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Synthesis of novel lariat azathia crown macrocycles containing two triazole rings and bis crown macrocycles containing four triazole rings

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Abstract—The 13-hydroxy macrocycles **7a-d** were prepared in 40–50% yields by the condensation of 1,ω-bis(4-amino-1,2,4-triazol-3-ylsulfany)alkanes **2a-d** with 1,3-bis(2-formyphenoxy)-2-propanol (**9**). Acylation of **7a-d** with 2-chloroacetylchloride gave the corresponding esters **11a**,**b**. Amination of **11a**,**b** with different amines in acetone furnished exclusively the target lariat macrocycles **12a**,**b** and **13** in 60–70% yields. Reaction of 2 equiv. of the macrocycles **11a**,**b** with 1 equiv. of piperazine afforded the novel bis macrocyles **14a**,**b** in 50–60% yields. Reduction of **7a-d** with $NaBH_4$ afforded the corresponding 13-hydroxyazathia crown ethers **15a-d** in 65–70% yields.

1. Introduction

A progressive interest was directed in the last few years to the chemistry of the crown ethers containing heterocyclic rings in the system. These macrocycles were found to exhibit interesting host-guest complexation characteristic.[1,2] Incorporation of heterocyclic moiety within the cavity of the crown ligands were also provides rigidity and are able to participate in complexation through their soft donor atoms, for example, macrocyclic ethers with pyridine and other nitrogen containing heterocyclic subunits were reported to form strong and selective interactions with various charged and neutral guest molecules.[3–7] Moreover, lariat crown ethers which bear side-chain containing donor atoms possess unique cation binding properties compared with the parent crown ether containing no extra donor sites.[8,9] Also, as efficient organic ligands lariat crown ethers meet the requirement of rapid, strong and three-dimensional cation binding and can mimic the properties of natural ionophores.[10] Furthermore, during the last decades considerable attention has been devoted to the chemistry of bis crown ethers for their applications in various area especially in ion-selective electrodes.[11–15] Moreover, bis crown ethers show extra binding properties than the monocrown ethers, where by the cooperatives action of two adjacent crown units, bis(crown ethers) tend to form stronger complexes with particular metal ion than the corresponding monocrown ethers, where it forms complexes with two crown moieties per cation: 'sandwich complexes' that improve the stability of the complex especially when the cation is too large to fit the cavity of the crown ethers.[16,17]

In connection with these findings and in continuation of our interest in synthesizing macrocyclic crown compounds containing heterocycles moieties,[18–20] and bis macrocyles.[21] We report here the synthesis of a series of 22–23 membered macrocycles fused with two triazole rings containing N, O and S inside the macrocyclic ring as donor atoms and possess pendant hydroxy group as precursor for the synthesis of lariat macrocycles. In an attempt to enhance the selectivity of these ligands and the stability of the complexes formed with both metals and organic cations. This project also describes the synthesis of the novel lariat macrocycles containing *N*,*N*-diethyamino, piperidino and morpholinoacetoxy moieties as side arm containing O and N as donor atoms and the corresponding bis macrocycles.

2. Results and discussion

Several methods have been described for the reaction of epichlorohydrin with bisphenols as precursor for the synthesis of crown ethers with pendant hydroxy group attached to the crown ether ring.[22,23] Heo et al[22] reported the synthesis of hydroxy crown ethers in a good yield 39–60% by the reaction of epichlorohydrin with the appropriate

