Synthesis of Novel Benzo-Substituted Macrocyclic Schiff Bases Containing Two Triazole Rings

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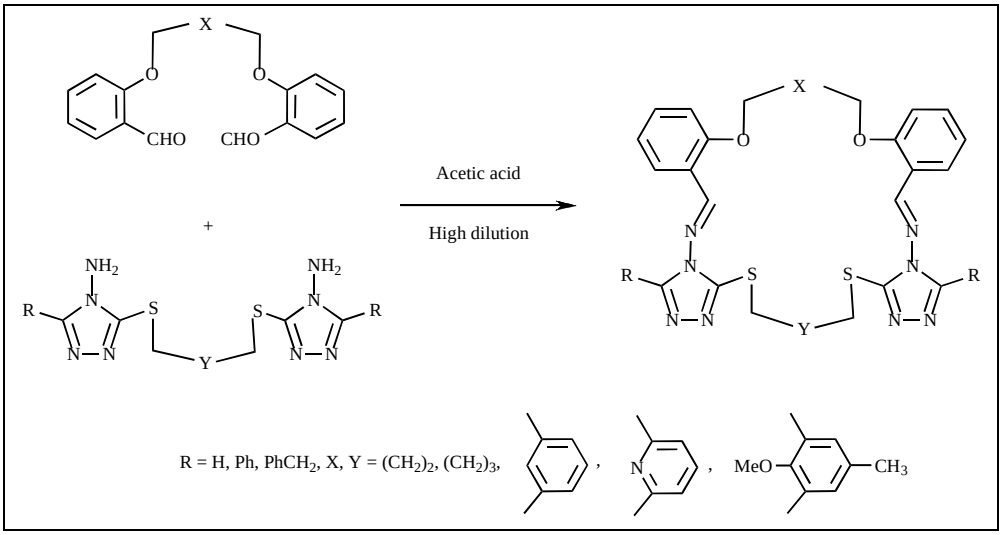

A synthesis of a series of novel macrocyclic Schiff bases containing two triazole rings **10a**,**b**, **11a**,**b**, **34-37** in good yields by heating the appropriate bis-amines **1f**, **6a**,**b**, **31** with the corresponding bis-aldehydes **2**, **9a**,**b**, **29** in refluxing acetic acid under high dilution conditions was described. Attempts to synthesize macrocyclic Schiff bases containing pyridine and two triazole rings were also described.

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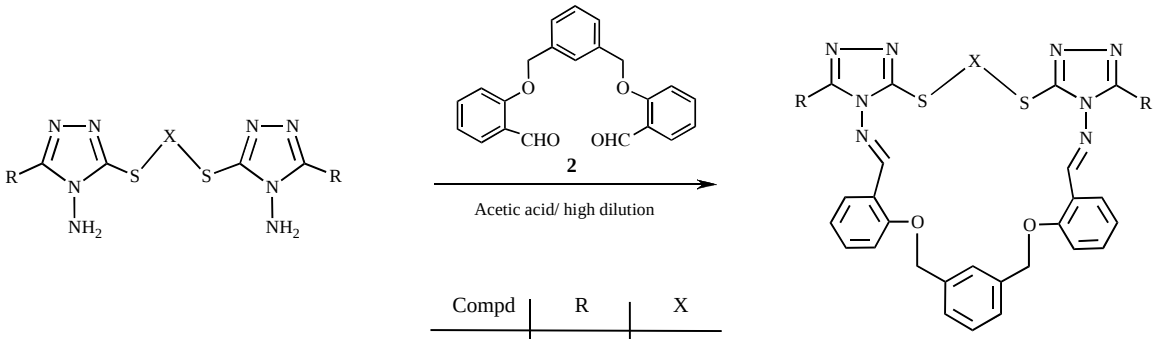
INTRODUCTION

Macrocyclic compounds have attracted increasing interest owing to their role in the understanding of molecular processes occurring in biochemistry, material science, catalysis, encapsulation, activation, transport phenomena, and hydrometallurgy [1-16]. Moreover, they have been shown to exhibit important applications including selective ion separation and detection, molecular recognition, biological applications as well as many other interesting applications in diverse fields of supramolecular chemistry [17-24]. Many ligands have been designed to mimic the function of natural carriers in recognizing and transporting specific metal ions, anions or neutral molecules and in understanding and reproducing the catalytic activity of metal co-enzymes and proteins [1-24]. In particular, macrocyclic Schiff bases have received much attention because they can be obtained by simple self-condensation of suitable formyl- or keto- and primary amine-precursors [25]. They can be functionalized by inserting appropriate groups in the aliphatic and/or aromatic chains of the formyl- or keto- and amine-precursors. They generally can contain additional donor group (O, S, P, *etc*.) and this makes them good candidates for metal ion complexation and for mimicking biological systems. Alternatively they can be obtained by template effect; this procedure directly gives the designed complexes in high yield and in a satisfactory purity grade. Moreover, these complexes can undergo transmetallation reactions when reacted with a different metal salt allowing the formation of the free ligand. Reduction of the free ligands as well as their complexes can give rise to the formation of the corresponding polyamine derivatives. These reduced compounds are less sensitive to hydrolysis and more flexible and contain NH groups which may be further functionalized by appropriate synthetic procedures. They can be also linked to an appropriate support (*e.g*. silica) giving rise to modified catalysts or modified surfaces, bearing well defined molecular assemblies [26].

In continuation of our interest in synthesizing novel macrocyclic ligands, we report here on our attempts to synthesize novel macrocyclic Schiff bases upon which fused triazole and pyridine units and contain N, O and S as donor atoms in the macrocyclic ring.

