1,ω-Bis(4-amino-1,2,4-triazole-5(1*H*)-thion-3-ylsulfanyl)alkanes: Versatile Precursors for Novel Bis(*S*-triazolo[3,4-*b*][1,3,4]thiadiazines) as well as Novel Bis(macrocyclic Schiff Bases)

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Two synthetic routes were attempted for the synthesis of the novel bis(5,6-dihydro-*S*-triazolo[3,4-*b*]thiadiazines) **12a,b** and **14**. In the first route the bis(aminotriazoles) **4a,b** were reacted with the appropriate α-haloketones or α-haloesters to give the corresponding bis(*S*-triazolo[3,4-*b*]thiadiazines) **11a-d** followed by reduction with $NaBH_4$. In the second route, the bis(Schiff bases) **13d** were reacted with the appropriate α-haloesters in refluxing DMF containing TEA to give the target compound **14**. Cyclocondensation of **4a,b** with the appropriate bis(carbonyl) ethers **15a,b** in refluxing acetic acid under high dilution conditions afforded the corresponding macrocyclic Schiff bases **16a-c**. The latter underwent alkylation with the appropriate halo compounds to give the corresponding alkylated derivatives **17a-d**.

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Introduction.

S-Triazoles and their condensed *S*-triazolo[3,4-*b*][1,2,4]-thiadiazines have been the subject of many publications because of their potential applications as antibacterial, antifungal and antiinflamatory agents [1-20].

Moreover, multiether compounds such as crown ether, aza-crown ether as well as their non-cyclic derivatives have received much attention due to their wide applications in host-guest interaction and supramolecular chemistry [21-27].

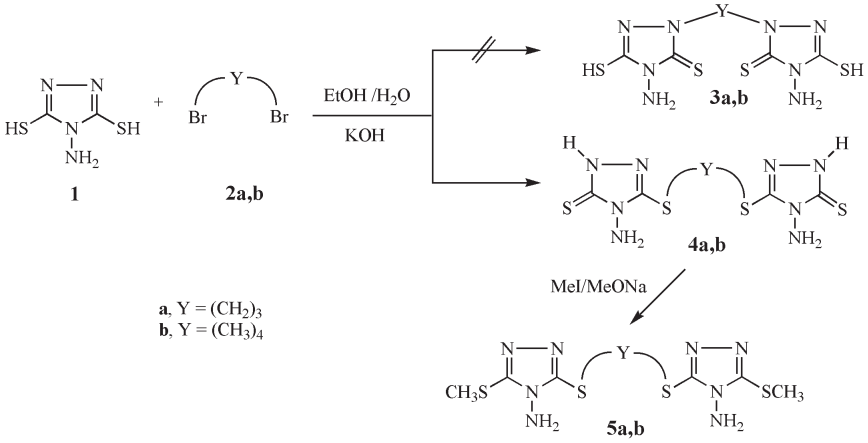
In connection with these findings and in continuation of our interest in the synthesis of bis(heterocycles) [28-33] as well as macroheterocyclic compounds [34-39], we report herein on the synthesis of novel bis(aminotriazoles) and studies on their synthetic utilitie as building blocks for novel bis(triazolo[3,4-*b*]thiadiazines) as well as novel macrocyclic Schiff bases.

Results and Discussions.

4-Amino-1,2,4-triazole-3,5-dithione **1** [40,41] was reacted with the appropriate dibromoalkanes **2a,b** in ethanol/water mixture containing KOH to give the corresponding 1,ω-bis(4-amino-1,2,4-triazol-3-ylsulfanyl)alkanes **4a,b** in 45-50% yield. The ^{1}H-NMR of the reaction mixture indicates that the *N*-alkylated products **3a,b** are not formed as shown in (Scheme 1).

The preferable formation of **4a,b** is in agreement with previous results that confirmed the facile alkylation of 4-substituted-1,2,4-triazolthiones on sulfur rather than on nitrogen [9,10,18,42-45]. The structure of **4a,b** was supported by its reaction with MeI in methanol containing sodium methoxide to give the corresponding bis-(methylthio) derivative **5a,b**. The structure of the latter was confirmed by the presence of two singlet signals at δ = 2.55 ppm and at δ = 2.50 ppm, respectively, in their ^{1}H-NMR spectra in DMSO-d_6. The bis amines **4a,b** were chosen as key intermediates for the synthesis of novel bis(fused heterocycles) and their reactivities towards condensation with aromatic aldehydes were firstly investigated. Thus, reaction of **4a,b** with each of benzaldehyde **6a** and *p*-methoxybenzaldehyde **6b** gave the corresponding

Scheme 1



bis(Schiff bases) **7a-d** in 50-70% yields.

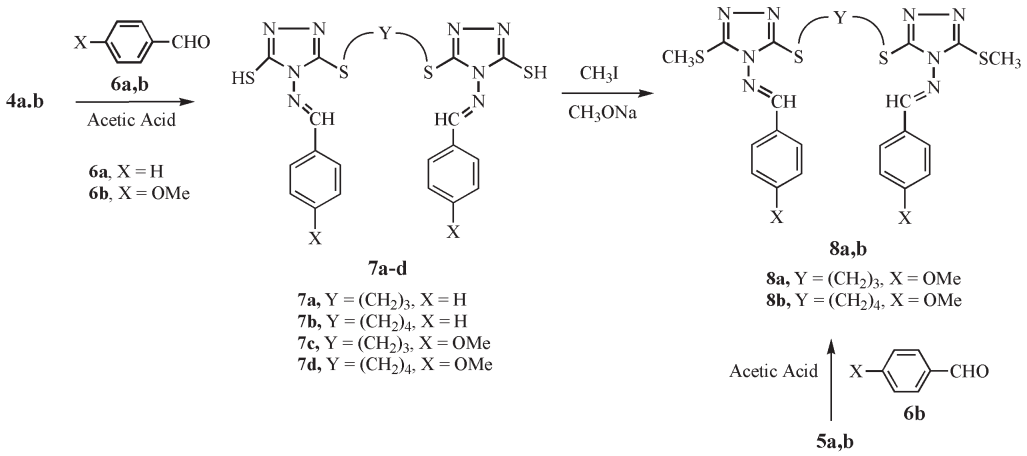
The reactivity of **7a-d** towards alkylation with haloalkanes was also investigated. Thus, reaction of **7a-d** with MeI in methanolic solution containing sodium methoxide afforded the corresponding bis(methylthio) derivatives **8a,b** in 52-55% yield. Compounds **8a,b** were alternatively obtained in 60% and 65% yields, respectively, by condensing **5a,b** with the appropriate aromatic aldehydes in refluxing acetic acid (Scheme 2).

