CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 28.2, 29.1, 34.0 66.2, 113.7, 120.3, 121.6, 122.5, 127.1, 132.8, 133.2, 134.4 135.0, 149.0, 151.1, 159.3, 161.4, 163.1. MS (EI): m/z = 674 (M^+), 646, 634, 604, 618, 578, 396, 278, 146 (base peak), 119, 105, 91. Anal. Calcd for $C_{34}H_{30}N_{10}O_2S_2$: C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.28; H, 4.24; N, 20.41; S, 9.37.

2,3:16,17-*Dibenzo*-6,7:12,13-*bis*[5-(4-*pyridyl*)]-1,2,4-*triazolo*-[1,18,8,11,5,6,13,14]-*dioxa dithia tetraaza cyclohenicosa*-4,14-*diene* (Table 2, entry **5e**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 1599 (C=N), 1530, 1438 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.21 (s, 2H, 2CH=N), 8.80 (d, 4H, $H_{arom.}$, J = 5.1 Hz), 7.92–8.07 (m, 6H, $H_{arom.}$), 7.61 (t, 2H, $H_{arom.}$, J = 7.6 Hz), 7.25 (d, 2H, $H_{arom.}$, J = 8.2 Hz), 7.08 (t, 2H, $H_{arom.}$, J = 7.3 Hz), 4.38 (t, 4H, 2 OCH_2 J = 5.6 Hz), 3.38 (s, 4H, 2SCH_2), 2.32 (d, 2H, CH_2 J = 5.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 29.1, 34.0, 66.1, 113.9, 120.5, 121.5, 122.4, 127.1, 133.4, 134.9, 147.1, 150.6, 159.1, 161.6, 163.2. MS (EI): m/z = 660 (M^+), 635, 632, 630, 592, 578, 382, 278, 146 (base peak), 119, 105. Anal. Calcd for $C_{33}H_{28}N_{10}O_2S_2$: C, 59.98; H, 4.27; N, 21.20; S, 9.71. Found: C, 59.74; H, 4.19; N, 21.04; S, 9.59.

2,3:16,17-*Dibenzo*-6,7:12,13-*bis*[5-(3-*pyridyl*)]-1,2,4-*triazolo*-[1,18,8,11,5,6,13,14]*dioxa dithia tetraaza cyclohenicosa*-4,14-*diene* (Table 2, entry **5f**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 1599 (C=N), 1530, 1445 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.25 (s, 2H, CH=N), 9.04 (s, 2H, $H_{arom.}$) 8.69 (s, 2H, $H_{arom.}$), 8.25 (d, 2H, $H_{arom.}$, J = 7.9 Hz), 7.86 (d, 2H, $H_{arom.}$, J = 7.1 Hz), 7.57–7.60 (m, 4H, $H_{arom.}$), 7.27 (d, 2H, $H_{arom.}$, J = 8.3 Hz), 7.07 (t, 2H, $H_{arom.}$, J = 7.5 Hz), 4.54 (t, 4H, 2OCH_2, J = 5.6 Hz), 3.85 (s, 4H, 2SCH_2), 2.31 (t, 2H, CH_2 J = 5.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 29.4, 36.3 66.1, 113.7, 120.4, 121.8, 122.5, 127.0, 132.9, 133.2, 134.4 135.2, 148.8, 151.1, 159.3, 161.6, 163.2. MS (EI): m/z = 660 (M^+), 630, 592, 578, 382, 278, 146 (base peak), 119, 105. Anal. Calcd for $C_{33}H_{28}N_{10}O_2S_2$: C, 59.98; H, 4.27; N, 21.20; S, 9.71. Found: C, 59.73; H, 4.22; N, 21.10; S, 9.56.

1,2-*Bis*[*o*-(*N*-*methylidenamino*-2-*thiol*-1,3,4-*thiadiazole*-5-*yl*)*phenoxy*]*ethane* (Table 3, entry **6a**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 2728 (SH stretch.) 1605 (C=N), 1532, 1428 (C=C ring stretch); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.30 (s, 2H, 2SH), 10.21 (s, 2H, 2CH=N), 7.65 (d, 2H, $H_{arom.}$, J = 5.0 Hz), 7.36 (t, 2H, $H_{arom.}$, J = 7.1 Hz), 7.19 (d, 2H, $H_{arom.}$, J = 8.0 Hz), 7.12 (t, 2H, $H_{arom.}$, J = 7.0 Hz), 4.59 (s, 4H, 2OCH_2). ^{13}C NMR (75 MHz, DMSO-d_6 75 MHz) δ (ppm): 64.8, 113.4, 121.5, 123.0, 128.1, 136.4, 159.6, 163.2, 163.3, 174.0. Anal. Calcd for $C_{20}H_{16}N_6O_2S_4$: C, 47.98; H, 3.22; N, 16.79; S, 25.62. Found: C, 47.71; H, 3.17; N, 16.56; S, 25.35.