Scheme 1



Compd	R	X
1a, 3a	H	$(CH_2)_2$
1b, 3b	Ph	$(CH_2)_3$
1c, 3c	$PhCH_2$	$(CH_2)_3$
1d, 3d	Ph	$(CH_2)_4$
1e, 3e	$PhCH_2$	$(CH_2)_4$
1f	Ph	$(CH_2)_2$

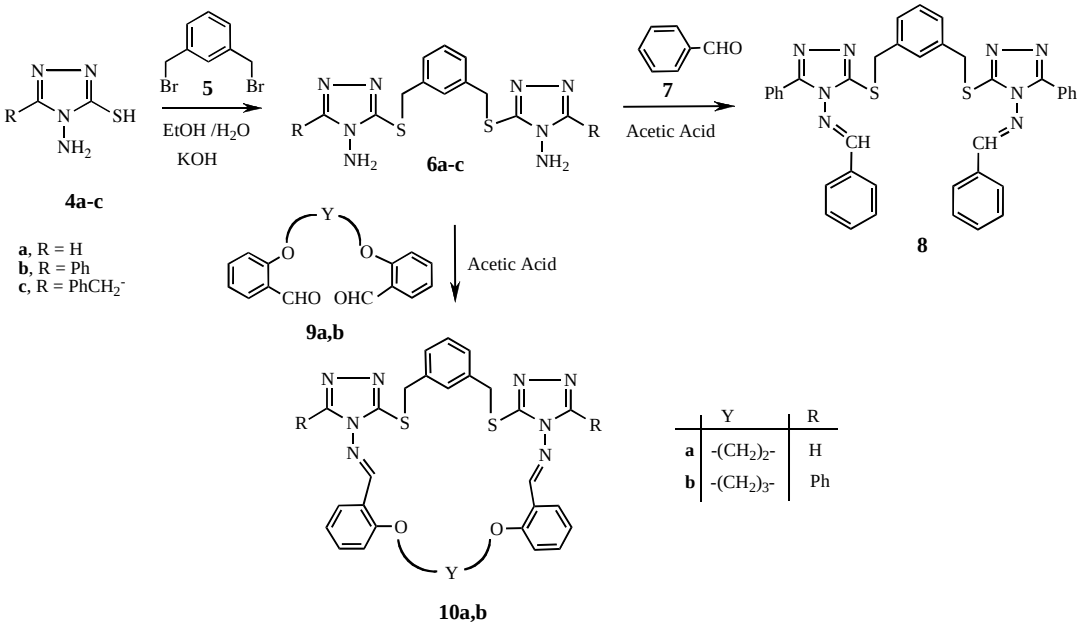
1a-f **3a-d**

RESULTS AND DISCUSSION

Recently we reported the synthesis of macrocyclic Schiff bases **3a-d** by cyclocondensation of the appropriate bis(carbonyl) ethers **2** with the corresponding bis(amines) **1a-f** in glacial acetic acid under high dilution conditions (Scheme 1) [27].

In this study we intended to make structure variations within the ligand **3** in an attempt to improve their binding properties. These structure variations involve the number of donor atoms in the macrocyclic ring, their relative position and the size of the chelating rings. These factors together with the flexibility and the shape of the coordinating moiety were reported to play an important role on the selective binding of charged or neutral species [28-35]. We first studied an alteration of the arrangement of the donor atoms in the macro ring by attachment of the 1,3-xylyl unit to the triazole part. Thus, 1,3-bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)benzenes **6a-c** were prepared in 68-75% yield from 4-amino-1,2,4-triazole-3-thione derivatives **4a-c** by reaction with 1,3-bis(bromomethyl)benzene **5** in ethanol/water mixture containing potassium hydroxide. The ^{1}H-NMR of the reaction mixture indicates the absence of the corresponding *N*-alkylated products. The exclusive formation of **6** is in accordance with previous results

Scheme 2



4a-c

a, R = H
b, R = Ph
c, R = $PhCH_2$-

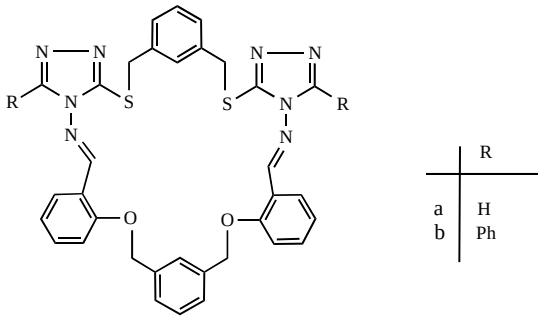
6a-c **8** **9a,b**

	Y	R
a	$-(CH_2)_2-$	H
b	$-(CH_2)_3-$	Ph

10a,b

which confirm the preferential alkylation of 4-substituted-1,2,4-triazole-3-thiones on sulfur [36-44]. The reactivity of the bis amines **6a-c** towards aromatic aldehydes was investigated by reaction of **6b** with benzaldehyde in refluxing acetic acid. As expected the corresponding benzylideneamino derivative **8** was obtained in 48% yield. On the other hand, the reaction of **6a** with 1,2-bis(2-formylphenoxy)ethane (**9a**) [45,46] in refluxing acetic acid under high dilution conditions afforded the corresponding macrocyclic Schiff base **10a** in 48% yield. Similarly, **6b** reacted with **9b** to give the target molecule **10b** in 56% yield (Scheme 2).

We also studied the insertion of an additional 1,3-xyly unit into the macrocyclic ring **10a,b** instead of the ethylene or the propylene moieties aiming at studying the effect of rigidity provided by these groups on the ability of the ligands to form stable complexes compared to other macrocyclic analogues. Thus, under similar conditions **6a,b** reacted with **2** to give the corresponding macrocyclic Schiff base **11a,b** in 55% and 61% yields, respectively.



	R
a	H
b	Ph

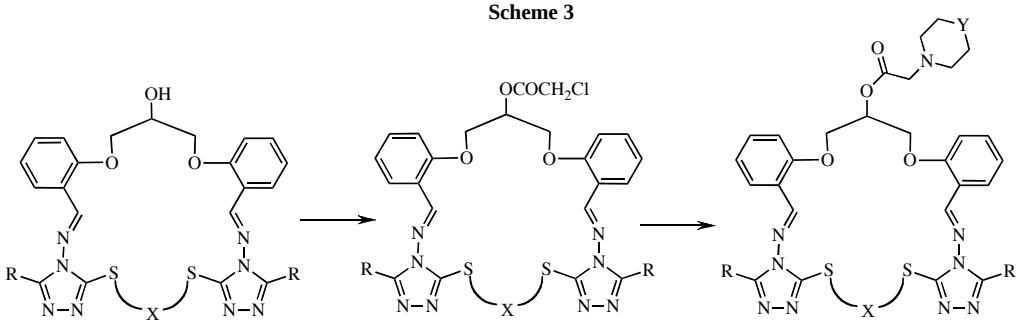
11a,b

We now attempted another structure variation of ligand **3** by insertion of additional donor atoms aiming at increasing their binding abilities. In this respect, Abbas recently reported the synthesis of macrocyclic Schiff bases **14** with additional donating sidearm from the hydroxyl macrocycle **12** by first acylation of the hydroxy group with 2-chloroacetylchloride to give the corresponding chloroacetoxy macrocycles **13** followed by reaction with a series of secondary amines (Scheme 3) [47].