Two routes were attempted to investigate the synthetic utility of compounds **4**, **7** as building blocks for novel bis(5,6-dihydro-*S*-triazolo[3,4-*b*]thiadiazines) **12a,b** and **14** as outlined in Schemes 3 and 4, respectively. In the first route (Scheme 3) compound **4a** was reacted with

In the second route (Scheme 4) compounds **7a-d** were allowed to react with each of phenacyl bromide **9b** and ethyl bromoacetate **9c** in DMF containing TEA at room temperature to give the corresponding *S*-alkylated derivatives **13a-d** in 50-68% yields. Heating of **13b** in refluxing DMF containing TEA led to the formation of the target **14** in 60% yield. The latter was alternatively obtained in 55% yield by reacting **7d** with ethyl bromoacetate in refluxing DMF containing TEA.

From the ^{1}H-NMR spectra of compounds **12, 14** the following conclusions were inferred: 1) Compound **14** showed a well-resolved doublet signal for N^5-H, a doublet signal for C^7-H and almost a triplet signal for C^6-H. 2) Compound **12** showed a well resolved doublet signal

Scheme 2



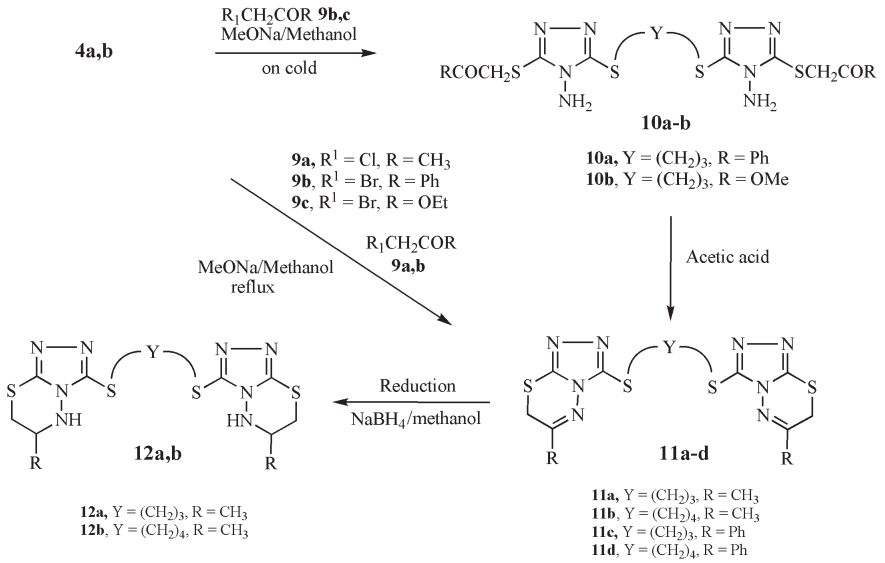
each of phenacyl bromide and ethyl bromoacetate in methanol containing sodium methoxide to give the corresponding *S*-alkylated derivatives **10a** and **10b** in 50% and 60% yields, respectively. It is noteworthy to mention that compound **10b** was isolated as the methyl ester but not as the expected ethyl ester. This may be attributed to the *trans* esterification of the latter under the reaction conditions. Heating of **10a** in refluxing acetic acid led to the formation of the corresponding bis(triazolo[3,4-*b*]thiadiazine) **11c** in 60% yield. Compound **11c** was alternatively obtained in 55% yield by reacting **4a** directly with phenacyl bromide in refluxing methanol containing sodium methoxide.

Similarly, compounds **11a,b,d** could also be obtained in 50-60% yields by reacting **4a,b** with each of phenacyl bromide and chloroacetone. Compounds **11a,b** underwent $NaBH_4$ reduction in methanol to give the target 1,ω-bis(5,6-dihydro-6-methyl-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazin-3-ylsulfanyl)alkanes **12a,b** in 60-65% yields.

for N^5-H, two dd singlet for C^7-Ha and C^7-He and a multiplet signal for C^6-H. 3) From the coupling constants $^3J_{5,6}$ = 6.0 Hz, $^3J_{6,7}$ = 3.4 Hz for compound **14**, it was assigned the *cis* stereochemistry (*i.e.*, The consecutive hydrogen atoms N^5-H, C^6-H and C^7-H are *cis* to each other. 4) The two protons of C^7-H$_2$ (for compound **12b**) each appears as dd as a result of the geminal coupling with the geminal coupling constant ^2J = 12.2 Hz. 5) The large vicinal coupling constants $^3J_{5,6}$ = 9.1 Hz, $^3J_{6,7}$ = 8.5 Hz for compound **12b** indicate *trans* relationship of N^5-H, C^6-H and C^6-H, C^7-Ha. On the other hand, the small vicinal coupling constant $^3J_{6,7}$ =2.1 Hz indicate the *cis* relationship of C^6-H, C^7-He.

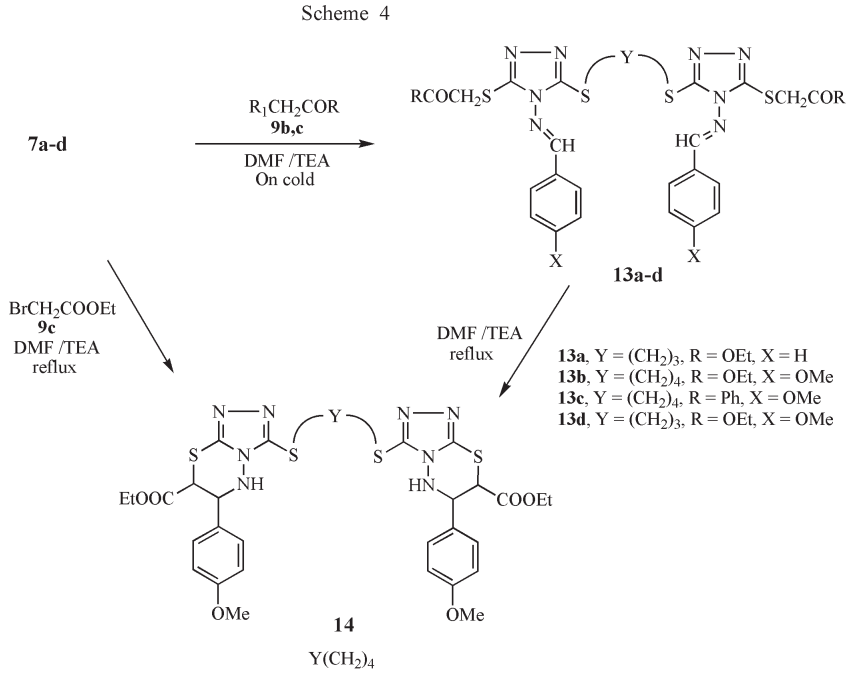
Our study was extended to investigate the synthetic utility of **4a,b** as building blocks for novel macrocyclic Schiff bases as outlined in (Scheme 5). Thus, cyclocondensation of **4a,b** with appropriate bis(carbonyl) ethers **15a,b** [46] in glacial acetic acid under high dilution conditions gave the corresponding macrocyclic Schiff bases **16a-c** in 55-60% yields. Such compounds are interesting in their own right

Scheme 3



as a new class of ionizable crown compounds. In addition, the presence of the free thiol group allows functionalization of these macrocyclic Schiff bases to produce side armed ligands which permit a more dynamic complexation of the metal ion than is found in bicyclic ligands. It is also possible to functionalize these macrocycles through the free thiol group with lipophilic groups which should be of great interest in case of using such ligands for solvent extraction of metal ions.