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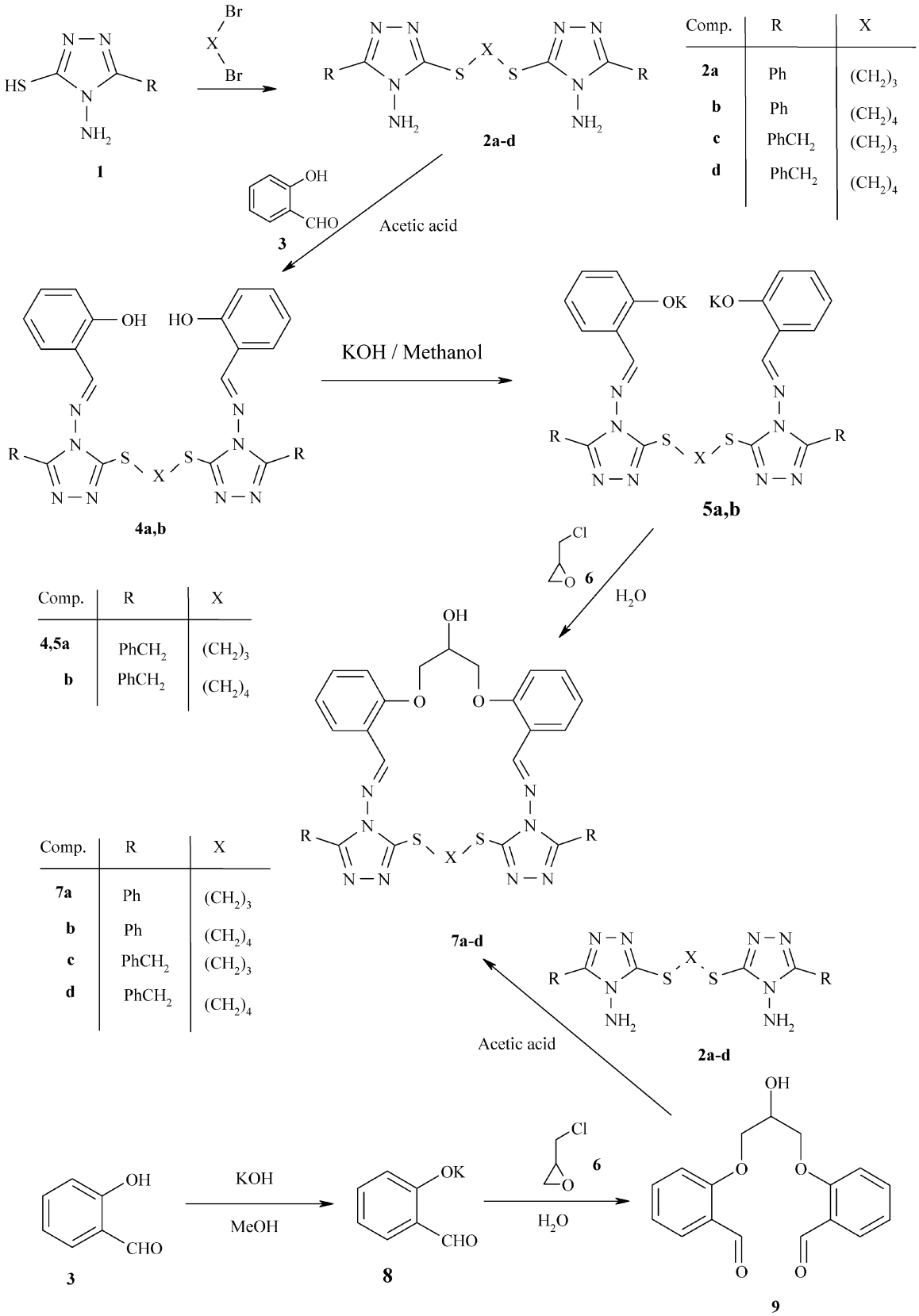
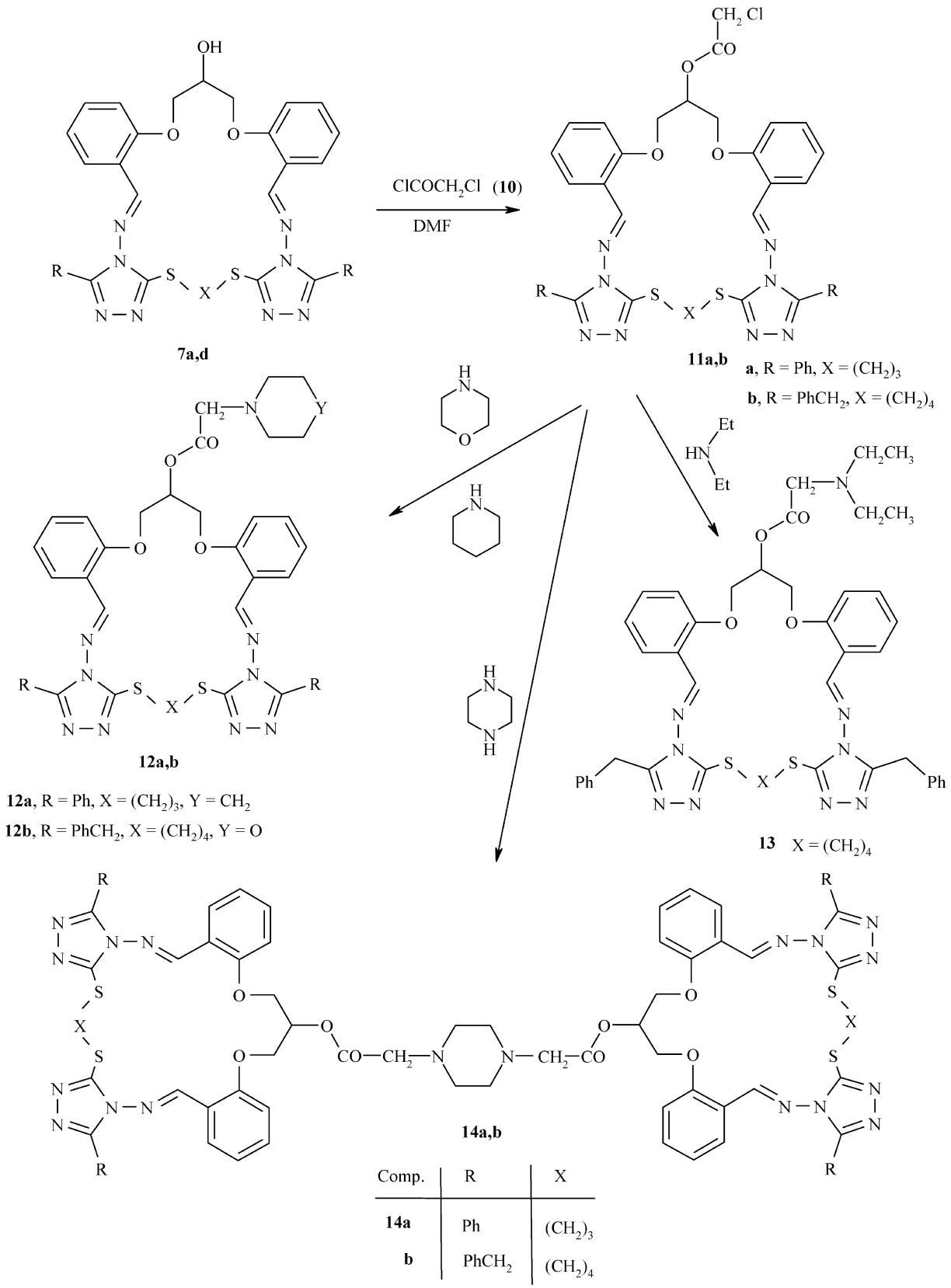
diphenols in basic aqueous media. This project describes the synthesis of novel 13-hydroxy aza-thia crown ethers containing two triazole rings as subcyclic unit as shown in Schemes 1–3.