On the other hand, Elwahy and Abbas attempted the incorporation of a pyridine ring as a subcyclic unit in the macrocycle **3** [27]. Such nitrogen heterocycles can participate in complexation through their soft donor atoms. They reacted 1, ω-bis(4-amino-1,2,4-triazole-3-yl-sulfanyl)alkanes **1** with 2,6-bis(2-formylphenoxy-methyl)pyridine **15** in refluxing acetic acid under high dilution conditions aiming at synthesizing the corresponding novel macrocycles **17**. Unfortunately, the reaction did not lead to the formation of **17** and gave instead the 2,6-bis[benzo(b)furan-2-yl]pyridine **16**. The formation of the latter proceeds *via* interamolecular cyclocondensation of the aldehydic group with the active methylene groups (Scheme 4).

We now studied the synthesis of isomeric structure of **17** by insertion of the pyridine moiety in the triazole part as outlined in Scheme 5. Thus, 2,6-bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)pyridine derivatives **19a-c** were prepared in 60-78% yield by reacting the appropriate 4-amino-1,2,4-triazole-3-thione derivatives **4a-c** with 1,3-bis(bromomethyl)pyridine **18** in ethanol/water mixture containing potassium hydroxide. Unfortunately repeated attempts to react **19b** with 1,3-bis(2-formylphenoxy-methyl)propane **9b** in refluxing acetic acid under high dilution conditions did not lead to the formation of pure sample of the expected macrocyclic Schiff base **20**. The ^{1}H NMR (DMSO) of the reaction products indicates the presence of a mixture of each of the corresponding Schiff base **20** and another product which may be characterized as the condensed heteromacrocycle **21** but we are still unable to isolate pure samples of each of them. The presence of a mixture of the products **20**, **21** was confirmed by the presence of a characteristic signal for the aldimine H-atom HC=N at δ 9.22 ppm [27, 40] together with the appearance of additional multiplet signals at δ 4.19-5.47 characteristic for the OCH_2 protons as well as the aliphatic CH-S and CH-N protons of the