Scheme 4

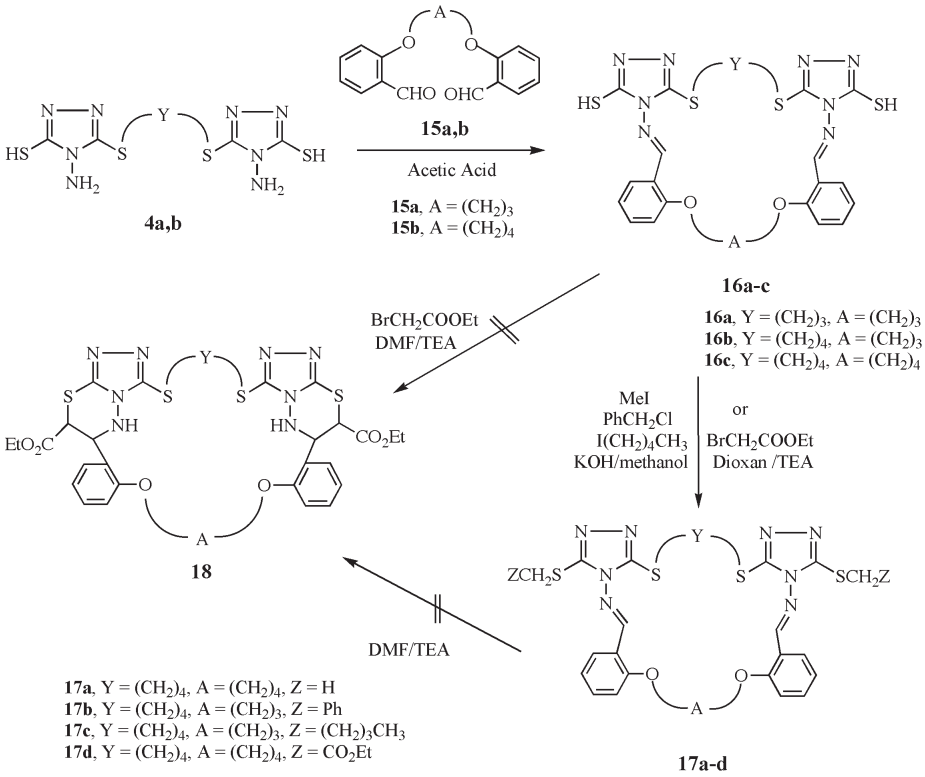


Thus, alkylation **16b,c** of with a series of haloalkanes namely, methyl iodide, benzyl chloride and iodopentane in methanol containing KOH gave the corresponding *S*-alkylated derivatives **17a-c** in 50-60% yields. Functionalization of **16** with ligating side arms could be achieved by reacting **16c** with ethyl bromoacetate in dioxane containing TEA to give **17d** in 65% yields. Repeated attempts to get the new condensed macrocycles **18** either by reacting **16** with the appropriate α-haloketones in refluxing DMF containing

TEA or by heating **17** in refluxing DMF/TEA were unsuccessful. Instead, the reaction gave a mixture of products that could not be easily handled nor characterized.

In conclusion, we synthesized new series of bis(Schiff bases), bis(fused heterocycles) and macrocyclic Schiff bases in a simple procedure from readily available starting materials. Some of the new compounds could be used as promising polydentate ligands, ionophores and extracting and analytical reagents as well as compounds with potentially high pharmacological and biological activities.

Scheme 5



EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian Mercury 300 (300 MHz ^{1}H-NMR, 75 MHz ^{13}C-NMR) spectrometer and chemical shifts are given in ppm from TMS. Mass spectra were recorded on HP 5988A (E1, 15 eV).

Synthesis of Bis(4-amino-1,2,4-triazol-5(1*H*)-thion-3-ylsulfanyl)alkanes (**4a,b**).

General Procedure.

To a solution of **1** (50 mmol) in aqueous ethanol (50 ml, 50%) containing KOH (50 mmol) was added the appropriate dibromoalkanes **2a,b** (25 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was collected and crystallized from DMF to give colorless crystals of compounds **4a,b.**

1,3-Bis(4-amino-1,2,4-triazol-5(1H)-thion-3-ylsulfanyl)propane (**4a**).

With the use of the general procedure **1** and **2a** gave crude **4a** which was crystallized from DMF to give colorless crystals (50%), mp 194-196 °C; IR (cm^{-1}): 3306, 3099 (NH_2, NH), 1300 (C=S); ^{1}H NMR (DMSO): δ 2.07 (brs, 2H, SCH_2CH_2), 3.21 (t, 4H, J = 6.6 Hz, SCH_2), 5.61 (2s, 4H, NH_2), 13.67 (brs, 2H, NH) ppm; ^{13}C NMR (DMSO): δ 28.45 ($CH_2CH_2CH_2$), 28.70 (CH_2S), 150.0 (*C*=N), 167.35 (*C*=S) ppm.

Anal. Calcd. for $C_7H_{12}N_8S_4$ (336.48): C, 24.99; H, 3.59; N, 33.3. Found: C, 24.90; H, 3.90; N, 33.50.

1,4-Bis(4-amino-1,2,4-triazol-5(1*H*)-thion-3-ylsulfanyl)butane (**4b**).

With the use of the general procedure **1** and **2b** gave crude **4b** which was crystallized from DMF to give colorless crystals (50%), mp 216-218 °C; IR (cm^{-1}): 3288, 3104 (NH_2, NH), 1290 (C=S); ^{1}H NMR (DMSO): δ 1.78 (s, 4H, SCH_2CH_2), 3.10 (s, 4H, SCH_2), 5.60 (s, 4H, NH_2), 13.69 (s, 2H, NH) ppm.