Two strategies were attempted for the synthesis of the 13-hydroxy macrocycles **7a-d**. In the first one (Scheme 1), we applied a similar approach to that described by Heo et al.[22] Thus, condensation of 1,ω-bis(4-amino-1,2,4-triazol-3-

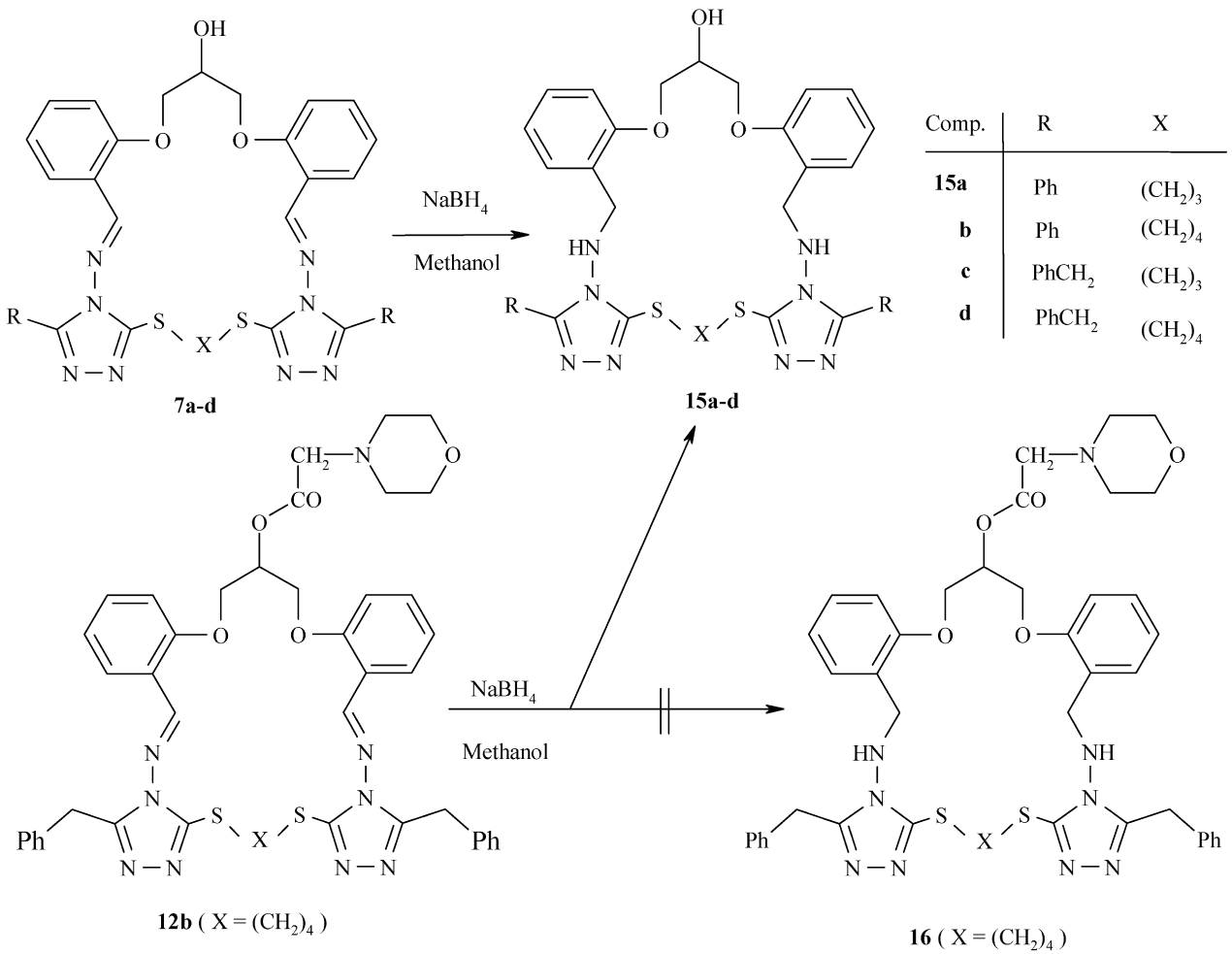


Scheme 1.



Scheme 2.

ylsulfany)alkanes **2a**-**d** with salicylaldehyde (**3**) in acetic acid gave the corresponding 1,ω-bis(4-*o*-hydroxybenzyl-ideneamino-5-aryl-1,2,4-triazol-3-ylsulfany)alkanes **4a**,**b** in 70–75% yield. Reaction of the latter compounds with methanolic potassiun hydroxide gave the corresponding bis potassium salt **5a**,**b**. Unfortunately, reaction of the bis potassium salts **5a**,**b** with epichlorohydrin (**6**) following the method described by Heo et al.[22] gave only 2% of the target



Scheme 3.

macrocycles **7c**,**d**. This may be attributed for the extent of the spacing between the terminal bis hydroxy groups. In anticipation of the low yield of the macrocycles **7c**,**d** we then applied the second strategy as outlined in Scheme 1. Thus, reactions of the potassium salt **8** [obtained upon treatment of salicyaldehyde (**3**) with methanolic potassium hydroxide solution] with epichlorohydrin (**6**) in aqueous media furnished the corresponding 1,3-bis(2-formyphenoxy)-2-propanol (**9**) in a good yield (65%). Condensation of **9** with the appropriate bis(aminotriazoles) **2a**-**d** in acetic acid under the high dilution condition which often used as the most versatile procedure used for the synthesis of the macrocycles[24] gave 50–60% of the target 13-hydroxy macrocycles Schiff bases **7a**-**d**. Having now available the 13-hydroxy macrocycles Schiff bases **7a**-**d** which stimulated the author to study their transformation into the first lariat aza-thia crown ethers containing two triazole rings as sub-cyclic units and their bis macrocycles containing two macrocyclic units connected by flexible bridge having piperazine moiety as shown in Schemes 2 and 3.