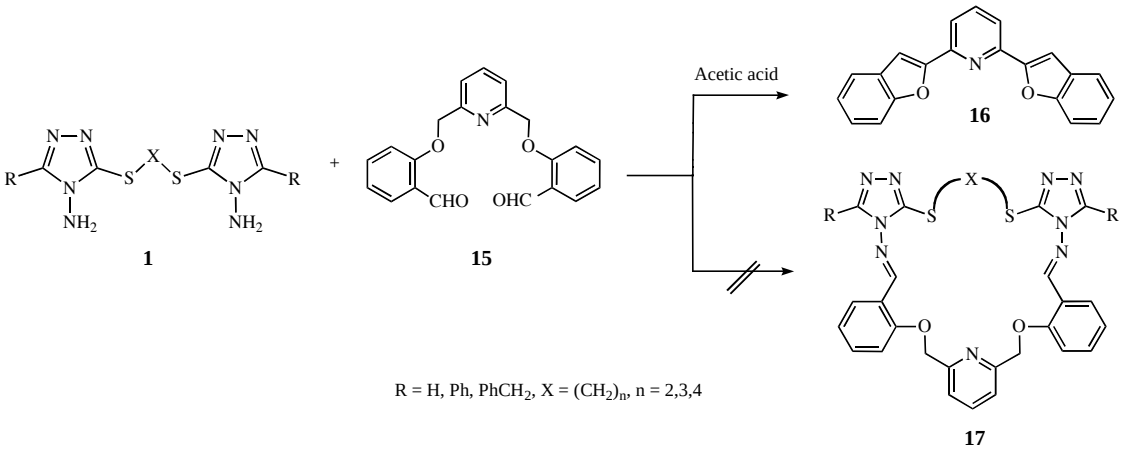
Scheme 3



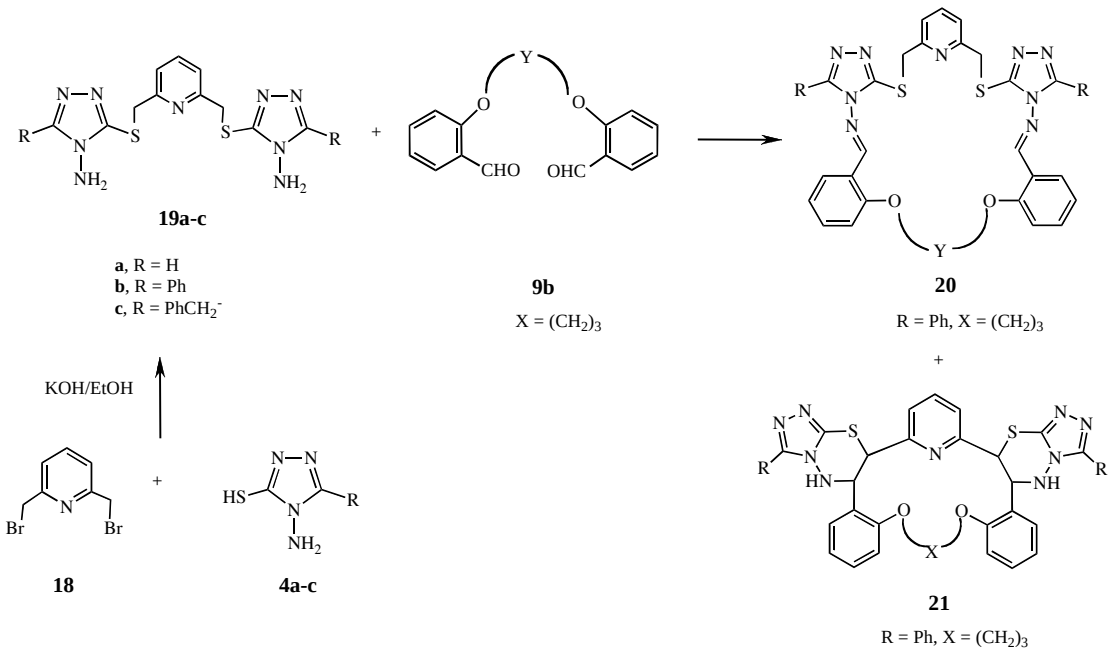
12 **13** **14**

R = Ph, $PhCH_2$, X = $(CH_2)_3$, $(CH_2)_4$, Y = CH_2, O

Scheme 4



Scheme 5

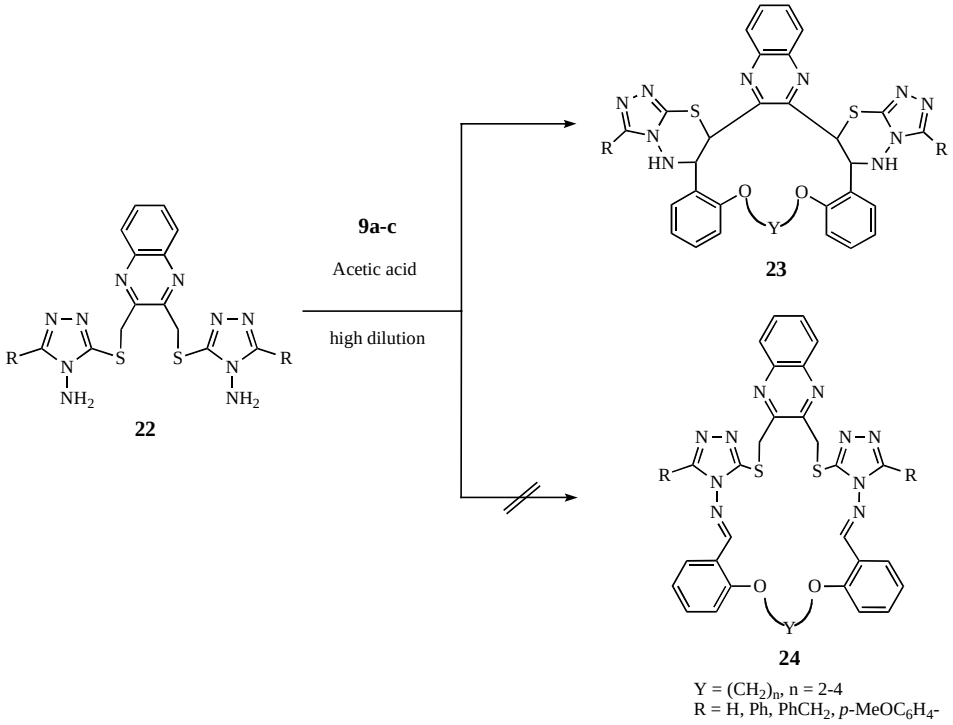


new formed six membered ring in the ^{1}H NMR spectrum. These multiplet signals assumes the generation of asymmetric center in this molecule.

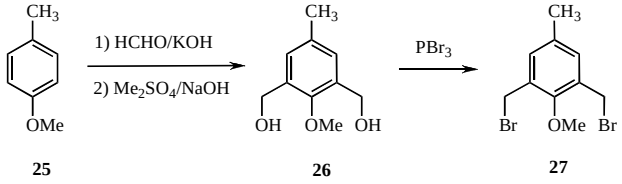
It is noteworthy to mention that we successfully synthesized the condensed hetero- macrocycles **23** by reacting 1,2-bis(4-amino-1,2,4-triazole-3-ylsulfanylmethyl)-quinoxalines **22** with the appropriate bis(carbonyl)ethers **9a-c** in refluxing acetic acid under high dilution conditions [48]. In the last reaction no traces of the corresponding macrocyclic Shiff bases **24** could be isolated from the reaction mixture (Scheme 6). The reaction can proceed *via* initial formation of the corresponding non isolated macrocyclic Schiff base **24** followed by reaction of the methylene group with the benzylideneamino carbon under the acidic reaction conditions.

The unsuccessful incorporation of pyridine rings into the macroring **3** prompted us to study the synthesis of modified derivatives of these macrocycles with additional donor atoms as outlined in Scheme 7. Thus, the dibromo compound **27** was prepared from **25** by first formylation of *p*-cresol in the presence of base to give the corresponding diol, which was selectively methylated with dimethyl sulfate to give diol **26**. The two hydroxymethyl groups of **26** were converted with PBr_3 to the bromomethyl derivative **27** in quantitative yield [49,50]. The methyl groups in the divergent 4-position of the benzene rings serve as blocking group that prevent unwanted substitution reaction from occurring during synthesis.

