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Synthesis of Novel Macrocyclic Di- and Tetralactams Containing Triazole Subunits

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ABSTRACT: *The new macrocyclic di- and tetralactams* **9, 15**, *and* **16** *were obtained in 16–24% yields by heating the appropriate bis-amines* **7** *or* **8** *with the corresponding bisaldehyde* **5** *or* **14** *in refluxing acetic acid under high-dilution conditions.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:551–559, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10191

INTRODUCTION

Crown ethers were discovered by Pederson at DuPont in 1967 [1]. 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 complexes formed with both metal and organic cations. These changes involve the substitution of ligand polyether oxygen donor atoms by sulfur and/or nitrogen atoms [2,3]. Other changes involve the insertion of aromatic and/or heterocyclic ring systems [4–10] into the macrocycles. Heterocyclic groups provide rigidity and are able, in some cases, in complexation through their soft donor atoms. To improve the binding ability of macrocyclic receptors for alkali metal cations, much attention has been paid to the development of functional groups in the ring, e.g. incorporation of an amide linkage in a polyether macrocycle has been reported to modify the binding properties of crown ether compounds [11–14]. Macrocyclic amides are precursors in the preparation of azacrown compounds, which are used for the synthesis of cryptands [15,16]. These have also been reported as new catalysts in the highly regioselective cleavage of epoxides with elemental halogens [17]. Moreover, heteronuclear metal ion receptors, which should possess two sets of binding sites, have recently received considerable attention [18,19].

In continuation of our interest in the synthesis of novel macrocyclic dilactams [20–25], we report herein our efforts to develop new macrocyclic di- and tetralactam, fused to two benzene and two 1,2,4-triazole rings, which can be used for heteronuclear binding with metal cations.

RESULTS AND DISCUSSION

We demonstrate a new method to introduce the amide groups into macrocycles employing the new precursors **5** and **7** (as outlined in Scheme 1). Thus, reaction of chloroacetyl chloride **1** with each of 1,2-diaminoethane, 1,3-diaminopropane, and 1,4-diaminobutane afforded 70–80% of the corresponding 1,ω-bis(chloroacetylamino)-alkanes **3a–c** followed the method described by Lin et al. [26] for **3a** after some modifications. Reaction of the latter with the potassium salt of salicylaldehyde in boiling DMF for 5 min afforded the corresponding 1,ω-bis(2-formylphenoxy-acetamido)alkanes **5a–c** in 72–78% yields. It is noteworthy to mention that Lindoy et al. [27] reported the synthesis of **5a** in 72% yield by reacting **4** with **3a** in DMF containing *t*-BuOK at 80°C overnight. Moreover, reaction of the appropriate 4-amino-1,2,4-triazole-3(2*H*)-thiones **6a–c** [28] with **3a,b** in ethanol/water mixture containing

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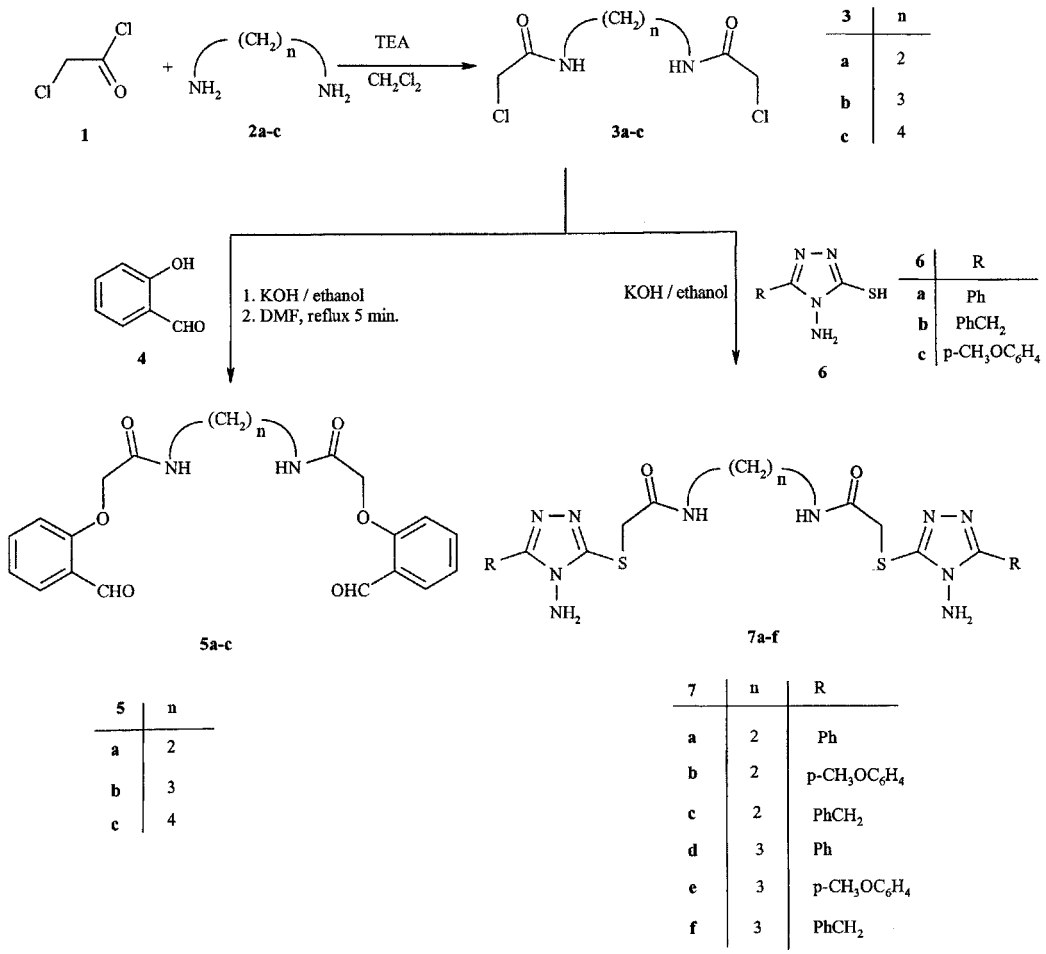