Thus, acylation the hydroxy group of compounds **7a**,**d** with 2-chloroacetylchloride (**10**) in DMF afforded the corresponding 13-chloroacetoxy macrocycles **11a**,**b** in 65–70% yields. The latter compound could be used as a key intermediate for the synthesis of lariat macrocycles **12a**,**b** and **13** containing different donor atoms in the side-arm. So, reaction of compounds **11a**,**b** with a series of secondary amines namely, *N*,*N*-diethylamine, piperidine and morpholine in refluxing acetone for 2 h furnished 50–60% yields of the corresponding lariat macrocycles **12a**,**b** and **13**. Similarly, the synthesis of the novel bis macrocycles **14a**,**b** was performed efficiently through the amination of esters **11a**,**b** with piperazine as shown in Scheme 2. Thus, reaction of 2 equiv. of chloroacetoxy macrocycles **11a**,**b** with 1 equiv. of piperazine in acetone gave the corresponding 1,4-bis[13-acetoxy macrocycles] piperazine derivatives **14a**,**b** in 50–55% yield. In order to increase the donor characters of the *N*-benzalimino and subsequently the cation binding ability of the macrocycle Schiff bases **7a**-**d** we successfully prepare the 13-hydroxy azathia crown ethers **15a**-**d** through the reduction of **7a**-**d** as shown in Scheme 3. Reduction of the macrocycles **7a**-**d** with $NaBH_4$ in methanol afforded the corresponding macrocycles **15a**-**d** in 65–72% yield. It is important to mention that all attempts for reduction of **12b** did not afford the corresponding lariat macrocyclic **16** but gave instead the 13-hydroxy macrocyclic **15d** in 65% yield which may be attributed to the basic hydrolysis of the ester group of compound **13b** in the reaction medium.

In conclusion of this project we successfully prepared macrocycles having pendant hydroxy group as a key intermediate for the synthesis of novel lariat macrocycles

containing a strong donor group as a supporting ligand at the end of the side-arm and bis macrocycles possess two crown units connected by flexible bridge. We believe that by development of the foregoing synthetic methodology lariat macrocyles and bis macrocycles with a wide variety of side-chains with different lengths and donor atoms aiming to improve the cation binding ability and the stability of the ligands metal complexes could be easily prepared.

3. Experimental

3.1. General

All melting points are uncorrected. Compounds prepared by different procedures were characterized by mixed melting points and IR. IR spectra (KBr) were recorded on Bruker Vector 22 spectrophotometer. NMR spectra were measured with a Varian Gemini 200 spectrometer (200 MHz, ^{1}H NMR) and chemical shift are given in ppm from TMS. ^{13}C NMR spectra were recorded using APT pulse sequence. with a Varian Mercury 300 (300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR). Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. 1,3-Dibromopropane, 1,4-dibromobutane, epichlorohydrin, diethylamine, piperidine, morpholine and piperazine were used as purchased from Aldrich. The starting bis(4-amino-1,2,4-triazol-3-ylsulfanyl)alkanes **2a**-**d** were prepared as reported.[18,19]

3.1.1. Bis(4-arylmethylideneamino-1,2,4-triazol-3-ylsulfanyl)alkanes 4a,b. *General procedure*. To a solution of each of **3c**,**d** (5 mmol) in glacial acetic acid (30 ml) was added salicylaldehyde (**3**) (10 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed in vacuo and the remaining residue washed with water. The solid obtained was collected and crystallized from the appropriate solvent to give crystals of **4a**,**b**.

3.1.2. 1,3-Bis(4-*o*-hydroxybenzylideneamino-5-benzyl-1,2,4-triazol-3-ylsulfanyl)propane (4a). With the use of the general procedure **2c** gave crude **4a** which was crystallized from ethanol as colorless crystals (75%), mp 164 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 (quintet, 2H, J=6.8 Hz, SCH_2CH_2), 3.27 (t, 4H, J=7 Hz, SCH_2), 4.13 (s, 4H, PhCH_2), 6.85–7.42 (m, 18H, ArH's), 8.39 (s, 2H, OH), 9.95 (s, 2H, CH=N) ppm. (Calcd for $C_{35}H_{32}N_8O_2S_2$ (660.82): C, 63.62; H, 4.88; N, 16.96; S, 9.70. Found: C, 63.41; H, 4.90; N, 16.80; S, 9.60%).