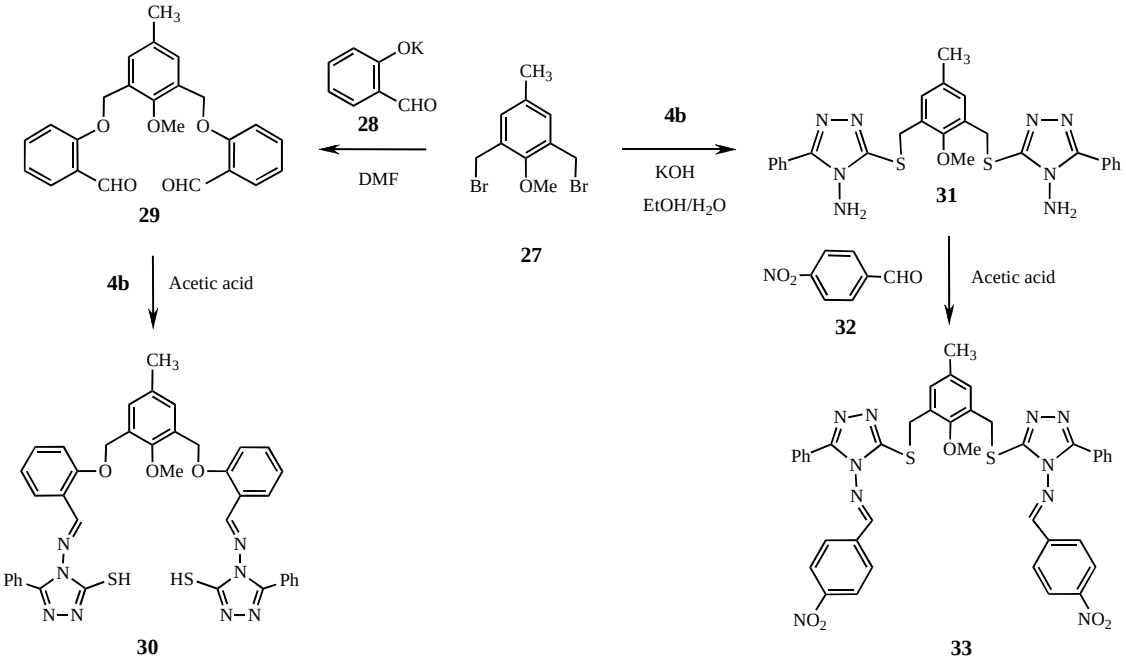
Scheme 6



Scheme 7

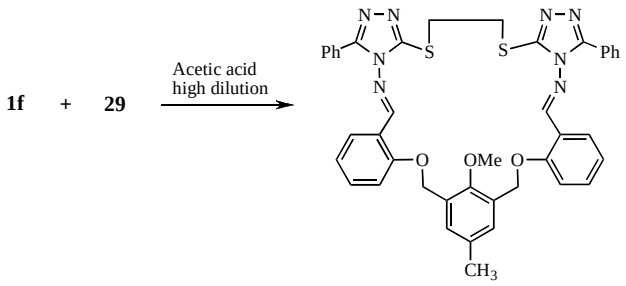


Scheme 8



Compound **27** serves as starting material for the synthesis of each of the novel bis(aldehyde) **29** as well as the bis(amines) **31**. Thus, reaction of **27** with the potassium salt **28** (obtained upon treatment of salicylaldehyde with ethanolic potassium hydroxide) in refluxing DMF afforded 2-methoxy-5-methyl-1,3-bis(2-formylphenoxymethyl)benzene **29** in 91% yield. On the other hand, reaction of **27** with **4b** in ethanol/water mixture containing potassium hydroxide afforded the corresponding 2-methoxy-5-methyl-1,3-bis(4-amino-1,2,4-triazol-3-ylsulfanyl)benzene **31** in 75% yield. The reactivity of the latter towards condensation with aromatic aldehydes was first investigated by reaction with 4-nitrobenzaldehyde **32** in refluxing acetic acid and as a result the expected bis(benzylideneamino) derivative **33** was successfully obtained in 65% yield. We have also investigated the reactivity of the bis(aldehyde) **29** towards condensation with 4-amino-5-phenyltriazole-3-thione **4b** in refluxing acetic acid. As expected the corresponding condensation product **30** could be successfully isolated in 79% yield (Scheme 8).

Scheme 9



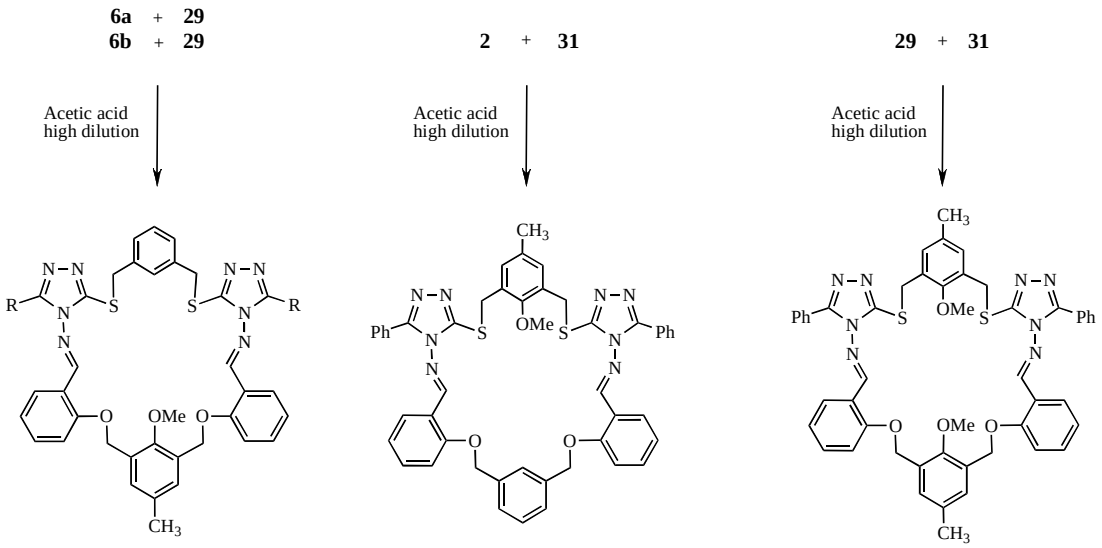
34

The synthetic utility of the novel bis aldehyde **29** and the bis amine **31** as building blocks for novel macrocyclic Schiff bases containing 4-methylanisole group incorporated into the ring system by substitution in their 2,6-positions was now investigated. Thus, cyclocondensation of **29** with 1,2-bis(4-amino-5-phenyl-3-ylsulfanyl)ethane (**1f**) in glacial acetic acid under high dilution conditions gave the corresponding macrocyclic Schiff base **34** in 71% yield as outlined in (Scheme 9).

The insertion of an additional 1,3-xylyl unit into the macrocyclic ring **34** instead of the ethylene moiety was also investigated. Thus, under similar conditions each of **6a,b** reacted with **29** to give the corresponding macrocyclic Schiff bases **35a,b** in 61% and 76% yields, respectively. Furthermore, the macrocyclic Schiff base **36** which is isomeric to **35b** could also synthesized in 70% yield by cyclocondensation of **2** with **31** in refluxing acetic acid. We could also synthesize the novel macrocyclic Schiff base **37** with two 4-methylanisole groups incorporated into the ring system in 77% yield by cyclocondensation of **29** with **31** in refluxing acetic acid under high dilution conditions (Scheme 10).

In conclusion, we prepared a new series of 1,3-bis(4-amino-1,2,4-triazol-3-ylsulfanyl) benzene derivatives and utilized them successfully as key intermediates for the synthesis of novel macrocyclic Schiff bases upon which fused triazole units and contain N, O and S inside the macrocyclic ring as donor atoms. We expect this should improve the binding abilities of the new macrocycles compared to their corresponding analogues where the additional donor atoms can effectively participate in the coordination and lead to higher cation-binding. Moreover, fusion of different coordinating entities (*i.e.* a Schiff base

Scheme 10



35a, R = H
35b, R = Ph

36

37

and crown-ether moiety) into a unique ligand can give rise to very interesting systems capable of multiple selective and/or different metal ions recognition processes. Furthermore the incorporation of additional aromatic and heterocyclic moieties into the macroring should provide the rigidity required to improve the stability of their complexes. The present paper also gives a brief description of some of our recent contribution to the utility of the cyclocondensation reactions under high dilution conditions as an efficient route to a large number of macrocyclic Schiff bases which of high interest in the fields of supramolecular chemistry, molecular recognition and organic synthesis.