3	n
a	2
b	3
c	4

6	R
a	Ph
b	$PhCH_2$
c	$p\text{-}CH_3OC_6H_4$

5	n
a	2
b	3
c	4

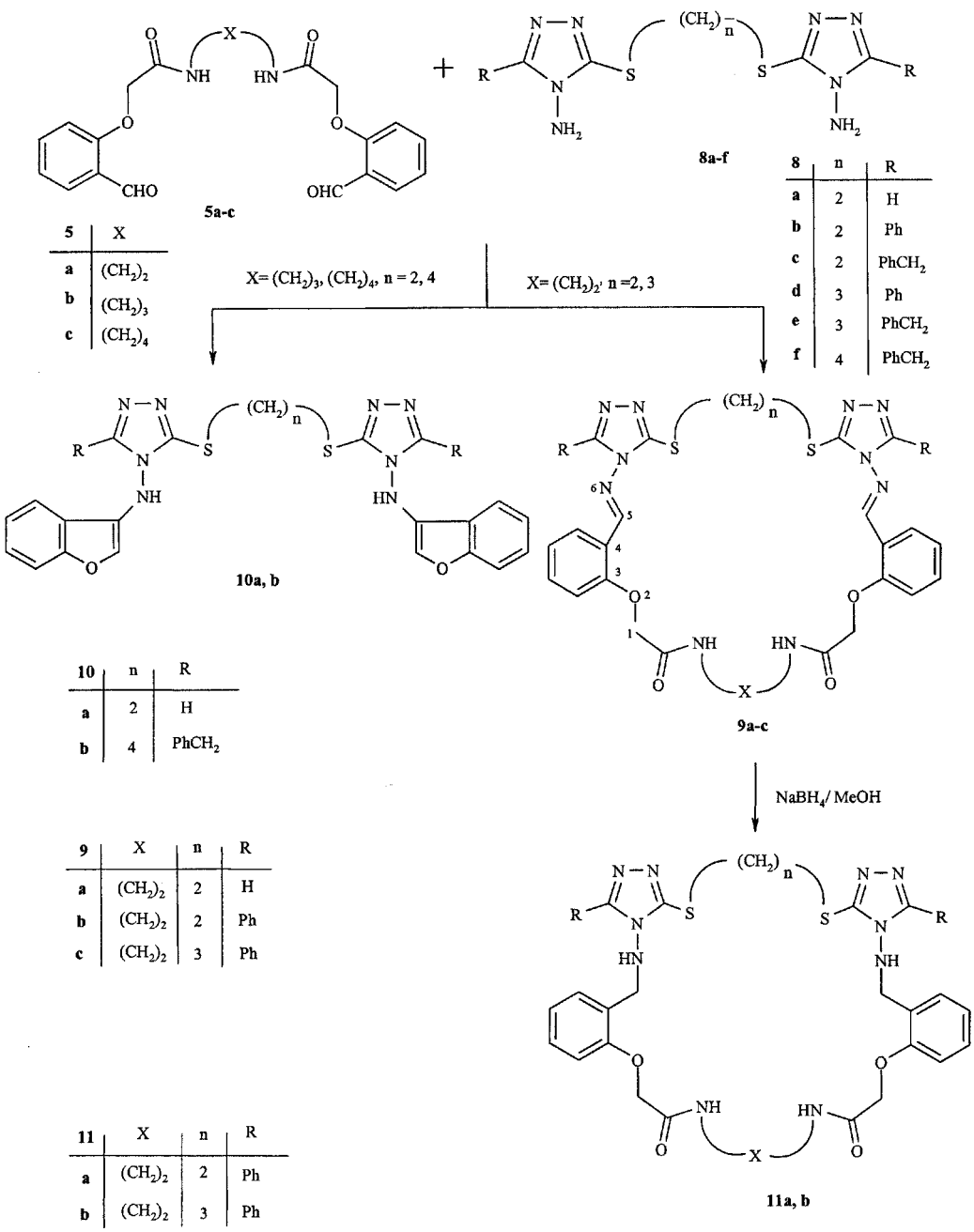
7	n	R
a	2	Ph
b	2	$p\text{-}CH_3OC_6H_4$
c	2	$PhCH_2$
d	3	Ph
e	3	$p\text{-}CH_3OC_6H_4$
f	3	$PhCH_2$

SCHEME 1

KOH gave the corresponding 1,ω-bis(4-amino-1,2,4-triazole-3-ylsulphanylacetamido)-alkane **7a–f** in 56–67% yields. The exclusive formation of the latter is in accordance with previous results [29–35], which assure the preferential alkylation of 4-substituted-1,2,4-triazolethiones on sulfur. The use of Schiff base condensation of the appropriate bisaldehyde with the corresponding bisamines under high dilution conditions should then afford the target molecules **9, 15**, and **16** as outlined in Schemes 2 and 3.

Thus, cyclocondensation of the bisaldehyde **5a** [X = $(CH_2)_2$] with the bisamines [29] [**8a,b**, $n = 2$] in refluxing acetic acid under high-dilution conditions afforded the corresponding macrocyclic Schiff bases **9a,b** in 18–24% yields. Elongation of the spacer group of the bis-triazole part from ethylene to 1,3-propylene (for example **8d**) while holding the ethylene spacer in the aldehyde part constant led to the formation of the expected macrocyclic Schiff base **9c** in 22% yields. On the other hand, when the spacer group in the aldehyde part (X) is elongated to 1,3-propylene (e.g., **5b**) while the spacer group in the triazole part is ethylene or 1,4-butylene ($n = 2$ or 4) (e.g., **8a,f**) we did not isolate the corresponding macrocyclic Schiff base. Instead, compound **10a,b**, respectively, were formed in 35–39% yields. Compound **10a** was alternatively obtained in 32% yield by cyclocondensation of **5c** with **8a** in refluxing acetic acid. The structure proposed for the new 1,ω-bis{4-[(benzo[*b*]furan-3-yl)amino]-1,2,4-triazol-3-ylsulfanyl}alkanes **10a,b** are consistent with the data obtained from their IR, ^{1}H NMR, and mass spectroscopy.

The reaction proceeds via an initial formation of the corresponding macrocyclic Schiff base **9**, (X = $(CH_2)_3$ or $(CH_2)_4$, $n = 2$ or 4) followed by attack of the active methylene C-1 on the benzylideneamino C-5 and subsequent aromatization with elimination of the amide part. Protonation of the benzylideneamino nitrogen N-6 under the acidic conditions enhanced the electrophilicity of the carbon atom C-5 and facilitate the attack of the methylene group.