3.1.3. 1,4-Bis(4-*o*-hydroxybenzylideneamino-5-benzyl-1,2,4-triazol-3-ylsulfanyl)butane (4b). With the use of the general procedure **2d** gave crude **4b** which was crystallized from DMF as colorless crystals (70%), mp 252–254 °C; IR (cm^{-1}) 3400 (CO),1607 (NH); ^{1}H NMR (DMSO) δ 1.74 (br s, 4H, SCH_2CH_2), 3.14 (br s, 4H, SCH_2), 4.19 (s, 4H, PhCH_2), 6.95–7.81 (m, 18H, ArH's), 8.88 (s, 2H, CH=N), 10.49 (br s, 2H, OH) ppm. (Calcd for $C_{36}H_{34}N_8O_2S_2$ (674.85): C, 64.07; H, 5.08; N, 16.60; S, 9.50. Found: C, 63.91; H, 4.90; N, 16.40; S, 9.31%.

3.1.4. Preparation of the potassium salts 5a,b and 8. To a solution of KOH (1.14 g, 10 mmol) in methanol (10 ml) was added each of salicylaldehyde (**3**) (10 mmol) or bis(phenols) **4a**,**b** (5 mmol). The mixture was stirred at room temperature for 10 min. The solvent was then removed in vacuo. The remaining solid was triturated with dry ether, collected, dried, and used in the next step without further purification.

3.1.5. Reaction of epichlorohydrin with phenolic compounds for preparation of compounds 9 and 7c,d. *General procedure* (*A*). Potassium salts **8** (20 mmol) or **5a**,**b** (10 mmol) were dissolved in boiling water (20 ml). The solution is cool to 50 °C, epichlorohydrin (10 mmol) was added drop by drop with stirring over a period of 3 h. The reaction mixture is stirred at 50 °C for an additional 4 h and then cooled to room temperature to give **9** and **7c**,**d**.

3.2. Synthesis of compound 9

3.2.1. 1,3-Bis(2-formayphenoxy)-2-propanol (9). With the use of the general procedure (A) potassium salt **8** gave oily product which was extracted with chloroform. The organic layer washed with 1 N NaOH solution, dried with anhydrous $MgSO_4$. The solvent was then removed in vacuo. The solid obtained was collected and crystallized from benzene as yellow crystals, to give (65%) of **9**, mp 105 °C [lit.[25] 109.5–110.5 °C]; IR (cm^{-1}) 3467 (OH), 1679 (CO); ^{1}H NMR ($CDCl_3$) δ 3.65 (br s, 1H, OH), 4.32 (d, 4H, J=5 Hz, OCH2), 4.53 (quintet, 1H, J=5.4 Hz, CHOH), 7.02–7.83 (m, 8H, ArH's), 10.4 (s, 2H, CHO) ppm. (Calcd for $C_{16}H_{16}O_5$ (288.29): C, 66.66; H, 5.59. Found: C, 66.80; H, 5.70).

3.3. Synthesis of the macrocycles 7a-d

General procedure (*B*). To a solution of bis(carbonyl) ether **9** (5 mmol) in glacial acetic acid (50 ml) was added a solution of the appropriate bis(4-amino-1,2,4-triazol-3-ylsulfanyl)alkanes **3a**-**d** (5 mmol) in glacial acetic acid (30 ml). The reaction mixture was then heated under reflux for 3 h. The solvent was then removed in vacuo and the remaining residue washed with water and the solid obtained was collected and crystallized from the proper solvent to give colorless crystals of **7a**-**d**.

3.3.1. 3,23-Diphenyl-13-hydroxy-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (7a). With the use of the general procedure (B) **9** and **2a** gave crude **7a** which was crystallized from acetic acid as colorless crystals (50%), mp 264–6 °C; IR (cm^{-1}) 3380 (OH), 1599 (C=N); MS: m/z 688 (M$^+$, 80%); ^{1}H NMR (DMSO) δ 2.31 (quintet, 2H, J=7 Hz, SCH_2CH_2), 3.34 (m, 4H, SCH_2), 4.15–4.41 (m, 5H, OCH_2, CH–OH), 5.51 (d, 1H, J=4.2 Hz, OH), 7.1–8.15 (m, 18H, ArH's), 9.38 (s, 2H, CH=N) ppm. (Calcd for $C_{36}H_{32}N_8O_3S_2$ (688.83): C, 62.77; H, 4.68; N, 16.27; S, 9.31. Found: C, 62.90; H, 4.57; N, 16.40; S, 9.20).

3.3.2. 3,23-Diphenyl-13-hydroxy-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (7b). With the use of the general procedure (B) **9** and **2b** gave crude **7b** which was crystallized from dioxan as

colorless crystals (45%), mp 240–42 °C; IR (cm^{-1}) 3197 (OH), 1595 (C═N); MS: *m/z* 703 (M^++1, 50%); ^1H NMR (DMSO) δ 1.9 (br s, 4H, SCH_2CH_2), 3.23 (m, 4H, SCH_2), 4.15–4.54 (m, 5H, OCH_2, *CH*–OH), 5.53 (d, 1H, *J*=3.6 Hz, OH), 7.11–8.03 (m, 18H, ArH's), 9.40 (s, 2H, CH═N) ppm. (Calcd for $C_{37}H_{34}N_8O_3S_2$ (702.86): C, 63.23; H, 4.88; N, 15.94; S, 9.12. Found: C, 62.99; H, 4.77; N, 16.01; S, 9.31).