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) spectrophotometer and chemical shifts are given in ppm from TMS. Mass spectra were recorded on a GC MS-QP1000 EX (70 eV) or MS 5988 (15 eV) spectrometers. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. 4-Aminotriazole-3-thione derivatives **4** were prepared as reported [51]. 1,3-Bis-(bromomethyl)benzene and 2,6-bis-(bromomethyl)pyridine were used as purchased from Aldrich.

Synthesis of 1,3-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)-benzenes (6a-c), 31 and 2,6-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)pyridines 19a-c.

General Procedure. To a solution of **4a-c** (50 mmol) in aqueous ethanol (50 ml, 50%) containing KOH (50 mmol) was added the appropriate dibromo compounds **5**, **18**, **27** (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 the proper solvent to give colorless crystals of compounds **6a-c**, **19a-c** and **31**.

2,6-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)benzene (6a). With the use of the general procedure **4a** and **5** gave crude **6a** which was crystallized from ethanol as colorless crystals (68%), mp 183 °C; ir: NH_2 3322, 3110 cm^{-1}; ^{1}H nmr: (DMSO-d_6): δ 4.35 (s, 4H, S-CH_2), 6.03 (s, 4H, NH_2), 7.25-7.43 (m, 4H, ArH's), 8.45 ppm (s, 2H, triazole H); ms: m/z (%) 334 (M^+, 8.5), 280 (2), 219 (43.9), 171 (2.7), 135 (11.1), 116 (100); *Anal.* Calcd for $C_{12}H_{14}N_8S_2$: (334.43): C, 43.11; H, 4.22; N, 33.51. Found: C, 43.30; H, 3.90; N, 33.70.

2,6-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylmethyl)-benzene (6b). With the use of the general procedure **4b** and **5** gave crude **6b** which was crystallized from acetic acid as colorless crystals (77%), mp 198 °C; ir: NH_2 3245, 3134 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.42 (s, 4H, S-CH_2), 6.09 (s, 4H, NH_2), 7.29-7.99 ppm (m, 4H, ArH's); ^{13}C nmr (DMSO-d_6): δ 35.05 (SCH_2), 126.88, 127.77, 128.13, 128.46, 128.56, 129.62, 137.68, 153.02, 154.09 ppm (Aromatic C's, triazoleC's); ms: m/z (%) 486 (M^+, 0.9), 471 (1.1), 339 (0.46), 295 (0.81), 259 (3.9), 192 (100), 121 (21). *Anal.* Calcd for: $C_{24}H_{22}N_8S_2$ (486.63): C, 59.24; H, 4.56; N, 23.03. Found: C, 59.40; H, 4.30; N, 23.00.

2,6-Bis(4-amino-5-benzyl-1,2,4-triazol-3-ylsulfanylmethyl)-benzene (6c). With the use of the general procedure **4c** and **5** gave crude **6c** which was crystallized from diluted acetic acid as colorless crystals (75%), mp 200 °C; ir: NH_2 3335, 3196 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.06 (s, 4H, CH_2-Ph), 4.30 (s, 4H, S-CH_2), 5.81 (s, 4H, NH_2), 7.20-7.39 ppm (m, 14H, ArH's); ms: m/z (%) 514 (M^+, 2), 421 (0.67), 321 (6.3), 273 (0.78), 206 (100), 116 (17.6). *Anal.* Calcd for $C_{26}H_{26}N_8S_2$ (514.68): C, 60.68; H, 5.09; N, 21.77. Found: C, 60.70; H, 5.40; N, 22.10.

1,3-Bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)pyridine (19a). With the use of the general procedure **4a** and **18** gave crude **19a** which was crystallized from ethanol as colorless crystals (60%), mp 203 °C; ir: NH_2 3258, 3157 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.45 (s, 4H, S-CH_2), 6.07 (s, 4H, NH_2), 7.36-7.73 (m, 3H, pyridine H's), 8.43 ppm (s, 2H, triazole H) ppm; ms: m/z (%) 335 (M^+, 1.8), 320 (3.71), 287 (0.9), 236 (2.5), 204 (15), 175 (4.1), 137 (9.5), 116 (100). *Anal.* Calcd for $C_{11}H_{13}N_9S_2$ (335.42): C, 39.39; H, 3.91; N, 37.58. Found: C, 39.20; H, 3.60; N, 37.80.

1,3-Bis(4-amino-5-phenyl-1,2,4-triazol-3-ylsulfanylmethyl)-pyridine (19b). With the use of the general procedure **4b** and **18** gave crude **19b** which was crystallized from acetic acid/ethanol (1:1) as colorless crystals (78%), mp 212 °C; ir: NH_2 3316, 3361 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.53 (s, 4H, S-CH_2), 6.15 (s, 4H, NH_2), 7.43-8.01 ppm (m, 13H, ArH'S, pyridine H's); ^{13}C nmr (DMSO-d_6): δ 37.37 (SCH_2), 121.84, 126.98, 127.77, 128.41, 129.57, 137.55, 152.83, 154.07, 156.47 ppm (Aromatic C's, pyridine C's); ms: m/z (%) 487 (M^+, 0.53), 402 (2.3), 393 (4.6), 342 (2.7), 291 (2.5), 177 (92), 145 (100); *Anal.* Calcd for $C_{23}H_{21}N_9S_2$ (487.62): C, 56.65; H, 4.34; N, 25.85. Found: C, 56.70; H, 4.60; N, 25.70.

1,3-Bis(4-amino-5-benzyl-1,2,4-triazol-3-ylsulfanylmethyl)-pyridine(19c). With the use of the general procedure **4c** and **18** gave crude **19c** which was crystallized from ethanol as colorless crystals (71%), mp 206 °C; ir: NH_2 3250, 3158 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.06 (s, 4H, CH_2-Ph), 4.39 (s, 4H, S-CH_2), 5.87 (s, 4H, NH_2), 7.12-7.65 ppm (m, 13H, ArH'S, pyridine H's); ms: m/z (%) 515 (M^+, 0.4), 500 (0.9), 453 (0.6), 346 (0.4), 296 (7.0), 206 (100), 117 (18.4). *Anal.* Calcd for $C_{25}H_{25}N_9S_2$ (515.67): C, 58.23; H, 4.89; N, 24.45. ound: C, 57.90; H, 5.10; N, 24.20.