5	X
a	$(CH_2)_2$
b	$(CH_2)_3$
c	$(CH_2)_4$

8	n	R
a	2	H
b	2	Ph
c	2	$PhCH_2$
d	3	Ph
e	3	$PhCH_2$
f	4	$PhCH_2$

10	n	R
a	2	H
b	4	$PhCH_2$

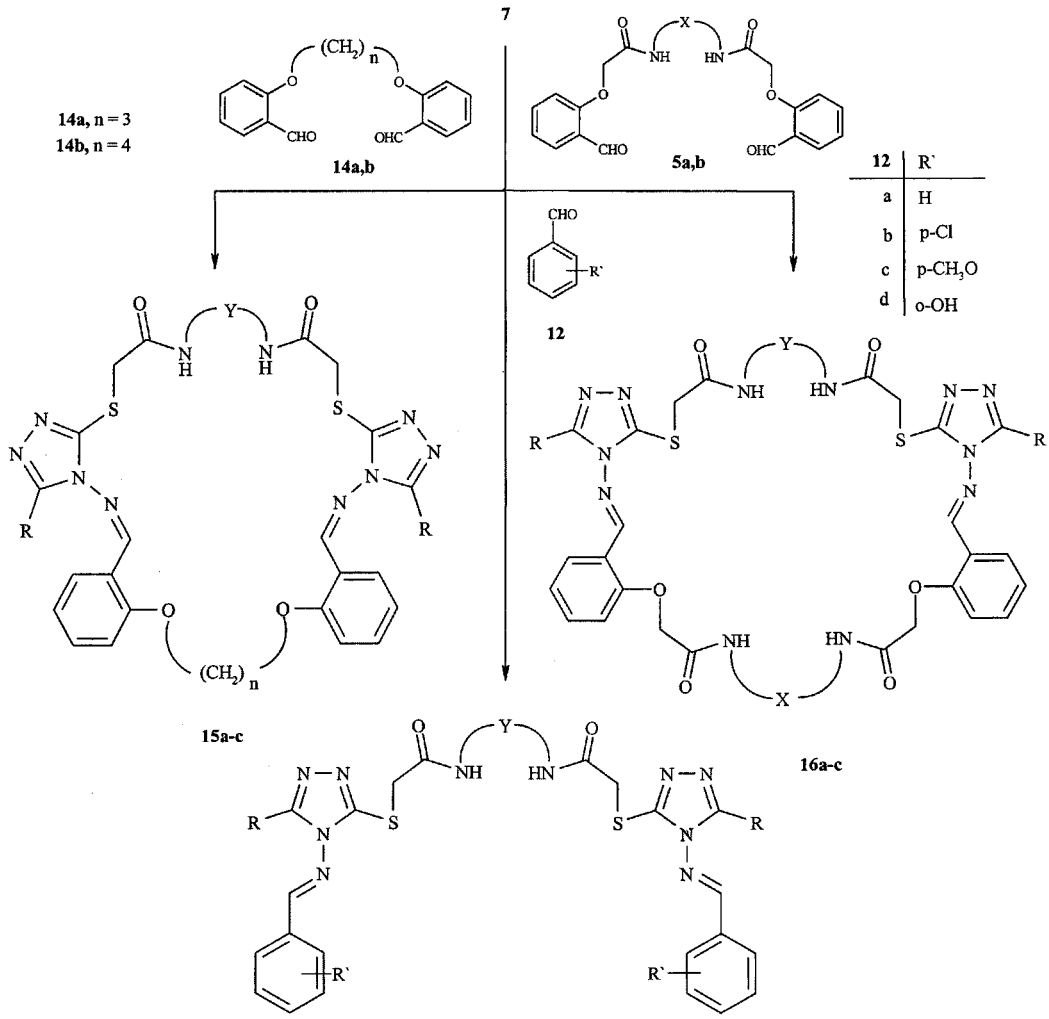
9	X	n	R
a	$(CH_2)_2$	2	H
b	$(CH_2)_2$	2	Ph
c	$(CH_2)_2$	3	Ph

11	X	n	R
a	$(CH_2)_2$	2	Ph
b	$(CH_2)_2$	3	Ph

SCHEME 2

Sodium borohydride reduction of **9b,c** in methanol furnished 79 and 80% yields, respectively, of the corresponding macrocyclic dilactams **11a,b**. We now studied the synthesis of new macrocyclic dilactams in which the amide linkage are located in the triazol part (see Scheme 3). The alteration of the position of the amide linkage might modify the binding properties of these macrocycles. The synthetic route is outlined in Scheme 3.

The bisamines **7** were chosen as key intermediates and their reactivities toward condensation with aromatic aldehydes were first investigated by reaction with a series of aromatic aldehydes **12a–d** in refluxing acetic acid. As expected, the corresponding bis(benzylideneamino) derivatives **13a–f** were formed in 50–80% yields. We then reacted each of **7b, 7c**, and **7a** with the appropriate bisaldehydes **14** [22] in refluxing acetic acid under high-dilution conditions to give the macrocycles **15a–c**, respectively,



12	R`
a	H
b	p-Cl
c	p-CH_3O
d	o-OH

15	n	Y	R
a	3	$(CH_2)_2$	p-$CH_3OC_6H_4$
b	3	$(CH_2)_2$	$PhCH_2$
c	4	$(CH_2)_2$	Ph

13	Y	R	R`
a	$(CH_2)_2$	Ph	H
b	$(CH_2)_2$	Ph	p-CH_3O
c	$(CH_2)_2$	p-$CH_3OC_6H_4$	o-OH
d	$(CH_2)_3$	p-$CH_3OC_6H_4$	p-Cl
e	$(CH_2)_3$	Ph	o-OH
f	$(CH_2)_3$	Ph	p-Cl

16	X	Y	R
a	$(CH_2)_2$	$(CH_2)_2$	Ph
b	$(CH_2)_3$	$(CH_2)_2$	Ph
c	$(CH_2)_2$	$(CH_2)_3$	Ph

SCHEME 3

in 18–24% yields. Similarly, the macrocyclic tetralactams **16a–c** could be obtained in 16–22% yields by reacting **7a,d** with **5a,b** in refluxing acetic acid under high-dilution conditions. Attempts to get **15c** and **16a** by reacting **13e** (R′ = *o*-OH) with the appropriate dihalo compounds in sodium ethoxide solutions were unsuccessful.