Anal. Calcd. for $C_8H_{14}N_8S_4$ (350.52): C, 27.41; H, 4.03; N, 31.97. Found: C, 27.20; H, 3.80; N, 32.10.

Synthesis of the S-Alkylated Derivatives **5a,b, 8a,b** and Bis(*S*-triazol[3,4-*b*]thiadiazines) **11a-d**.

General Procedure.

To a solution of each of **4a,b** and **7c,d** (10 mmol) in methanol

(50 ml) containing sodium methoxide [prepared by dissolving sodium metal (20 mmol) in methanol (20 ml)] was added methyl iodide or the appropriate α-haloketones **9a,b** (20 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was diluted with ice-cold water (100 ml). The precipitate obtained was collected and crystallized from the proper solvent for each derivative to give compounds **5a,b, 8a,b** and **11a-d**.

1,3-Bis(4-amino-5-methylthio-1,2,4-triazol-3-ylsulfanyl)-propane (**5a**).

With the use of the general procedure **4a** and methyl iodide gave crude **5a** which was crystallized from acetic acid/ethanol mixture to give yellow crystals (60%), mp 196-198 °C; IR (cm^{-1}): 3294, 3174 (NH_2); ^1H NMR (DMSO): δ 2.03 (quintet, 2H, *J* = 7.2 Hz, SCH_2CH_2), 2.55 (s, 6H, SCH_3), 3.19 (t, 4H, *J* = 7.2 Hz, SCH_2), 5.88 (s, 4H, NH_2) ppm.

Anal. Calcd. for $C_9H_{16}N_8S_4$ (364.54): C, 29.65; H, 4.42; N, 30.74. Found: C, 29.80; H, 4.30; N, 30.80.

1,4-Bis(4-amino-5-methylthio-1,2,4-triazol-3-ylsulfanyl)butane (**5b**).

With the use of the general procedure **4b** and methyl iodide gave crude **5b** which was crystallized from dioxane to give yellow crystals (55%), mp 208-210 °C; IR (cm^{-1}): 3291, 3171 (NH_2); ^1H NMR (DMSO): δ 1.77 (s, 4H, SCH_2CH_2), 2.5 (s, 6H, SCH_3), 3.10 (s, 4H, SCH_2), 5.86 (s, 4H, NH_2) ppm.

Anal. Calcd. for $C_{10}H_{18}N_8S_4$ (378.57): C, 31.73; H, 4.79; N, 29.60. Found: C, 31.80; H, 4.90; N, 29.40.

1,3-Bis(4-*p*-methoxybenzylideneamino-5-methylthio-1,2,4-triazol-3-ylsulfanyl)propane (**8a**).

With the use of the general procedure **7c** and methyl iodide gave crude **8a** which was crystallized from ethanol to give pale yellow crystals (52%), mp 160-162 °C; ^1H NMR (DMSO): δ 2.28 (quintet, 2H, *J* = 6.9 Hz, SCH_2CH_2), 2.71 (s, 6H, SCH_3), 3.36 (t, 4H, *J* = 6.9 Hz, SCH_2), 3.89 (s, 6H, OCH_3), 7.0, 7.82 (2d, 8H, *J* = 6.8 Hz, ArH's), 8.51 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{25}H_{28}N_8O_2S_4$ (600.81): C, 49.98; H, 4.70; N, 18.65. Found: C, 50.10; H, 4.40; N, 18.50.

1,4-Bis(4-*p*-methoxybenzylideneamino-5-methylthio-1,2,4-triazol-3-ylsulfanyl)butane (**8b**).

With the use of the general procedure **7d** and methyl iodide gave crude **8b** which was crystallized from ethanol as pale yellow crystals (55%), mp 138-140 °C; ^1H NMR (DMSO): δ 1.93 (s, 4H, SCH_2CH_2), 2.70 (s, 6H, SCH_3), 3.22 (s, 4H, SCH_2), 3.89 (s, 6H, OCH_3), 7.0, 7.82 (2d, 8H, *J* = 6.9 Hz, ArH's), 8.51 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{26}H_{30}N_8O_2S_4$ (614.84): C, 50.79; H, 4.92; N, 18.22. Found: C, 50.60; H, 5.20; N, 18.00.

1,3-Bis{6-methyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylsulfanyl}propane (**11a**).

With the use of the general procedure **4a** and **9a** gave crude **11a** which was crystallized from dioxane/acetic acid mixture to give yellow crystals (50%), mp 200-202 °C; ^1H NMR (DMSO): δ 2.12 (quintet, 2H, *J* = 7.2 Hz, SCH_2CH_2), 2.27 (s, 6H, CH_3), 3.29 (t, 4H, *J* = 7.2 Hz, SCH_2CH_2), 3.86 (s, 4H, SCH_2) ppm.

Anal. Calcd. for $C_{13}H_{16}N_8S_4$ (412.59): C, 37.84; H, 3.91; N, 27.16. Found: C, 38.00; H, 3.80; N, 27.20.

1,4-Bis{6-methyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylsulfanyl}butane (**11b**).

With the use of the general procedure **4b** and **9a** gave crude **11b** which was crystallized from dioxane/ethanol mixture as yellow crystals (50%), mp 228-230 °C; ^1H NMR (DMSO): δ 1.82 (s, 4H, SCH_2CH_2), 2.27 (s, 6H, CH_3), 3.21 (s, 4H, SCH_2CH_2), 3.86 (s, 4H, SCH_2) ppm.

Anal. Calcd. for $C_{14}H_{18}N_8S_4$ (426.61): C, 39.42; H, 4.25; N, 26.27. Found: C, 39.10; H, 4.40; N, 26.40.

1,3-Bis{6-phenyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylsulfanyl}propane (**11c**).

With the use of the general procedure **4a** and **9b** gave crude **11c** which was crystallized from dioxane/ethanol mixture to give yellow crystals (55%), mp 106-108 °C; ^1H NMR (DMSO): δ 2.37 (t, 2H, *J* = 6.9 Hz, SCH_2CH_2), 3.47 (t, 4H, *J* = 6.9 Hz, SCH_2CH_2), 3.99 (s,4H, SCH_2), 7.47-7.89 (m, 10H, ArH's) ppm.

Anal. Calcd. for $C_{23}H_{20}N_8S_4$ (536.73): C, 51.47; H, 3.76; N, 20.88. Found: C, 51.60; H, 3.50; N, 21.00.

Synthesis of **11c** from **10a**.

A solution of **10a** (10 mmol) in acetic acid (15 ml) was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was crystallized from dioxane/ethanol mixture to give yellow crystals of **11** (60%).