3.3.3. 3,23-Dibenzyl-13-hydroxy-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*]-[1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (7c). (a) With the use of the general procedure (B) **9** and **2c** gave crude **7c** which was crystallized from ethanol as colorless crystals (40%), mp 182–84 °C; IR (cm^{-1}) 3197 (OH), 1596 (C═N); MS: *m/z* 716 (M^+, 53%); ^1H NMR (DMSO) δ 2.23 (quintet, 2H, *J*=5.6 Hz, SCH_2CH_2), 3.28 (t, 4H, *J*=6.6 Hz, SCH_2), 4.1–4.35 (m, 5H, OCH_2, *CH*–OH), 4.22 (s, 4H, CH_2Ph), 5.5 (d, 1H, *J*=4.4 Hz, OH), 7.10–7.97 (m, 18H, ArH's), 9.28 (s, 2H, CH═N) ppm. (Calcd for $C_{38}H_{36}N_8O_3S_2$ (716.89): C, 63.67; H, 5.06; N, 15.63; S, 8.95. Found: C, 62.92; H, 5.22; N, 15.80; S, 9.21).

(b) With the use of the general procedure (A) **4a** gave 2% of **7c**

3.3.4. 3,23-Dibenzyl-13-hydroxy-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*]-[1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (7d). (a) With the use of the general procedure (B) **9** and **2d** gave crude **7d** which was crystallized from dioxan as colorless crystals (50%), mp 170–72 °C; IR (cm^{-1}) 3199 (OH), 1599 (C═N); MS: *m/z* 730 (M^+, 62%); ^1H NMR (DMSO) δ 1.8 (br s, 4H, SCH_2CH_2), 3.15 (m, 4H, SCH_2), 4.19 (s, 4H, CH_2Ph), 4.05–4.32 (m, 5H, OCH_2, *CH*–OH), 5.51 (d, 1H, *J*=4 Hz, OH), 7.10–7.99 (m, 18H, ArH's), 9.29 (s, 2H, CH═N) ppm. (Calcd for $C_{39}H_{38}N_8O_3S_2$ (730.91): C, 64.09; H, 5.24; N, 15.33; S, 8.77. Found: C, 63.99; H, 4.97; N, 15.11; S, 8.59).

(b) With the use of the general procedure (A) **4b** 2% of **7d**

3.4. Synthesis of chloroacetoxy macrocycles 11a,b

General procedure. A solution of each of macrocycles **7a**,**d** (5 mmol) in DMF (10 ml) was added 2-chloroacetyl chloride (5 mmol). The reaction mixture was stirred at room temperature for 3 h. then poured on cursed ice. The solid obtained was collected by filtration and crystallized from benzene to afforded colorless crystals of **11a**,**b**.

3.4.1. 13-Chloroacetoxy-3,23-diphenyl-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (11a). With the use of the general procedure **7a** gave **11a** (65%), mp 182–84 °C; IR (cm^{-1}) 1749 (CO), 1599 (C═N); ^1H NMR ($CDCl_3$) δ 2.43 (m, 2H, SCH_2CH_2), 3.48 (m, 4H, SCH_2), 4.02 (s, 2H, CH_2Cl), 4.42 (d, 4H, *J*=5 Hz, OCH_2), 5.74 (quintet, 1H, *J*=5.4 Hz, *CH*–OCO), 7.0–8.06 (m, 18H, ArH's), 9.15 (s, 2H, CH═N) ppm; ^{13}C ($CDCl_3$) δ 27.18, 32.77, 40.50, 66.90, 120.90, 126.65, 145.71, 152.80, 157.87, 166.44 (CH_2's and C's); 72.36, 112.61, 122.28, 127.62, 128.29, 128.45, 129.75, 134.38, 159.30 (CH's) ppm. (Calcd for $C_{38}H_{33}N_8O_4S_2Cl$ (765.31): C, 56.64; H, 4.35; N, 14.64; S, 8.38, Cl, 4.63. Found: C, 59.88; H, 4.44; N, 14.80; S, 8.20; Cl, 4.50).

3.4.2. 13-Chloroacetoxy-3,23-dibenzyl-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (11b). With the use of the general procedure **7d** gave **11b** (70%), mp 170–72 °C; IR (cm^{-1}) 1766 (CO), 1600 (C═N); ^1H NMR ($CDCl_3$) δ 1.93 (br s, 4H, SCH_2CH_2), 3.27 (br s, 4H, SCH_2), 3.96 (s, 2H, CH_2Cl), 4.25 (s, 4H, CH_2Ph), 4.36 (d, 4H, *J*=5.6 Hz, OCH_2), 5.79 (quintet, 1H, *J*=5.4 Hz, *CH*–OCO), 6.93–7.99 (m, 18H, ArH's), 9.16 (s, 2H, CH═N) ppm. (Calcd for $C_{41}H_{39}N_8O_4S_2Cl$ (807.40): C, 60.99; H, 4.87; N, 13.88; S, 7.94, Cl, 4.39. Found: C, 60.70; H, 4.74; N, 13.95; S, 8.10; Cl, 4.52).

3.5. Reaction of esters 11a,b with secondary amines (synthesis of compounds 12a,b, 13 and 14a,b)

General procedure. A mixture of each of **11a**,**b** (5 mmol) and excess of the appropriate secondary amines (*N*,*N*-diethylamine, morpholine, piperidine and piperazine) [6 mmol for compounds **13a**,**b**, **14** and 2.5 mmol of piperazine for compounds **11a**,**b**] in acetone (30 ml) was heated under reflux for 2 h. The solvent was then removed in vacuo. The solid obtained was crystallized from the proper solvent to give compounds **12a**,**b**, **13** and **14a**,**b**, respectively.