2-Methoxy-5-methyl-1,3-bis(4-amino-1,2,4-triazol-3-ylsulfanylmethyl)benzene (31). With the use of the general procedure **4b** and **27** gave crude **31** which was crystallized from ethanol as colorless crystals (75%), mp 195-197 °C; ir: NH_2 3308, 3165 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.21 (s, 3H, $CH_3C_6H_2$), 3.89 (s, 3H, OCH_3), 4.42 (s, 4H, SCH_2), 6.16 (s, 4H, NH_2), 7.23-8.03 ppm (m, 12H, ArH's); ^{13}C nmr (DMSO-d_6): δ 20.33 ($CH_3C_6H_2$), 30.19 (S-CH_2), 62.13 (O-CH_3), 126.89, 127.77, 128.25, 128.47, 129.63, 130.13, 130.93, 133.25, 153.17, 154.13 ppm (Aromatic C's); ms: m/z (%) m/z 530 (M^+, 6.6), 515 (7.2), 499 (3.2), 483 (14), 468 (21), 324 (71.8), 292 (66), 190 (100), 147 (86.1). *Anal.* Calcd for $C_{26}H_{26}N_8OS_2$ (530.68): C, 58.85; H, 4.94; N, 21.12. Found: C, 58.60; H, 5.20; N, 21.40.

Synthesis of 2-methoxy-5-methyl-1,3-bis(2-formylphenoxy-methyl)benzene (29). A solution of the potassium salt of salicylaldehyde **28** (20 mmol) and the dibromo compound **27** (10 mmol) in DMF (20 ml) was heated under reflux for 5 min. during which potassium chloride was precipitated. The solution was concentrated to small volume (*ca.* 2 ml) and then cold water (*ca.* 10 ml) was added. The solid obtained was collected and crystallized from acetic acid as pale yellow crystals of **29** (91%), mp 137.5-138 °C; ir: CHO 2853, 2755 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.29 (s, 3H, $CH_3C_6H_2$), 3.78 (s, 3H, OCH_3), 5.25 (s, 4H, OCH_2), 7.09-7.76 (m, 10H, ArH's), 10.40 ppm (s, 2H, CHO);

^{13}C nmr (DMSO-d_6): δ 20.36 ($CH_3C_6H_2$), 62.56 (O-CH_3), 65.42 (O-CH_2), 113.76, 120.81, 124.50, 127.79, 129.03, 130.57, 133.44, 136.12, 154.25, 160.47 (Aromatic C's), 188.87 ppm (C=O); ms: m/z (%) 390 (M^+, 5), 332 (6.3), 293 (9.8), 250 (7), 197 (11.9), 148 (62), 97 (88.5), 71 (100). *Anal.* Calcd for $C_{24}H_{22}O_5$ (390.44): C, 73.83; H, 5.68. Found: C, 74.00; H, 5.60.

Synthesis of the Bis-Schiff Bases 8, 33. To a solution of the appropriate bis amines **6b** and **31** (20 mmol) in glacial acetic acid (15 ml) was added the corresponding aromatic aldehydes **7**, **32**. The reaction mixture was heated under reflux for 1 h and the solvent was then removed *in vacuo*. The remaining solid was collected and crystallized from the proper solvent to give crystals of **8** and **33**.

1,3-Bis[(4-benzylideneamino-5-phenyl-1,2,4-triazolo-3-yl)-sulfanylmethyl]benzene (8). With the use of the general procedure **6b** and **7** gave crude **8** which was crystallized from benzene/*n*-pentane as yellow crystals (48%), mp 98-100°C; ^{1}H nmr (DMSO-d_6): δ 4.34 (s, 4H, S-CH_2), 7.22-7.84 (m, 24H, ArH's), 8.73 ppm (s, 2H, CH=N). *Anal.* Calcd for $C_{38}H_{30}N_8S_2$ (662.85): C, 68.86; H, 4.56; N, 16.91. Found: C, 68.70; H, 4.20; N, 16.90.

2-Methoxy-5-methyl-1,3-bis{[4-*p*-(nitro)benzylideneamino-5-phenyl-1,2,4-triazolo-3-ylsulfanyl]methyl}benzene (33). With the use of the general procedure **31** and **32** gave crude **33** which was crystallized from ethanol as as colorless crystals (65%), mp 117 °C; ^{1}H nmr (DMSO-d_6): δ 2.0 (s, 3H, $CH_3C_6H_2$), 3.64 (s, 3H, OCH_3), 4.29 (s, 4H, SCH_2), 6.94-8.37 (m, 20H, ArH's), 8.96 ppm (s, 2H, CH=N); ms: m/z (%) 796 (4.6), 613 (4.18), 551(21.76), 496 (12.6), 339 (22.2), 239 (40.2), 185 (25.1), 131(51.5), 96 (31.8), 57 (100). *Anal.* Calcd for $C_{40}H_{32}N_{10}O_5S_2$ (796.90): C, 60.29; H, 4.05; N, 17.58. Found: C, 60.40; H, 4.30; N, 17.70.

Synthesis of 2-Methoxy-5-methyl-1,3-Bis{2-[(5-phenyl-3-sulfanyl-1,2,4-triazol-4-yl)-1-azavinyl]phenoxymethyl}benzene (30). To a solution of each of **29** (20 mmol) in glacial acetic acid (15 ml) was added a solution of 4-aminotriazole-3-thione **4b** (40 mmol). The reaction mixture was heated under reflux for 1 h and the solvent was then removed *in vacuo*. The remaining solid was collected and crystallized from ethanol to give **30** as colorless crystals (79%), mp 142 °C; ^{1}H nmr (DMSO-d_6): δ 2.0 (s, 4H, CH_3), 3.79 (s, 3H, OCH_3), 5.26 (s, 4H, O-CH_2), 7.09-7.97 (m, 22H, ArH's), 10.24 (s, 2H, CH=N), 14.16 ppm (s, 2H, SH); ms: m/z (%) 738 (M^+, 0.3), 737 (0.3), 691 (0.4), 610 (0.4), 508 (0.5), 406 (0.7), 278 (2.7), 149 (97), 97 (100). *Anal.* Calcd for $C_{40}H_{34}N_8O_3S_2$ (738.90): C, 65.02; H, 4.64; N, 15.17. Found: C, 65.30; H, 4.80; N, 15.30.