1,4-Bis{6-phenyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylsulfanyl}butane (**11d**).

With the use of the general procedure **4b** and **9b** gave crude **11d** which was crystallized from a dioxane/ethanol mixture to give yellow crystals (50%), mp 224-226 °C; ^1H NMR (DMSO): δ 2.03 (m, 4H, SCH_2CH_2), 3.36 (m, 4H, SCH_2CH_2), 3.98 (s, 4H, SCH_2), 7.49-7.9 (m, 10H, ArH's) ppm.

Anal. Calcd. for $C_{24}H_{22}N_8S_4$ (550.76): C, 52.34; H, 4.03; N, 20.35. Found: C, 52.20; H, 4.10; N, 20.20.

Synthesis of Acyclic Schiff Bases **7a-d** and **8a,b**.

General Procedure.

To a solution of each of **4a,b** and **5a,b** (20 mmol) in glacial acetic acid (15 ml) was added each of **6a,b** (40 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was collected and crystallized from the proper solvent to give crystals of **7a-d** and **8a,b**.

1,3-Bis(4-benzylideneamino-1,2,4-triazol-5(1*H*)-thion-3-ylsulfanyl)propane (**7a**).

With the use of the general procedure **4a** and **6a** gave crude **7a** which was crystallized from a DMF/acetic acid mixture to give colorless crystals (55%), mp 230-232 °C; IR (cm^{-1}): 2729 (SH), 1656 (C=N); ^1H NMR (DMSO): δ 2.15 (quintet, 2H, *J* = 6.6 Hz, SCH_2CH_2), 3.25 (t, 4H, *J* = 6.9 Hz, SCH_2), 7.52-7.87 (m, 10H, ArH's), 10.02 (s, 2H, CH=N), 14.05 (s, 2H, SH) ppm.

Anal. Calcd. for $C_{21}H_{20}N_8S_4$ (512.71): C, 49.20; H, 3.93; N, 21.86. Found: C, 49.00; H, 4.20; N, 21.70.

1,4-Bis(4-benzylideneamino-1,2,4-triazol-5(1*H*)-thion-3-ylsulfanyl)butane (**7b**).

With the use of the general procedure **4b** and **6a** gave crude **7b** which was crystallized from a DMF/acetic acid mixture to give

white crystals (55%), mp 208-210 °C; ^{1}H NMR (DMSO): δ 1.85 (s, 4H, SCH_2CH_2), 3.18 (s, 4H, SCH_2), 7.53-7.91 (m, 10H, ArH's), 10.09 (s, 2H, CH=N), 14.08 (s, 2H, SH) ppm.

Anal. Calcd. for $C_{22}H_{22}N_8S_4$ (526.73): C, 50.17; H, 4.21; N, 21.27. Found: C, 49.90; H, 4.30; N, 21.40.

1,3-Bis(4-*p*-methoxybenzylideneamino-1,2,4-triazol-5(1*H*)-thion-3-ylsulfanyl)propane (**7c**).

With the use of the general procedure **4a** and **6b** gave crude **7c** which was crystallized from DMF as colorless crystals (70%), mp 254-256 °C; IR (cm^{-1}): 2557 (SH), 1670 (C=N); ^{1}H NMR (DMSO): δ 2.14 (quintet, 2H, *J* = 5.7 Hz, SCH_2CH_2), 3.25 (t, 4H, *J* = 6.7 Hz, SCH_2), 3.86 (s, 6H, OCH_3), 7.11, 7.84 (2d, 8H, *J* = 8.6 Hz, ArH's), 9.77 (s, 2H, CH=N), 14.04 (s, 2H, SH) ppm.

Anal. Calcd. for $C_{23}H_{24}N_8O_2S_4$ (572.76): C,48.23; H, 4.22; N, 19.56. Found: C, 48.30; H, 4.10; N, 19.80.

1,4-Bis(4-*p*-methoxybenzylideneamino-1,2,4-triazol-5(1*H*)-thion-3-ylsulfanyl)butane (**7d**).

With the use of the general procedure **4b** and **6b** gave crude **7d** which was crystallized from a DMF/acetic acid mixture to give colorless crystals (50%), mp 240-242 °C; IR (cm^{-1}): 2561 (SH); ^{1}H NMR (DMSO): δ 1.81 (s, 4H, SCH_2CH_2), 3.14 (s, 4H, SCH_2), 3.84 (s, 6H, OCH_3), 7.09, 7.82 (2d, 8H, *J* = 8.7 Hz, ArH's), 9.75 (s, 2H, CH=N), 13.97 (s, 2H, SH) ppm.

Anal. Calcd. for $C_{24}H_{26}N_8O_2S_4$ (586.79): C, 49.13; H, 4.47; N, 19.10. Found: C, 48.90; H, 4.20; N, 19.30.

1,3-Bis(4-*p*-methoxybenzylideneamino-5-methylthio-1,2,4-triazol-3-ylsulfanyl)propane (**8a**).

With the use of the general procedure **5a** and **6b** gave **8a** (60%) mp 160-162 °C; ^{1}H NMR (DMSO) δ 2.28 (quintet, 2H, J = 6.9 Hz, SCH_2CH_2), 2.71 (s, 6H, SCH_3), 3.36 (t, 4H, J = 6.9 Hz, SCH_2), 3.89 (s, 6H, OCH_3), 7.0, 7.82 (2d, 8H, J = 6.8 Hz, ArH's), 8.51 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{25}H_{28}N_8O_2S_4$ (600.81): C, 49.98; H, 4.70; N, 18.65. Found: C, 50.10; H, 4.40; N, 18.50.

1,4-Bis(4-*p*-methoxybenzylideneamino-5-methylthio-1,2,4-triazol-3-ylsulfanyl)butane (**8b**).

With the use of the general procedure **5b** and **6b** gave **8b** (55%), mp 138 °C; ^{1}H NMR (DMSO) δ 1.93 (s, 4H, SCH_2CH_2), 2.70 (s, 6H, SCH_3), 3.22 (s, 4H, SCH_2), 3.89 (s, 6H, OCH_3), 7.0, 7.82 (2d, 8H, J = 6.9 Hz, ArH's), 8.51 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{26}H_{30}N_8O_2S_4$ (614.84): C, 50.79; H, 4.92; N, 18.22. Found: C, 50.60; H, 5.20; N, 18.00.

Synthesis of S-alkylated derivatives **10a,b** and **13a-d**.

General Procedure.

Method A for Preparation of **10a,b**.