This proves that the use of Schiff base condensation under high-dilution conditions is still the most versatile procedure for the synthesis of the target macrocycles **9, 15**, and **16**. Unfortunately, repeated attempts to reduce compounds **15** or **16** to the corresponding azamacrocycles in methanolic solution containing $NaBH_4$ were unsuccessful. This may be

attributed to the insolubility of the macrocycle Schiff base **15** and **16** in the reaction media.

In conclusion, we prepared a series of new benzo substituted macrocyclic di- and tetraamides upon which are fused two triazole rings and contain N, O, and S as donor atoms. We could also introduce the amide linkages in different positions in the macrocycles. We expect this should modify the binding ability of the new macrocycles. Study of the cation binding properties of these macrocycles is still underway.

EXPERIMENTAL

All melting points are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian Gemini 200 spectrometer (200 MHz ^{1}H NMR). Mass spectra were recorded on a GC MS-QP1000 EX (70 eV) or MS 5 988 (15 eV) spectrometers. Elemental analyses were carried out at the Microanalytical Centre, Cairo University, Egypt.

Synthesis of **5a–c***, General Procedure*

A solution of the potassium salt of salicylaldehyde **4** (20 mmol) and the appropriate dichloro compound **3a–c** (10 mmol) in DMF (20 ml) was heated under reflux for 5 min during which the potassium chloride was precipitated. The solution was then concentrated to small volume (ca. 2 ml) and then cold water (ca. 10 ml) was added and the precipitate was collected and recrystallized from acetic acid as pale yellow crystals of **5a–c**.

*1,2-Bis(2-formylphenoxyacetamido)ethane (***5a***).* The potassium salt of **4** and **3a** gave **5a** (78%), mp 188–190°C; (lit. [27] mp 188–189°C).

*1,3-Bis(2-formylphenoxyacetamido)propane (***5b***).* The potassium salt of **4** and **3b** gave **5b** (72%), mp 164–165°C; IR: 3400 (NH), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (t, 2H, $J = 6$ Hz, $\underline{CH_2}CH_2NH$), 3.42 (q, 4H, $J = 6$ Hz, $\underline{CH_2}NH$), 4.57 (s, 4H, OCH_2), 6.9–8.0 (m, 10H, ArH's, NH), 10.28 (s, 2H, CHO).

Anal. for $C_{21}H_{22}N_2O_6$ (398.41). Calcd.: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.33; H, 5.51; N, 7.09.

*1,4-Bis(2-formylphenoxyacetamido)butane (***5c***).* The potassium salt of **4** and **3c** gave **5c** (75%), mp 178°C, IR: 3400 (NH), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (br, 4H, $\underline{CH_2}CH_2NH$), 3.4 (q, 4H, $J = 5.8$ Hz, $\underline{CH_2}NH$), 4.58 (s, 4H, OCH_2), 6.9–7.79 (m, 10H, ArH's, NH), 10.16 (s, 2H, CHO).

Anal. for $C_{22}H_{24}N_2O_6$ (412.44). Calcd.: C, 64.07; H, 5.86; N, 6.79. Found: C, 63.98; H, 5.91; N, 6.69.

Synthesis of **7a–f***, General Procedure*

To a solution of potassium hydroxide (0.12 g, 20 mmol), ethanol/water mixture (1:1) (15 ml) was added with stirring the triazole **6a–d** (20 mmol). To the formed potassium salt was added the appropriate dichloro compound **3a–c** (10 mmol). The mixture was heated under reflux for 1 h during which a colorless solid was precipitated. The product was collected and recrystallized from acetic acid to give colorless crystals of **7a–f**.

*1,2-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylacetamido)ethane (***7a***).* Compounds **6b** and **3a** gave **7a** (61%), mp 250°C; IR: 3286.5 (NH), 1651 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.16 (br, 4H, $\underline{CH_2}NH$), 3.92 (s, 4H, SCH_2), 6.22 (s, 4H, NH_2), 7.5–8.0 (m, 10H, ArH's), 8.34 (br, 2H, NH).

Anal. for $C_{22}H_{24}N_{10}O_2S_2$ (524.62). Calcd.: C, 50.37; H, 4.61; N, 26.70. Found: C, 50.32; H, 4.52; N, 26.51.

*1,2-Bis{4-amino-5-(p-methoxyphenyl)-1,2,4-triazol-3-ylsulfanylacetamido}ethane (***7b***).* Compounds **6d** and **3a** gave **7b** (55%), mp 228–230°C; IR: 3278.8 (NH), 1651 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.16 (br, 4H, $\underline{CH_2}NH$), 3.89 (s, 6H, OCH_3), 3.92 (s, 4H, SCH_2), 6.18 (s, 4H, NH_2), 7.06–7.98 (m, 8H, ArH's), 8.33 (br, 2H, NH).

Anal. for $C_{24}H_{28}N_{10}O_4S_2$ (584.68). Calcd.: C, 49.3; H, 4.30; N, 23.96. Found: C, 49.42; H, 4.35; N, 23.90.

*1,2-Bis(4-amino-5-benzyl-1,2,4-triazol-3-ylsulfanylacetamido)ethane (***7c***).* Compounds **6c** and **3a** gave **7c** (62%), mp 228–230°C; IR: 3286.5 (NH), 1651.0 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.1 (s, 4H, $\underline{CH_2}NH$), 3.8 (s, 4H, SCH_2), 4.07 (s, 4H, $PhCH_2$), 5.95 (s, 4H, NH_2), 7.28 (m, 10H, ArH's), 8.25 (br, 2H, NH).

Anal. for $C_{24}H_{28}N_{10}O_2S_2$ (552.68). Calcd.: C, 52.16; H, 5.11; N, 25.34. Found: C, 52.05; H, 5.11; N, 25.2.

*1,3-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylacetamido)propane (***7d***).* Compounds **6b** and **3b** gave **7d** (56%), mp 224–225°C; IR: 3201.6 (NH), 1674.1 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.55 (quintet, 2H, $J = 6.8$ Hz, $\underline{CH_2}CH_2NH$), 3.1 (q, 4H, $J = 6.2$ Hz, $\underline{CH_2}NH$), 3.9 (s, 4H, SCH_2), 6.2 (s, 4H, NH_2), 7.5–8.1 (m, 10H, ArH's), 8.28 (t, 2H, $J = 5.2$ Hz, NH).