3.5.1. 3,23-Diphenyl-13-[2-(*N*-piperidino)acetoxy]-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (12a). With the use of the general procedure **11a** and morpholine gave crude **12b** which was crystallized from ethanol as colorless crystals (70%), mp 216–18 °C; ^1H NMR ($CDCl_3$) δ 1.32 (quintet, 2H, *J*=4.6 Hz, N–$CH_2CH_2CH_2$), 1.49 (quintet, 4H, *J*=4.8 Hz, N–$CH_2CH_2CH_2$), 2.4 (m, 6H, SCH_2CH_2, N–CH_2CH_2-CH_2), 3.17 (s, 2H, CH_2CO), 3.48 (br s, 4H, SCH_2), 4.41 (d, 4H, *J*=5.4 Hz, OCH_2), 5.68 (quintet, 1H, *J*=5.2 Hz, *CH*–OCO), 7.02–8.08 (m, 18H, ArH's), 9.16 (s, 2H, CH═N) ppm. (Calcd for $C_{43}H_{43}N_9O_4S_2$ (814.00): C, 63.45; H, 5.32; N, 15.49; S, 7.88. Found: C, 63.30; H, 5.50; N, 15.52; S, 7.80).

3.5.2. 3,23-Dibenzyl-13-[2-(*N*-morpholino)acetoxy]-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (12b). (a) With the use of the general procedure **11b** and morpholine gave crude **12b** which was crystallized from benzene as colorless crystals (65%), mp 204–6 °C; IR (cm^{-1}) 1749 (CO), 1599 (C═N), ^1H NMR ($CDCl_3$) δ 1.89 (br s, 4H, SCH_2CH_2), 2.43 (t, 4H, *J*=4.4 Hz, N–CH_2CH_2–O), 3.17 (s, 2H, CH_2CO), 3.23 (br s, 4H, SCH_2), 3.58 (t, 4H, *J*=4.4 Hz, N–CH_2CH_2–O), 4.25 (s, 4H, CH_2Ph), 4.35 (d, 4H, *J*=4.8 Hz, OCH_2), 5.73 (quintet, 1H, *J*=5 Hz, *CH*–OCO), 6.94–8.03 (m, 18H, ArH's), 9.18 (s, 2H, CH═N) ppm; ^{13}C ($CDCl_3$) δ 27.72, 31.58, 33.21, 52.88, 59.15, 66.58, 66.93, 120.82, 135.83, 144.82, 154.02, 157.62, 168.99 (CH_2's and C's); 70.16, 112.04, 121.96, 126.65, 127.02, 128.37, 128.79, 134.10, 156.35 (CH's) ppm. (Calcd for $C_{45}H_{47}N_9O_5S_2$ (858.06): C,

62.99; H, 5.52; N, 14.69; S, 7.47. Found: C, 63.10; H, 5.37; N, 14.80; S, 7.36).

3.5.3. 3,23-Dibenzyl-13-[2-(*N*,*N*-diethylamino)acetoxy]-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo-[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (13). With the use of the general procedure **11b** and diethylamine gave crude **13** which was crystallized from ethanol as colorless crystals (60%), mp 162–4 °C; IR (cm^{-1}) 1599 (C═N), 1746 (CO); ^1H NMR ((CDCl$_3$) δ 0.84 (t, 6H, J=7.2 Hz, CH_3), 1.81 (br s, 4H, SCH_2CH_2), 2.47 (q, 4H, J=7.2 Hz, CH_2CH_3), 3.13 (br s, 4H, SCH_2), 3.28 (s, 2H, CH_2CO), 4.18 (s, 4H, CH_2Ph), 4.34 (d, 4H, J=5.8 Hz, OCH_2), 5.75 (quintet, 1H, J=5.4 Hz, *CH*–OCO), 6.97–8.15 (m, 18H, ArH's), 9.25 (s, 2H, CH═N) ppm. (Calcd for $C_{45}H_{49}N_9O_4S_2$ (844.07): C, 64.03; H, 5.85; N, 14.93; S, 7.60. Found: C, 63.91; H, 5.75; N, 14.79; S, 7.40).

3.5.4. 1,4-Bis{(3,23-diphenyl-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*q*]-[1,19,5,6,14,15,8,12]dioxatetraazadithiacyclododocosine)-13-yloxycarbonylmethyl}piperazine (14a). With the use of the general procedure **11a** and piperazine gave crude **14a** which was crystallized from acetic acid as colorless crystals (50%), mp 204–205 °C; IR (cm^{-1}) 1747 (CO), 1600 (C═N); ^1H NMR (CDCl$_3$) δ 2.42 (quintet, 4H, J=6.4 Hz, SCH_2CH_2), 2.77 (br s, 8H, NCH_2), 3.38 (s, 4H, CH_2CO), 3.48 (m, 8H, SCH_2), 4.41 (m, 8H, OCH_2),5.79 (br s, 2H, CH–OCO), 7.02–8.04 (m, 36H, ArH's), 9.15 (s, 4H, CH═N) ppm. (Calcd for $C_{80}H_{74}N_{18}O_8S_4$ (1543.84): C, 62.24; H, 4.83; N, 16.33; S, 8.31. Found: C, 62.33; H, 4.92; N, 16.45; S, 8.51).