To a stirred solution of **4a** (10 mmol) in methanol (50 ml) containing sodium methoxide [prepared by dissolving sodium metal (20 mmol) in methanol (20 ml)] was added the appropriate halo compounds **9b,c** (20 mmol). Stirring was continued for 1 h and the reaction was then allowed to stand at room temperature overnight. The precipitate obtained was collected and crystallized from the proper solvent to give **10a,b**.

Method B for Preparation of **13a-d**.

To a solution of **7a-d** (10 mmol) in DMF (15 ml) containing triethylamine (20 mmol) was added the appropriate halo compounds **9b,c** (20 mmol). The reaction mixture was then stirred at room temperature for 24 h. After dilution with water, the precipitate that had formed was collected and crystallized from the proper solvent to give **13a-d**.

1,3-Bis(4-amino-5-benzoylmethylthio-1,2,4-triazol-3-ylsulfanyl)propane (**10a**).

With the use of the general procedure (Method A) **4a** and **9b** gave crude **10a** which was crystallized from dioxane as colorless crystals (50%), mp 160-162 °C; IR (cm^{-1}): 3281, 3158 (NH_2), 1677 (C=O); ^{1}H NMR (DMSO): δ 2.03 (quintet, 2H, *J* = 6.9 Hz, SCH_2CH_2), 3.19 (t, 4H, *J* = 6.9 Hz, SCH_2), 4.85 (s, 4H, $COCH_2$), 5.98 (s, 4H, NH_2), 7.53-8.04 (m, 10H, ArH's) ppm.

Anal. Calcd. for $C_{23}H_{24}N_8O_2S_4$ (572.76): C, 48.23; H, 4.22; N, 19.56. Found: C, 48.10; H, 4.30; N, 19.30.

1,3-Bis(4-amino-5-methoxycarbonylmethylthio-1,2,4-triazol-3-ylsulfanyl)propane (**10b**).

With the use of the general procedure (Method A) **4a** and **9c** gave crude **10b** which was crystallized from dioxane as colorless crystals (60%), mp 180-182 °C; IR (cm^{-1}): 3302, 3176 (NH_2), 1732 (C=O); ^{1}H NMR (DMSO): δ 2.04 (quintet, 2H, *J* = 6.6 Hz, SCH_2CH_2), 3.19 (t, 4H, *J* = 7.2 Hz, SCH_2), 3.65 (s, 6H, CH_3), 4.03 (s, 4H, CH_2COO), 5.96 (s, 4H, NH_2) ppm.

Anal. Calcd. for $C_{13}H_{20}N_8O_4S_4$ (480.62): C, 32.49; H, 4.19; N, 23.31. Found: C, 32.30; H, 4.10; N, 23.50.

1,3-Bis(4-benzylideneamino-5-ethoxycarbonylmethylthio-1,2,4-triazol-3-ylsulfanyl)propane (**13a**).

With the use of the general procedure (Method B) **7a** and **9c** gave an oily product which was extracted from methylene chloride (65%); IR (cm^{-1}): 1734 (C=O); ^{1}H NMR (DMSO): δ 1.14 (t, 6H, *J* = 7.1 Hz, CH_3), 2.19 (quintet, 2H, *J* = 6.9 Hz, SCH_2CH_2), 3.28 (t, 4H, *J* = 7 Hz, SCH_2), 3.96 (s, 4H, CH_2CO), 4.05 (q, 4H, *J* = 7.2 Hz, CH_2CH_3), 7.35-7.89 (m, 10H, ArH's), 8.58 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{29}H_{32}N_8O_4S_4$ (684.89): C, 50.86; H, 4.71; N, 16.36. Found: C, 51.00; H, 4.60; N, 16.20.

1,4-Bis(4-*p*-methoxybenzylideneamino-5-ethoxycarbonylmethylthio-1,2,4-triazol-3-ylsulfanyl)butane (**13b**).

With the use of the general procedure (Method B) **7d** and **9c** gave an oily product which was extracted from methylene chloride (60%); IR (cm^{-1}): 1735 (C=O), 1651 (C=N); ^{1}H NMR (DMSO): δ 1.26 (t, 6H, *J* = 7.2 Hz, CH_3), 1.91 (s, 4H, SCH_2CH_2), 3.23 (s, 4H, SCH_2), 3.88 (s, 6H, OCH_3), 4.04 (s, 4H, CH_2CO), 4.19 (q, 4H, *J* = 7.1 Hz, OCH_2CH_3), 6.99, 7.82 (2d, 8H, *J* = 8.8 Hz, ArH's), 8.53 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{32}H_{38}N_8O_6S_4$ (758.97): C, 50.64; H, 5.05; N, 14.76. Found: C, 50.50; H, 5.20; N, 14.80.

1,4-Bis(4-*p*-methoxybenzylideneamino-5-benzoylmethylthio-1,2,4-triazol-3-ylsulfanyl)butane (**13c**).

With the use of the general procedure (Method B) **7d** and **9b** gave crude **13c** which was crystallized from benzene to give colorless crystals (68%), mp 80-82 °C; IR (cm^{-1}): 1741 (C=O); ^{1}H NMR (DMSO): δ 1.92 (s, 4H, SCH_2CH_2), 3.24 (s, 4H, SCH_2), 3.88 (s, 6H, OCH_3), 4.90 (s, 4H, CH_2CO), 6.97-8.03 (m, 18H, ArH's), 8.55 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{40}H_{38}N_8O_4S_4$ (823.06): C, 58.37; H, 4.65; N, 13.61. Found: C, 58.20; H, 5.00; N, 13.70.

1,3-Bis(4-*p*-methoxybenzylideneamino-5-ethoxycarbonyl-methylthio-1,2,4-triazol-3-ylsulfanyl)propane (**13d**).

With the use of the general procedure (Method B) **7c** and **9c** gave crude **13d** which was crystallized from benzene to give colorless crystals (50%), mp 128-130 °C; IR (cm^{-1}): 1738 (C=O), 1683 (C=N); ^1H NMR (DMSO): δ 1.28 (t, 6H, *J* = 7.2 Hz, CH_3), 2.21 (quintet, 2H, *J* = 6.9 Hz, SCH_2CH_2), 3.29 (t, 4H, *J* = 6.8 Hz, SCH_2), 3.83 (s, 6H, OCH_3), 4.03 (s, 4H, CH_2CO), 4.19 (q, 4H, *J* = 7.2 Hz, CH_2CH_3), 6.94, 7.77 (2d, 8H, *J* = 8.6 Hz, ArH's), 8.49 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{31}H_{36}N_8O_6S_4$ (744.94): C, 49.98; H, 4.87; N, 15.04. Found: C, 49.70; H, 4.70; N, 14.80.

Action of Sodium borohydride on **11a,b**: Synthesis of **12a,b**.