Anal. for $C_{23}H_{26}N_{10}O_2S_2$ (538.65). Calcd.: C, 51.29; H, 4.86; N, 26.00. Found: C, 51.11; H, 4.65; N, 25.85.

*1,3-Bis[4-amino-5-(p-methoxyphenyl)-1,2,4-triazol-3-ylsulphanylacetamido]propane (***7e***).* Compounds **6d** and **3b** gave **7e** (52%), mp 238°C; IR: 3286.5 (NH), 1643.2 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.54 (quintet, 2H, $J = 6$ Hz, $\underline{CH_2}CH_2NH$), 3.1 (q, 4H, $J = 5.8$ Hz, $\underline{CH_2}NH$), 3.83 (s, 6H, OCH_3), 3.88 (s, 4H, SCH_2), 6.16 (s, 4H, NH_2), 7.1–7.9 (m, 8H, ArH's), 8.26 (br, 2H, NH).

Anal. for $C_{25}H_{30}N_{10}O_4S_2$ (598.71). Calcd.: C, 50.15; H, 5.05; N, 23.39. Found: C, 50.20; H, 5.60; N, 23.20.

*1,3-Bis(4-amino-5-benzyl-1,2,4-triazol-3-ylsulfanylacetamido)propane (***7f***).* Compounds **6c** and **3b** gave **7f** (67%), mp 178–180°C; IR: 3309 (NH), 1651.0 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.48 (quintet, 2H, $J = 4.8$ Hz, $\underline{CH_2}CH_2NH$), 3.0 (q, 4H, $J = 5.6$ Hz, $\underline{CH_2}NH$), 3.76 (s, 4H, SCH_2), 4.03 (s, 4H, $PhCH_2$), 5.89 (s, 4H, NH_2), 7.29 (m, 10H, ArH's), 8.2 (t, 2H, $J = 5.6$ Hz, NH).

Anal. for $C_{25}H_{30}N_{10}O_2S_2$ (566.7). Calcd.: C, 52.99; H, 5.34; N, 24.72. Found: C, 53.00; H, 5.25; N, 24.60.

Synthesis of Macrocyclic Schiff Bases **9a–c**, **15a–c**, *and* **16a–c**, *1,ω-Bis{(benzofuranyl)-amino-1,2,4-triazol-3-ylsulfanylacetamido}-alkanes* **10a,b**, *and Bis-Schiff Bases* **13a–f**, *General Procedure*

To a solution of each of the appropriate bisaldehyde **5a,c** or **14b,c** (10 mmol) or the aromatic aldehyde **12a–d** (20 mmol) in glacial acetic acid (50 ml) was added a solution of the bisamine **7a–f** or **8a–f** (10 mmol) in glacial acetic acid (50 ml). The reaction mixture was then heated under reflux for 2 h. The solution was concentrated to small volume (ca. 2 ml). Then cold water (ca. 15 ml) was added and the precipitate was collected and recrystallized from the proper solvent to give crystals of **9a–c, 10a,b, 13a–f, 15a–c**, and **16a–c**.

*15,16,32,33-Tetrahydro-12H,19H-bis[1,2,4]triazolo[4,3-f:3,4-l]dibenzo[b,p][1,18]dioxa[8,11]dithia[5,6,13,14,21,24]hexaazahexacosine-13,18-(14H,17H)-dione (***9a***).* Reaction of **5a** and **8a** gave crude **9a**, which was recrystallized from ethanol as colorless crystals (22%), mp 250°C; MS: *m/z* 606 (M^+, 68.8%), 537 (62.5%), 405 (68.8%), 365 (68.8%), 213 (100%); 192 (68.8%), 73 (87.5%); ^1H NMR (DMSO-d_6) δ 3.2 (br, 4H CH_2NH), 3.6 (s, 4H, SCH_2), 4.7 (s, 4H, OCH_2), 6.8–7.7 (m, 8H, ArH's), 8.24 (s, 2H, NH), 8.75 (s, 2H, CH=N), 9.48 (s, 2H, triazole-H).

Anal. for $C_{26}H_{26}N_{10}O_4S_2$ (606.68). Calcd.: C, 51.47; H, 4.32; N, 23.09. Found: C, 51.43; H, 4.51; N, 22.85.

*3,28-Diphenyl-15,16,32,33-tetrahydro-12H,19H-bis[1,2,4]triazolo[4,3-f:3,4-l]dibenzo[b,p][1,18]dioxa[8,11]dithia[5,6,13,14,21,24]hexaazahexacosine-13,18-(14H,17H)dione (***9b***).* Reaction of **5a** and **8b** gave crude **9b**, which was recrystallized from acetic acid/ethanol as colorless crystals (18%), mp 273°C; ^1H NMR (DMSO-d_6) δ 3.32 (s, 4H, $\underline{CH_2}NH$), 3.69 (s, 4H, SCH_2), 4.62 (s, 4H, OCH_2), 7.1–8.02 (m, 8H, ArH's), 8.25 (br, 2H, NH), 9.39 (s, 2H, CH=N).

Anal. for $C_{38}H_{34}N_{10}O_4S_2$ (758.88). Calcd.: C, 60.14; H, 4.52; N, 18.46. Found: C, 59.93; H, 4.55; N, 18.6.

*3,28-Diphenyl-15,16,32,33-tetrahydro-12H,19H,34H-bis[1,2,4]triazolo[4,3-f:3,4-m]dibenzo[b,q][1,19]-dioxa[8,12]dithia[5,6,14,15,22,25]hexaazaheptacosine-13,18-(14H,17H)dione (***9c***).* Reaction of **5a** and **8d** gave crude **9d**, which was recrystallized from acetic acid as colorless crystals (24%), mp 230–232°C; MS: *m/z* 772.45 (M^+, 66.7%), 700 (86.7%), 642 (100%), 531 (60%), 496 (15%), 359 (66.7%), 203 (93.3%), 145 (86.7%), ^1H NMR (DMSO-d_6) δ 2.29 (br, 2H, S, $CH_2\underline{CH_2}$), 3.28 (br, 4H, CH_2NH), 3.4 (s, 4H, SCH_2), 4.62 (s, 4H, OCH_2), 7.15–8.01 (m, 18H, ArH's), 8.21 (br, 2H, NH), 9.45 (s, 2H, CH=N).