1,2-*Bis*[*o*-(*N*-*methylidenamino*-2-*thiol*-1,3,4-*thiadiazole*-5-*yl*)*phenoxy*]*propane* (Table 3, entry **6b**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 2725 (SH stretch.) 1605 (C=N), 1530, 1432 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.21 (s, 2H, 2SH), 10.19 (s, 2H, 2CH=N), 7.61–7.70 (m, 4H, $H_{arom.}$), 7.24 (d, 2H, $H_{arom.}$ J = 8.0 Hz), 7.07 (t, 2H, $H_{arom.}$, J = 6.9 Hz), 4.40 (t, 4H, 2OCH_2, J = 5.4 Hz), 2.26 (t, 2H, CH_2, J = 5.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 29.1, 65.1, 113.6, 121.8, 122.9, 128.3, 136.3, 159.6, 163.1, 163.3, 174.9. Anal. Calcd for $C_{21}H_{18}N_6O_2S_4$: C, 49.01; H, 3.53; N, 16.33; S, 24.92. Found: C, 48.88; H, 3.66; N, 16.51; S, 24.72.

1,2-*Bis*[*o*-(*N*-*methylidenamino*-2-*thiol*-1,3,4-*thiadiazole*-5-*yl*)*phenoxy*]*butane* (Table 3, entry **6c**): IR (KBr): ν (cm^{-1}): 3070 (aromatic CH stretch.), 2731 (SH stretch.) 1600 (C=N), 1530, 1427 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.25 (s, 2H, 2 SH), 10.38 (s, 2H, 2 CH=N), 7.60–7.70 (m, 4H, $H_{arom.}$), 7.24 (d, 2H, $H_{arom.}$ J = 8.0), 7.06 (t, 2H, $H_{arom.}$, J = 7.0), 4.23 (br s, 4H, 2OCH_2), 2.00 (br s, 4H, 2CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 27.6, 64.9, 113.6, 121.3, 122.5, 128.1, 136.1, 159.8, 163.2, 163.4, 175.0. Anal. Calcd for $C_{22}H_{20}N_6O_2S_4$: C, 49.98; H, 3.81; N, 15.90; S, 24.26. Found: C, 49.74; H, 3.75; N, 15.72; S, 24.01.

2,3:18,19-*Dibenzo*-6,8:13,15 *bis*-1,3,4-*thiadiazolo*-[1,20,7,9,12,14,5,16] *dioxa tetrathia diaza cyclodocosa*-4,16-*diene* (Table 3, entry **8a**): IR (KBr): ν (cm^{-1}): 3070 (aromatic CH stretch.), 1600 (C=N), 1540, 1440 (C=C ring stretch.); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.47 (s, 2H, 2CH=N), 7.57–7.62 (m, 4H, $H_{arom.}$), 7.29 (d, 2H, H_{arom}, J = 8.1 Hz), 7.09 (t, 2H, H_{arom}, J = 7.4 Hz), 4.77 (s, 4H, 2OCH_2), 3.75 (s, 4H, 2SCH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 34.0, 66.6, 113.6, 121.8, 122.9, 128.4, 136.6, 159.5, 163.2, 163.4, 174.9. MS (EI): m/z = 526 (M^+), 495, 467, 439, 411, 324, 271, 133, 121, 83 (base peak). Anal. Calcd for $C_{22}H_{18}N_6O_2S_4$: C, 50.17; H, 3.44; N, 15.96; S, 24.35. Found: C, 49.89; H, 3.39; N, 15.73; S, 24.12.