General Procedure.

To a stirred hot (40-50 °C) solution of each of **11a,b** (0.7 mmol) in methanol (10 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 solid was collected, washed with water and crystallized from the proper solvent to give colorless crystals of **12a,b**.

1,3-Bis{5,6-dihydro-6-methyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylsulfanyl}-propane (**12a**).

With the use of the general procedure **11a** gave crude **12a** which was crystallized from alcohol as white crystals (50%), mp 158-160 °C; IR (cm^{-1}): 3151 (NH); ^1H NMR (DMSO): δ 1.18 (d, 6H, *J* = 6.3 Hz, CH_3), 1.99 (quintet, 2H, *J* = 6.9 Hz, SCH_2CH_2), 2.95 (dd, 2H, ^3J = 8.4 Hz, ^2J = 12.6 Hz, H_a-7), 3.39 (dd, 2H, ^3J = 2.4 Hz, ^2J = 12.4 Hz, H_e-7), 3.16-3.23 (m, 6H, SCH_2, HN-CH-CH_3), 6.43 (d, 2H, *J* = 9.3 Hz, NH) ppm.

Anal. Calcd. for $C_{13}H_{20}N_8S_4$ (416.62): C, 37.48; H, 4.84; N, 26.90. Found: C, 37.40; H, 4.60; N, 26.90.

1,4-Bis{5,6-dihydro-6-methyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylsulfanyl}-butane (**12b**).

With the use of the general procedure **11b** gave crude **12b** which was crystallized from a dioxane/acetic acid mixture to give white crystals (65%), mp 232-234 °C; IR (cm^{-1}): 3151 (NH); ^1H NMR (DMSO): δ 1.19 (d, 6H, *J* = 6.6 Hz, CH_3), 1.7 (m, 4H, SCH_2CH_2), 2.93 (dd, 2H, ^3J = 9.1 Hz, ^2J = 12.2 Hz, H_a-7), 3.22 (dd, 2H, ^3J = 2.1 Hz, ^2J = 12.2 Hz, H_e-7), 3.10-3.16 (m, 6H, SCH_2CH_2, NHCH), 6.43 (d, 2H, *J* = 9.1 Hz, NH) ppm.

Anal. Calcd. for $C_{14}H_{22}N_8S_4$ (430.65), Calcd.: C, 39.05; H, 5.15; N, 26.02. Found: C, 39.40; H, 4.80; N, 26.30.

Synthesis of 1,4-Bis{(6-*p*-methoxyphenyl-5*H*-7-ethoxycarbonyl-6,7-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-sulfanyl}butane (**14**).

a) A solution of **7d** (10 mmol) and ethyl bromoacetate (**9c**) (20 mmol) in DMF (10 ml) and TEA (1.5 ml) was heated under reflux for 10 minutes. After cooling and dilution with water, the precipitate that had formed was collected and crystallized from a dioxane/ethanol mixture to give colorless crystals (55%), mp 228-230 °C; IR (cm^{-1}): 3150 (NH), 1735 (C=O); ^1H NMR ($CDCl_3$): δ 1.23 (m, 6H, CH_3),1.84 (s, 4H, SCH_2CH_2), 3.15 (s, 4H, SCH_2), 3.78 (s, 6H, OCH_3), 4.18 (m, 4H, CH_2CH_3), 4.41 (d, 2H, *J* = 3.6 Hz, CHCOOEt), 4.76 (t, 2H, *J* = 5.4 Hz, CH-Ar), 6.36 (d, 2H, *J* = 6 Hz, NH), 6.84 (d, 4H, *J* = 9 Hz, ArH's), 7.31 (d, 4H, *J* = 8.7 Hz, ArH's) ppm.

Anal. Calcd. for $C_{32}H_{38}N_8O_6S_4$ (758.97): C, 50.64; H, 5.05; N, 14.76. Found: C, 50.50; H, 5.20; N, 14.60.

b) A solution of **13d** (10 mmol) in DMF (10 ml) and TEA (1.5 ml) was heated under reflux for 10 minutes. After cooling and dilution with water, the precipitate that had formed was collected and crystallized from a dioxane/ethanol mixture to give yellow crystals of **14** (60%).

Synthesis of macrocyclic Schiff Bases **16a-c**.

General Procedure.

To a solution of each of **15a,b** (10 mmol) in glacial acetic acid (30 ml) was added a solution of the appropriate bis(4-amino-1,2,4-triazol-3-yl-sulfanyl)alkanes **4a,b** (10 mmol) in glacial acetic acid (30 mmol). The reaction mixture was then heated under reflux for 2 h. The solvent was then removed *in vacuo* and the remaining solid was crystallized from the proper solvent to give colorless crystals of **16a-c**.

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]dioxa[8,12]dithia[5,6,14,15]tetraazacyclodicosin-3,23(2*H*,24*H*)-dithione (**16a**).

With the use of the general procedure **4a** and **15a** gave crude **16a** which was crystallized from a DMF/acetic acid mixture to give colorless crystals (60%), mp 222-224 °C; IR (cm^{-1}): 3082 (NH), 1654 (CH=N; ^1H NMR (DMSO): δ 2.04 (brs, 2H, SCH_2CH_2), 2.23 (brs, 2H, OCH_2CH_2), 3.23 (s, 4H, SCH_2), 4.34 (s, 4H, OCH_2), 7.02-7.89 (m, 8H, ArH's), 10.52 (s, 2H, CH=N), 13.99 (brs, 2H, SH) ppm.

Anal. Calcd. for $C_{24}H_{24}N_8O_2S_4$ (584.77): C, 49.30; H, 4.14; N, 19.16. Found: C, 49.00; H, 3.90; N, 19.30.

12,13,27,28,29,30-Hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*n*]-dibenzo[*b*,*r*][1,20]dioxa[8,13]dithia[5,6,15,16]tetraazacyclotricosin-3,23(2*H*,24*H*)-dithione (**16b**).

With the use of the general procedure **4b** and **15a** gave crude **16b** which was crystallized from DMF to give colorless crystals (55%), mp 228-230 °C; IR (cm^{-1}): 3069 (NH), 1653 (CH=N); MS: m/z 599 (M^+, 0.7%), 578 (1.6%), 521 (3.2%), 409 (4.8%), 242 (19.7%), 187 (15.8%), 69 (100%); ^1H NMR (DMSO): δ 1.78 (brs, 4H, SCH_2CH_2), 2.24 (brs, 2H, OCH_2CH_2), 3.12 (brs, 4H, SCH_2), 4.34 (brs, 4H, OCH_2), 7.0-7.9 (m, 8H, ArH's), 10.52 (s, 2H, CH=N), 13.87 (s, 2H, SH) ppm.