3.5.5. 1,4-Bis{(3,23-dibenzyl-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*]-[1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine)-13-yloxycarbonylmethyl}piperazine (14b). With the use of the general procedure **11b** and piperazine gave crude **14b** which was crystallized from acetic acid as colorless crystals (60%), mp 236–38 °C; IR (cm^{-1}) 1759 (CO), 1600 (C═N); ^1H NMR (CDCl$_3$) δ 1.8 (br s, 8H, SCH_2CH_2), 2.26 (s, 8H, NCH_2), 3.02 (s, 4H, CH_2CO), 3.14 (br s, 8H, SCH_2), 4.14 (s, 8H, CH_2Ph), 4.27 (d, 8H, J=5.2 Hz, OCH_2), 5.66 (quintet, 2H, J=5 Hz, CH–OCO), 6.89–7.93 (m, 36H, ArH's), 9.10 (s, 4H, CH═N) ppm; ^{13}C NMR (DMSO) δ 26.65, 29.98, 31.91, 50.63, 57.35, 66.55, 119.28, 135.36, 143.48, 152.32, 157.15, 168.26 (CH_2's and C's), 69.43, 112.31, 120.75, 125.81, 125.91, 127.61, 127.89, 133.90, 157.87 (CH's). (Calcd for $C_{86}H_{86}N_{18}O_8S_4$ (1628.01): C, 63.45; H, 5.32; N, 15.49; S, 7.88. Found: C, 63.52; H, 5.42; N, 15.60; S, 7.72).

3.6. Action of sodium borohydride on 7a-d and 12b. Synthesis of 15a-d

General procedure. To a stirred boiling solution of each of **7a-d** and **12b** (0.7 mmol) in methanol (30 ml) was added sodium borohydride (0.4 g) over a period of 15 min. The reaction mixture was heated under reflux for 1 h. The solvent was then removed in vacuo and the remaining residue washed with water. The solid obtained was collected and crystallized from the proper solvent to give colorless crystals of **15a-d**.

3.6.1. 3,23-Diphenyl-13-hydroxy-5,6,12,13,20,21,27,28-octahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclododocosine (15a). With the use of the general procedure **7a** gave crude **15a** which was crystallized from dil. ethanol as colorless crystals (70%), mp 270–72 °C; IR (cm^{-1}) 3347 (NH), 3181 (OH); ^1H NMR (DMSO) δ 2.15 (quintet, 2H, J=6.8 Hz, SCH_2CH_2), 3.23 (t, 4H, J=6.8 Hz, SCH_2), 3.91–4.25 (m, 9H, OCH_2, Ar–CH_2, *CH*–OH), 4.39 (t, 2H, J=5 Hz, NH), 5.26 (d, 1H, J=4.6 Hz, OH), 6.83–8.06 (m, 18H, ArH's) ppm. (Calcd for $C_{36}H_{36}N_8O_3S_2$ (692.86): C, 62.41; H, 5.24; N, 16.17; S, 9.26. Found: C, 62.60; H, 5.33; N, 16.23; S, 9.10).

3.6.2. 3,23-Diphenyl-13-hydroxy-5,6,12,13,20,21,27,28,29,30-decahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (15b). With the use of the general procedure **7b** gave crude **15b** which was crystallized from acetic/ethanol mixture as colorless crystals (70%), mp 262–64 °C; IR (cm^{-1}) 3537 (NH), 3276 (OH); ^1H NMR (DMSO) δ 1.79 (br s, 4H, SCH_2CH_2), 3.2 (br s, 4H, SCH_2), 3.9–4.35 (m, 9H, OCH_2, Ar–CH_2, *CH*–OH), 5.3 (br s, 1H, OH), 6.81–8.05 (m, 20H, ArH's, NH) ppm. (Calcd for $C_{37}H_{38}N_8O_3S_2$ (706.89): C, 62.87; H, 5.42; N, 15.85; S, 9.07. Found: C, 62.59; H, 5.60; N, 15.70; S, 8.90).

3.6.3. 3,23-Dibenzyl-13-hydroxy-5,6,12,13,20,21,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo][*b*,*q*[1,19,5,6,14,15,8,12]dioxatetraazadithiacyclododocosine (15c). With the use of the general procedure **7c** gave crude **15c** which was crystallized from ethanol as colorless crystals (65%), mp 268–70 °C; IR (cm^{-1}) 3347 (NH), 3181 (OH); ^1H NMR (DMSO) δ 2.09 (br s, 2H, SCH_2CH_2), 3.22 (br s, 4H, SCH_2), 3.98–4.35 (m, 13H, PhCH_2, OCH_2, Ar–CH_2, *CH*–OH), 5.21 (s, 1H, OH), 6.72 (t, 2H, J=5.2 Hz, NH), 6.92–7.33 (m, 18H, ArH's) ppm. (Calcd for $C_{38}H_{40}N_8O_3S_2$ (720.92): C, 63.31; H, 5.59; N, 15.54; S, 8.90. Found: C, 63.20; H, 5.65; N, 15.31; S, 8.74).

3.6.4. 3,23-Dibenzyl-13-hydroxy-5,6,12,13,20,21,27,28,29,30-decahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (15d). (a) With the use of the general procedure **7d** gave crude **15d** which was crystallized from acetic / ethanol mixture as colorless crystals (68%), mp 138–40 °C; IR (cm^{-1}) 3300 (NH), 3230 (OH); ^1H NMR (CDCl$_3$) δ 1.82 (br s, 4H, SCH_2CH_2), 3.2 (m, 4H, SCH_2), 3.71–4.13 (m, 9H, OCH_2, Ar–CH_2, *CH*–OH), 4.01 (s, 4H, CH_2Ph), 4.54 (br s, 1H, OH), 5.35 (t, 2H, J=6.4 Hz, NH), 6.85–7.35 (m, 18H, ArH's) ppm. (Calcd for $C_{39}H_{42}N_8O_3S_2$ (734.94): C, 63.74; H, 5.76; N, 15.25; S, 8.73. Found: C, 63.59; H, 5.63; N, 15.45; S, 8.70).

(b) Compound **12b** gave 65% of **15d**.

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