Anal. for $C_{39}H_{36}N_{10}O_4S_2$ (772.91). Calcd.: C, 60.61; H, 4.69; N, 18.12. Found: C, 60.42; H, 4.46; N, 17.99.

*1,2-Bis{4-(benzo[b]furan-3-yl)amino-1,2,4-triazol-3-ylsulfanylacetamido}ethane (***10a***).* Reaction of **5b** (or **5c**) and **8a** gave crude **10a**, which was recrystallized from acetic acid as colorless crystals (35%), mp 257°C; IR: 3165.0 (NH); MS: *m/z* 490 (M^+, 37.5%), 443 (62.5%), 453 (100%), 302 (41.6%), 229 (75%), 119 (75%), 61 (66.6%); ^1H NMR (DMSO-d_6) δ 3.65 (s, 4H, SCH_2), 6.9–7.8 (m, 8H, ArH's), 9.1 (s, 2H, Benzofuran-H), 9.44 (s, 2H, triazole-H), 10.6 (br, 2H, NH).

Anal. for $C_{22}H_{18}N_8O_2S_2$ (490.0). Calcd.: C, 53.86; H, 3.70; N, 22.84. Found: C, 53.65; H, 3.50; N, 23.10.

*1,4-Bis{4-(benzo[b]furan-3-yl)amino-5-benzyl-1,2,4-triazol-3-ylsulfanylacetamido}butane (***10b***).* Reaction of **5b** and **8f** gave crude **10b**, which was recrystallized from acetic acid as colorless crystals (39%), mp 250°C; IR: 3128 (NH); MS: *m/z* 698.4 (M^+, 22.5%), 569 (22.5%), 389 (32.5%), 326 (30%), 287 (37.5%), 118 (77%), 60 (100%); ^1H NMR ($CDCl_3$) δ 1.72 (t, 4H, $\underline{CH_2}CH_2S$), 3.13 (br, 4H, SCH_2), 4.19 (s, 4H, $Ph\underline{CH_2}$), 6.9–7.8 (m, 18H, ArH's), 8.87 (s, 2H, Benzofuran-H), 10.5 (br, 2H, NH).

Anal. for $C_{38}H_{34}N_4O_2S_2$ (698.87). Calcd.: C, 65.3; H, 4.90; N, 16.03. Found: C, 65.20; H, 4.67; N, 16.00.

*1,2-Bis(4-benzyledineamino-5-phenyl-1,2,4-triazol-3-ylsulfanylacetamino)ethane (***13a***).* Reaction of **12a** and **7a** gave crude **13a**, which was recrystallized from acetic acid as colorless crystals (70%), mp 228–230°C; IR: 3332.8 (NH), 1651.0 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.14 (br, 4H: $\underline{CH_2}NH$), 3.97 (s, 4H, SCH_2), 7.4–7.94 (m, 20H, ArH's), 8.31 (br, 2H, NH), 8.9 (s, 2H, CH=N).

Anal. for $C_{36}H_{32}N_{10}O_2S_2$ (700.8). Calcd.: C, 61.7; H, 4.6; N, 19.94. Found: C, 61.56; H, 4.43; N, 19.79.

*1,2-Bis{4-(p-methoxy)benzylideneamino-5-phenyl-1,2,4-triazol-3-ylsulfanylacetamino}ethane (***13b***).* Reaction of **12c** and **7a** gave crude **13b**, which was recrystallized from ethanol/acetic acid as colorless crystals (75%), mp 232°C; IR: 3348.2 (NH), 1658.7 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.16 (br, 4H, $\underline{CH_2}NH$), 3.87 (s, 6H, OCH_2), 3.96 (s, 4H, SCH_2), 7.11–7.90 (m, 18H, ArH's), 8.29 (br, 2H, NH), 8.78 (s, 2H, CH=N).

Anal. for $C_{38}H_{36}N_{10}O_4S_2$ (760.9). Calcd.: C, 59.98; H, 4.77; N, 18.41. Found: C, 59.88; H, 4.59; N, 18.23.

*1,2-Bis{4-(o-hydroxy)benzylideneamino-5-(p-methoxy)phenyl-1,2,4-triazol-3-yl-sulfanylacetamino}-ethane (***13c***).* Reaction of **12d** and **7b** gave crude **13c**, which was recrystallized from acetic acid as colorless crystals (80%), mp 220–222°C; IR: 3220 (NH), 1651.0 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.16 (br, 4H, $\underline{CH_2}NH$), 3.87 (s, 6H, OCH_3), 3.96 (s, 4H, SCH_2), 6.98–7.89 (m, 16H, ArH's), 8.33 (br, 2H, NH), 8.97 (s, 2H, CH=N), 8.97 (s, 2H, OH).

Anal. for $C_{38}H_{36}N_{10}O_6O_6S_2$ (792.8). Calcd.: C, 57.56; H, 4.58; N, 17.67. Found: C, 57.52; H, 4.51; N, 17.49.

*1,3-Bis{4-(p-chloro)benzylideneamino-5-(p-methoxy)phenyl-1,2,4-triazol-3-ylsulfanylacetamino}-propane (***13d***).* Reaction of **12b** and **7e** gave crude **13d**, which was recrystallized from acetic acid as colorless crystals (76%), mp 218–220°C; IR: 3220 (NH), 1651.0 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.53 (quintet, 2H, $J = 1.2$ Hz, $\underline{CH_2}CH_2NH$), 3.04 (q, 4H, $J = 5.8$ Hz, $\underline{CH_2}NH$), 3.8 (s, 6H, OCH_3), 3.94 (s, 4H, SCH_2), 7.04–7.97 (m, 16H, ArH's), 8.21 (br, 2H, NH), 8.92 (s, 2H, CH=N).

Anal. for $C_{39}H_{36}Cl_2N_{10}O_4S_2$ (843). Calcd.: C, 55.51; H, 4.30; N, 16.6. Found: C, 55.27; H, 4.52; N, 16.4.