Anal. Calcd. for $C_{25}H_{26}N_8O_2S_4$ (598.80): C, 50.15; H, 4.38; N, 18.71. Found: C, 49.90; H, 4.50; N, 18.50.

12,13,14,15,28,29,30.31-Octahydrobis[1,2,4]triazolo[4,3-*f*:3,4-*n*]-dibenzo[*b*,*r*][1,20]dioxa[8,13]dithia[5,6,15,16]tetraazacyclotetracosin-3,24(2*H*,25*H*)-dithione (**16c**).

With the use of the general procedure **4b** and **15b** gave crude **16c** which was crystallized from DMF to give colorless crystals (60%), mp 224-226 °C; IR (cm^{-1}): 3075 (NH); MS: m/z 612 (M^+, 0.1%), 563 (0.42%), 368 (9.2%), 288 (11.2%), 242 (10.2%), 187 (26%), 101 (100%); ^1H NMR (DMSO): δ 1.82 (s, 4H, SCH_2CH_2), 2.0 (s, 4H, OCH_2CH_2), 3.15 (s, 4H, SCH_2), 4.17 (s, 4H, OCH_2), 7.03-7.91 (m, 8H, ArH's), 10.53 (s, 2H, CH=N), 13.71 (brs, 2H, SH) ppm.

Anal. Calcd. for $C_{26}H_{28}N_8O_2S_4$ (612.82), Calcd.: C, 50.96; H, 4.61; N, 18.28. Found: C, 51.10; H, 4.30; N, 18.10.

Synthesis of Compounds **17a-d**.

General Procedure.

To a solution of each of **16b,c** (10 mmol) in methanol (50 ml) containing solid KOH (20 mmol) was added each of methyl iodide, benzyl chloride and iodopentane (20 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining solid was diluted with ice-cold water (100 ml). The precipitate obtained was collected and crystallized from the proper solvent for each derivative to afford compounds **17a-d**.

3,24-Dimethylthio-12,13,14,15,28,29,30.31-Octahydrobis-[1,2,4]triazolo[4,3-*f*:-3,4-*n*]dibenzo[*b,r*][1,20]dioxa[8,13]dithia-[5,6,15,16]tetraazacyclotetracosine (**17a**).

With the use of the general procedure **16c** and methyl iodide gave crude **17a** which was crystallized from dioxane to give yellow crystals (30%), mp 10-112 °C; ^{1}H NMR ($CDCl_3$): δ 1.71 (s, 4H, SCH_2CH_2), 2.01 (s, 4H, OCH_2CH_2), 2.66 (s, 6H, SCH_3), 3.19 (s, 4H, SCH_2), 4.16 (s,4H, OCH_2), 6.93-8.05 (m, 8H, ArH's), 8.99 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{28}H_{32}N_8O_2S_4$ (640.88), Calcd.: C, 52.48; H, 5.03; N, 17.48. Found: C, 52.20; H, 4.80; N, 17.30.

3,23-Dibenzylthio-12,13,27,28,29,30-Hexahydro-14*H*-bis-[1,2,4]triazolo[4,3-*f*:3,4-*n*]dibenzo[*b,r*][1,20]dioxa[8,13]dithia-[5,6,15,16]tetraazacyclotricosine (**17b**).

With the use of the general procedure **16b** and benzyl chloride gave crude **17b** which was crystallized from a methylene chloride/petroleum ether (40-60) mixture to give colorless crystals (55%), mp 88-90 °C; ^{1}H NMR ($CDCl_3$): δ 1.89 (s, 4H, SCH_2CH_2), 2.23 (m, 2H, OCH_2CH_2), 3.19 (s, 4H, SCH_2), 4.27 (t, 4H, J = 5.6 Hz, OCH_2), 4.41 (s, 4H, $PhCH_2$), 6.83-7.98 (m, 18H, ArH's), 8.91 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{39}H_{38}N_8O_2S_4$ (779.05): C, 60.13; H, 4.92; N, 14.38. Found: C, 59.80; H, 5.20; N, 14.40.

3,23-Di-*n*-pentylthio-12,13,27,28,29,30-Hexahydro-14*H*-bis-[1,2,4]triazolo[4,3-*f*:3,4-*n*]dibenzo[*b,r*][1,20]dioxa[8,13]dithia-[5,6,15,16]tetraazacyclotricosine (**17c**).

With the use of the general procedure **16b** and iodopentane gave an oily product which was purified by column chromatography using ethyl acetate:methanol (10:1) as an eluent to give an oily product (60%); ^{1}H NMR ($CDCl_3$): δ 0.85 (brs, 6H, CH_3), 1.3 (brs, 12H, $(CH_2)_3CH_3$), 1.87 (brs, 4H, SCH_2CH_2), 2.37 (m, 2H, OCH_2CH_2), 3.07-3.18 (m, 8H, SCH_2), 4.29 (s, 4H, OCH_2), 6.94-8.05 (m, 8H, ArH's), 8.97 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{35}H_{46}N_8O_2S_4$ (739.06): C, 56.88; H, 6.27; N, 15.16. Found: C, 56.70; H, 6.40; N, 15.00.

3,23-Diethoxycarbonylmetylthio-12,13,14,15,28,29,30.31-Octahydrobis[1,2,4]triazolo[4,3-*f*:3,4-*n*]dibenzo[*b,r*][1,20]dioxa-[8,13]dithia[5,6,15,16]tetraazacyclotetracosine (**17d**).

To a solution of **16c** (10 mmol) in dioxane (15 ml) containing triethylamine (20 mmol) was added ethyl bromoacetate **9c** (20 mmol). The reaction mixture was then stirred at room temperature for 24 h. After dilution with water, the oily product that had formed was purified using preparative thin layer chromatography using ethyl acetate:petroleum ether (40-60) (10:1) as an eluent to give an oily product (65%); IR (cm^{-1}): 1734 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 6H, J = 7.1 Hz, CH_3), 1.88 (brs, 4H, SCH_2CH_2), 2.08 (brs, 4H, OCH_2CH_2), 3.19 (brs, 4H, SCH_2), 4.04 (s, 4H, CH_2CO), 4.19-4.25 (m, 8H, OCH_2CH_2, OCH_2CH_3), 6.91-8.04 (m, 8H, ArH's), 8.98 (s, 2H, CH=N) ppm.

Anal. Calcd. for $C_{34}H_{40}N_8O_6S_4$ (785.00), Calcd.: C,52.02; H, 5.14; N, 14.27. Found: C, 52.20; H, 4.90; N, 14.10.

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