2,3:19,20-*Dibenzo*-6,8:14,16 *bis*-1,3,4-*thiadiazolo*-[1,21,7,9, 13,15,5,17]*dioxa tetrathia diaza cyclotetracosa*-4,17-*diene* (Table 3, entry **8b**): IR (KBr): ν (cm^{-1}): 3075 (aromatic CH stretch.), 1610 (C=N), 1547, 1438 (C=C ring stretch.); ^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 9.49 (s, 2H, 2CH=N), 8.23 (d, 2H, $H_{arom.}$, J = 7.5 Hz), 7.61 (t, 2H, H_{arom}, J = 8.0 Hz), 7.32 (d, 2H, H_{arom}, J = 8.1 Hz), 7.11 (t, 2H, H_{arom}, J = 7.4 Hz), 4.41 (br s, 4H, 2OCH_2), 3.76 (br s, 4H, 2SCH_2), 2.27–2.34 (m, 4H, 2CH_2). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 28.0, 29.1, 34.0, 66.2, 113.7, 121.6, 122.7, 128.4, 136.0, 159.5, 163.1, 163.3, 175.0. MS (EI): m/z = 554 (M^+), 523, 495, 467, 425, 285, 133, 83 (base peak). Anal. Calcd for $C_{24}H_{22}N_6O_2S_4$: C, 51.96; H, 4.00; N, 15.15; S, 23.12. Found: 52.18; H, 4.12; N, 15.32; S, 23.37.

2,3:18,19-*Dibenzo*-6,8:13,15 *bis*-1,3,4-*thiadiazolo*-[1,20,7,9, 12,14,5,16]*dioxa tetrathia diaza cyclotricosa*-4,16-*diene* (Table 3, entry **8c**): IR (KBr): ν (cm^{-1}): 3070 (aromatic CH stretch.), 1600 (C=N), 1535, 1436 (C=C ring stretch.); ^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 9.48 (s, 2H, 2CH=N), 8.21 (d, 2H, $H_{arom.}$, J = 7.3 Hz), 7.63 (t, 2H, $H_{arom.}$, J = 7.9 Hz), 7.33 (d, 2H, $H_{arom.}$, J = 8.3 Hz), 7.13 (t, 2H, $H_{arom.}$, J = 7.5 Hz), 4.40 (br s, 4H, 2OCH_2), 3.78 (s, 4H, 2SCH_2), 2.26 (br s, 2H, CH_2). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 29.1, 34.1, 66.5, 113.6, 121.8, 122.9, 128.5, 136.1, 159.5, 163.2, 163.3, and 175.0. MS (EI): m/z = 540 (M^+), 509, 481, 453, 285, 133, 83 (base peak). Anal. Calcd for $C_{23}H_{20}N_6O_2S_4$: C, 51.09; H, 3.73; N, 15.54; S, 23.72. Found: C, 50.87; H, 3.69; N, 15.63; S, 23.81.

2,3:18,19-*Dibenzo*-6,8:13,15 *bis*-1,3,4-*thiadiazolo*-[1,20,7,9, 12,14,5,16]*dioxa tetrathia diaza cyclotetracosa*-4,16-*diene* (Table 3, entry **8d**): IR (KBr): ν (cm^{-1}): 3074 (aromatic CH stretch.), 1606 (C=N), 1540, 1435 (C=C ring stretch.); ^{1}H NMR (300 MHz, CD_3COCD_3) δ (ppm): 9.47 (s, 2H, 2CH=N), 8.21 (d, 2H, $H_{arom.}$, J = 7.5 Hz), 7.60 (t, 2H, $H_{arom.}$, J = 8.1 Hz), 7.30 (d, 2H, $H_{arom.}$, J = 8.5 Hz), 7.11 (t, 2H, $H_{arom.}$, J = 7.4 Hz), 4.21 (br s, 4H, 2OCH_2), 3.76 (s, 4H, 2SCH_2), 1.99 (br s, 4H, 2CH_2). ^{13}C NMR (75 MHz, CD_3COCD_3) δ (ppm): 27.6, 34.2, 64.8, 113.7, 121.5, 122.7, 128.4, 136.1, 159.8, 163.1, 163.3, and 175.0. MS (EI): m/z = 554 (M^+), 495, 467, 439, 352, 299, 133, 121, 83, 57 (base peak). Anal. Calcd for $C_{24}H_{22}N_6O_2S_4$: C, 51.96; H, 4.00; N, 15.15; S, 23.12. Found: 51.75; H, 3.88; N, 14.87; S, 22.97.