*1,3-Bis{4-(o-hydroxy)benzylideneamino-5-phenyl-1,2,4-triazol-3-ylsulfanylacetamino}propane (***13e***).* Reaction of **12d** and **7d** gave crude **13e**, which was recrystallized from ethanol/acetic acid as colorless crystals (50%), mp 210°C; IR: 3317 (NH), 1674.1 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.55 (quintet, 2H, $J = 2.4$ Hz, $\underline{CH_2}CH_2NH$), 3.04 (q, 4H, $J = 6.4$ Hz, $\underline{CH_2}NH$), 3.99 (s, 4H, SCH_2), 6.9–7.90 (m, 18H, ArH's), 8.27 (br, 2H, NH), 8.98 (s, 2H, CH=N), 10.3 (s, 2H, OH).

Anal. for $C_{37}H_{34}N_{10}O_4S_2$ (746.87). Calcd.: C, 59.5; H, 4.59; N, 18.75. Found: C, 59.25; H, 4.3; N, 18.6.

*1,3-Bis{4-(p-chloro)benzylideneamino-5-phenyl-1,2,4-triazol-3-ylsulfanylacetamino)propane (***13f***).* Reaction of **12b** and **7d** gave crude **13f**, which was recrystallized from acetic acid as colorless crystals (75%), mp 202–224°C; IR: 3240.2 (NH), 1658.7 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7 (br, 2H, $\underline{CH_2}CH_2NH$), 3.40 (q, 4H, $\underline{CH_2}NH$), 4.02 (s, 4H, SCH_2), 7.26–7.83 (m, 18H, ArH's), 8.38 (br, 2H, NH), 8.55 (s, 2H, CH=N).

Anal. for $C_{37}H_{32}Cl_2N_{10}O_2S_2$ (783.76). Calcd.: C, 56.7; H. 4.12; N, 17.69. Found: C, 56.6; H, 4.30; N, 17.69.

*3,23-Di(p-methoxyphenyl)-12,13,30,31-tetrahydro-14H,27H,34H-bis[1,2,4]triazolo-[4,3-f:3,4-r]dibenzo-[b,v][1,24]dioxa[8,17]dithia[5,6,11,14,19,20]hexaazaheptacosine-28,33-(29H,32H)dione (***15a***).* Reaction of **14b** and **7b** gave crude **15a**, which was recrystallized from DMF as colorless crystals (21%), mp 250–252°C; MS: *m/z* 832.75 (M^+, 64.3%), 826 (71.4%), 709 (100%), 581 (78.6%), 429 (85.7%), 260 (85.7%), 163 (78.5%); IR: 3286.5 (NH), 1674.1 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.08 (br, 2H, $OCH_2\underline{CH_2}$), 3.2 (br, 4H, $\underline{CH_2}NH$), 3.71 (s, 6H, OCH_3), 3.91 (s, 2H, SCH_2), 4.10 (br, 4H, OCH_2), 6.9–7.83 (m, 16H, ArH's), 8.34 (br, 2H, NH), 8.94 (s, 2H, CH=N).

Anal. for $C_{41}H_{40}N_{10}O_6S_2$ (832.96). Calcd.: C, 59.12; H, 4.84; N, 16.82. Found: C, 58.89; H, 4.60; N, 16.58.

*3,23-Dibenzyl-12,13,30,31-tetrahydro-14H,27H,34H-bis[1,2,4]triazolo[4,3-f:3,4-r]dibenzo[b,v][1,24]dioxa[8,17]dithia[5,6,11,14,19,20]hexaazaheptacosine-28,33-(29H,32H)dione (***15b***).* Reaction of **14b** and **7c** gave crude **15b**, which was recrystallized from dioxane/acetic acid as colorless crystals (24%), mp 242–244°C; MS: *m/z* 801 (M^+, 52.9%), 668 (82.3%), 488 (70.6%), 394 (82.3%), 277 (100%), 131 (82.3); IR: 3201.6 (NH), 1674.1 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.12 (br, 2H, $OCH_2\underline{CH_2}$), 3.1 (br, 4H, $\underline{CH_2}NH$), 3.89 (s, 4H, SCH_2), 4.12 (s, 4H, OCH_2), 4.17 (s, 4H, CH_2Ph), 7.1–7.81 (m, 18H, ArH's), 8.26 (br, 2H, NH), 8.94 (s, 2H, CH=N).

Anal. for $C_{41}H_{40}N_{10}O_4S_2$ (800.96). Calcd.: C, 61.48; H, 5.03; N, 17.49. Found: C, 61.6; H, 5.1; N, 17.2.

*3,24-Diphenyl-12,13,14,15,31,32-hexahydro-28H, 35H-bis[1,2,4]triazolo[4,3-f:3,4-r]dibenzo[b,v][1,24] dioxa[8,17]dithia[5,6,11,14,19,20]hexaazaoctaacosine-29,34-(30H,33H)dione (***16c***).* Reaction of **14c** and **7a** gave crude **16c**, which was recrystallized from acetic acid as colorless crystals (18%), mp 250°C; MS: *m/z* 787 (M^+, 80%), 584 (60%), 484 (86.6%), 371 (100%), 303 (86.6%), 204 (93.3%); IR: 3271 (NH), 1666.4 (C=O cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.73 (br, 4H, $OCH_2\underline{CH_2}$), 3.2 (s, 4H, $\underline{CH_2}NH$), 3.9 (s, 4H, SCH_2), 4.06 (s, 4H, OCH_2), 6.97–7.88 (m, 18H, ArH's), 8.28 (br, 2H, NH), 8.91 (s, 2H, CH=N).

Anal. for $C_{40}H_{38}N_{10}O_4S_2$ (786.93). Calcd.: C, 61.05; H, 4.87; N, 17.80. Found: C, 60.92; H, 4.91; N, 17.75.

*3,28-Diphenyl-15,16,35,36-tetrahydro-12H,19H, 32H,39H-bis[1,2,4]triazolo[4,3-f:3,4-r]dibenzo[b,v]-[1,24]dioxa[8,17]dithia[5,6,11,14,19,20,27,30]octaazadotricontin-13,18,33,38-(14H,17H,34H,37H)-tetraone (***16a***).* Reaction of **5a** and **7a** gave crude **16a**, which was recrystallized from dioxane as pale yellow crystals (18%), mp 273–275°C; MS: *m/z* (FD) 872 (M^+, 100%), IR: 3278.8 (NH), 1666.4 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11 (br, 4H, CH_2NH), 3.12 (br, 4H, CH_2NH), 3.92 (s, 4H, SCH_2), 4.54 (s, 4H, OCH_2), 7.1–8.04 (m, 18H, ArH's), 8.19 (br, 2H, NH), 8.31 (br, 2H, NH), 9.37 (s, 2H, CH=N).

Anal. for $C_{42}H_{40}N_{12}O_6S_2$ (872.98). Calcd.: C, 57.79; H, 4.62; N, 19.25. Found: C, 57.61; H, 4.8; N, 19.00.

*3,29-Diphenyl-15,16,36,37-tetrahydro-12H,17H, 20H,33H,40H-bis[1,2,4]triazolo[4,3-f:3,4-r]dibenzo-[b,v][1,24]dioxa[8,17]dithia[5,6,11,14,19,20,27,31]-octaazatritricontin-13,19,34,39-(14H,18H,35H,38H)-tetraone (***16b***).* Reaction of **5b** and **7a** gave crude **16b**, which was recrystallized from dioxane as pale yellow crystals (20%), mp 250°C; MS (EI): *m/z* 886 (12%), 540 (22.2%), 300 (18.5%), 198 (100%), 81 (57.41%); IR: 3278.8 (NH), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.4 (br, 2H, $\underline{CH_2}CH_2NH$), 3.09 (br, 8H, $2\underline{CH_2}NH$), 3.86 (s, 4H, SCH_2), 4.48 (s, 4H, OCH_2), 7.1–8.26 (m, 18H, ArH's, 2NH), 9.42 (s, 2H, CH=N); ^{13}C NMR (DMSO-d_6) (APT) δ 28.55, 34.27, 36.18, 37.91, 66.69 (CH_2'S), 119.06, 125.60, 145.87, 156.73, 156.77, 166.07, 166.25 (ArC's, Triazole C's); 112.792, 121.215, 126.967, 127.271, 129.183, 134.472, 163.332, 164.212 (ArCH's, CH=N).

Anal. for $C_{43}H_{40}N_{12}O_6S_2$ (887.01). Calcd.: C, 58.23; H, 4.77; N, 18.95. Found: C, 58.51; H, 4.81; N, 18.70.

*3,28-Diphenyl-15,16,35,36-tetrahydro-12H,19H, 32H,37H,40H-bis[1,2,4]triazolo[4,3-f:3,4-s]dibenzo-[b,w][1,25]dioxa[8,18]dithia[5,6,11,15,20,21,28,31]-octaazatritricontin-13,18,33,39-(14H,17H,34H,38H)-tetraone (***16c***).* Reaction of **5a** and **7d** gave crude **16c**, which was recrystallized from dioxane as pale yellow crystals (16%), mp 267–269°C; MS (EI): *m/z* 886 (M^+, 2.74%), 672 (2.60%), 501 (3.23%), 201 (21.1%), 178 (100%), 145 (15.9%); IR: 3271 (NH), 1666.4 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.5 (br, 2H, $\underline{CH_2}CH_2NH$), 3.05 (br, 4H, CH_2NH), 3.24 (br, 4H, $\underline{CH_2}NHCOCH_2O$), 3.97 (s, 4H, $\underline{CH_2}NHCOCH_2S$), 4.55 (s, 4H, OCH_2), 7.1–8.05 (m, 18H, ArH's), 8.19 (br, 2H, NH), 8.32 (br, 2H, NH), 9.40 (s, 2H, CH=N).

Anal. for $C_{43}H_{42}N_{12}O_6S_2$ (887.01). Calcd.: C, 58.23; H, 4.77; N, 18.95. Found: C, 58.23; H, 4.71; N, 18.84.

Action of Sodium Borohydride on **9b,d**, *General Procedure*

To a stirred hot (40–50°C) solution of each of **9b,d** (10 mmol) in methanol (10 ml) was added sodium borohydride (0.4 g, 13 mmol) 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 solid was collected, washed with water, and crystallized from the proper solvent to give colorless crystals of **11a,b**.

*3,28-Diphenyl-5,6,15,16,25,26,32,33-octahydro-12H,19H-bis[1,2,4]triazolo[4,3-f:3,4-l]dibenzo[b,p]-[1,18]dioxa[8,11]dithia[5,6,13,14,21,24]hexaazahexacosine-13,18-(14H,17H)dione (***11a***).* Compound **9b** gave crude **11a**, which was recrystallized from dil. acetic acid as colorless crystals (79%), mp 251–253°C; IR: 3278.8 (NH), 1666.4 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.32 (br, 4H, CH_2NH), 3.55 (s, 4H, SCH_2), 3.89 (br, 2H, $\underline{NH}CH_2$), 4.17 (br, 4H, $Ar\underline{CH_2}$), 4.42 (s, 4H, OCH_2), 6.79–7.94 (m, 20H, ArH's, NHC=O).

Anal. for $C_{38}H_{38}N_{10}O_2S_2$ (762.91). Calcd.: C, 59.83; H, 5.02; N, 18.36. Found: C, 59.75; H, 4.92; N, 18.05.

*3,28-Diphenyl-5,6,15,16,25,26,32,33-octahydro-12H,19H,34H-bis[1,2,4]triazolo[4,3-f:3,4-m]dibenzo-[b,q][1,19]dioxa[8,12]dithia[5,6,14,15,22,25]hexaazaheptacosine-13,18-(14H,17H)dione (***11b***).* Compound **9d** gave crude **11b**, which was recrystallized from acetic acid as colorless crystals (18%), mp 252°C; ^1H NMR (DMSO-d_6) δ 1.64 (br, 2H, $SCH_2\underline{CH_2}$), 3.16 (q, 4H, J = 2.8 Hz, CH_2NH), 3.47 (s, 4H, SCH_2), 4.13 (d, 4H, J = 5 Hz, $Ar\underline{CH_2}$), 4.45 (s, 4H, $O\underline{CH_2}$),

4.62 (t, 2H, $J = 5.4$ Hz, $\underline{NH}CH_2$), 6.8–7.94 (m, 20H, ArH's, NHC=O).

Anal. for $C_{39}H_{40}N_{10}O_4S_2$ (776.96). Calcd.: C, 60.29; H, 5.19; N, 18.03. Found: C, 60.15; H, 5.00; N, 17.95.

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