Synthesis of the Macrocyclic Bis-Schiff Bases 10a, b, 11a, b and 34-37.

General procedure. To a solution of the appropriate bis aldehydes **2**, **9a, b** and **29** (10 mmol) in glacial acetic acid (50 ml) was added a solution of the appropriate bis amines **1f**, **6a, b** and **31** (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) and then cold water (*ca*. 15 ml) was added. The precipitate obtained was collected and recrystallized from the proper solvent to give crystals of **10a, b, 11a, b** and **34-37.**

27,31-Metheno-12,13-dihydro-26*H*,32*H*-bis[1,2,4]triazolo-[4,3-*f*:3,4-*q*]dibenzo[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacycloopentacosine (10a). With the use of the general procedure **6a** and **9a** gave crude **10a** which was crystallized from acetic acid/ethanol (1:1) as colorless crystals (48%), mp 230 °C; ^{1}H nmr (DMSO-d_6): δ 4.26 (s, 4H, S-CH_2), 4.56 (s, 4H, OCH_2), 6.97-7.71 (m, 12H, ArH's), 8.76 ppm (s, 2H, triazole H's); ms: m/z (%) 568 (0.1), 406 (0.1), 332 (0.6), 264 (26.7), 204 (22.3), 146 (100), 91(50). *Anal.* Calcd for $C_{28}H_{24}N_8O_2S_2$ (568.69): C, 59.14; H, 4.25; N, 19.70. Found: C, 59.20; H, 4.40; N, 19.60.

28,32-Metheno-3,23-diphenyl-12,13-dihydro-14*H*,27*H*,33*H*-bis[1,2,4]-triazolo[4,3-*f*:3,4-*q*]dibenzo[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacyclohexacosine (10b). With the use of the general procedure **6b** and **9b** gave crude **10b** which was crystallized from ethanol as colorless crystals (66%), mp 244 °C; ^{1}H nmr (DMSO-d_6): δ 1.91 (s, 3H, $CH_3C_6H_2$), 2.20 (quintet, 2H, J = 6.0 Hz, OCH_2CH_3), 4.10 (s, 4H, OCH_2), 4.32 (t, 4H, J = 6.0 Hz, OCH_2), 7.08-7.91 (m, 22H, ArH's), 9.10 ppm (s, 2H, CH=N); ^{13}C nmr (DMSO-d_6): δ 20.98 (OCH_2CH_3), 37.87 (S-CH_2), 64.96 (O-CH_2), 113.23, 119.69, 121.12, 126.55, 126.97, 127.90, 128.46, 128.61, 129.17, 129.91, 134.95, 136.52, 145.46, 151.65, 158.63, 162.16, 171.92 ppm (Aromatic C's, triazole C's, CH=N); ms: m/z (%) 735 (M^++1, 0.1), 691 (0.1), 579 (0.2), 445 (0.3), 402 (0.8), 313 (2.5), 278 (46), 160 (100). *Anal.* Calcd for $C_{41}H_{34}N_8O_2S_2$ (734.91): C, 67.01; H, 4.66; N, 15.25. Found: C, 67.30; H, 4.80; N, 14.90.

13,17,32,36-Dimetheno-12*H*,18*H*,27*H*,31*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*q*]dibenzo[*b*,*u*]-1,23-dioxa-5,6-18,19-tetraaza-8,16-dithiacyclotricontin (11a). With the use of the general procedure **6a** and **2** gave crude **11a** which was crystallized from acetic acid as colorless crystals (55%), mp 231 °C; ^{1}H nmr (DMSO-d_6): δ 4.35 (s, 4H, SCH_2), 5.26 (s, 4H, OCH_2), 7.07-7.76 (m, 16H, ArH's), 8.89 (s, 2H, CH=N), 9.08 ppm (s, 2H, triazole H' s); ^{13}C nmr (DMSO-d_6): δ 35.38 (S-CH_2), 70.02 (O-CH_2), 113.87, 120.41, 121.16, 125.66, 126.97, 128.35, 128.48, 129.27, 129.38, 133.98, 136.56, 137.34, 138.81, 147.63, 155.47, 157.81 ppm (Aromatic C's, triazole C's, CH=N); ms: m/z (%) 644 (0.9), 577(29), 551 (26.9), 423 (8), 368 (23), 313 (100), 264 (73), 129 (59.4), 98 (77.3). *Anal.* Calcd for $C_{34}H_{28}N_8O_2S_2$ (644.79): C, 63.34; H, 4.38; N, 17.38. Found: C, 63.10; H, 4.50; N, 17.10.

13,17,32,36-Dimetheno-3,27-diphenyl-12*H*,18*H*,31*H*,37*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*q*]dibenzo[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacyclotricontin (11b). With the use of the general procedure **6b** and **2** gave crude **11b** which was crystallized from acetic acid as colorless crystals (61%), mp 251°C; ^{1}H nmr (DMSO-d_6): δ 4.43 (s, 4H, S-CH_2), 5.24 (s, 4H, OCH_2), 6.6-7.9 ppm (m, 26H, ArH's), 9.05 (s, 2H, CH=N); ms: m/z (%) 796 (0.1), 792 (0.1), 747 (0.2), 690 (0.2), 559 (0.4), 456 (1.8), 398 (15.4), 280 (100), 222 (42), 104 (70.3). *Anal.* Calcd for $C_{46}H_{36}N_8O_2S_2$ (796.98): C, 69.33; H, 4.55; N, 14.06. Found: C, 69.30; H, 4.80; N, 13.80.

13,17-Metheno-15-methyl-34-methoxy-3,27-diphenyl-31,32-dihydro-12*H*,18*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*l*]dibenzo[*b*,*p*]-1,18-dioxa-5,6,13-14-tetraaza-30,33-dithiacyclopentacosine (34). With the use of the general procedure **1f** and **29** gave crude **34** which was crystallized from ethanol as colorless crystals (71%), mp 247-250 °C; ^{1}H nmr (DMSO-d_6): δ 2.30 (s, 3H, $CH_3C_6H_2$), 3.46 (s, 4H, SCH_2), 3.77 (s, 3H, OCH_3), 5.17 (s, 4H, OCH_2), 7.16-7.95 (m, 20H, ArH's), 9.04 ppm (s, 2H, CH=N); ms: m/z (%) 764 (M^+, 2.8), 733 (0.3), 713 (4.8), 552 (11.5), 368 (36.2), 269 (43.5), 135 (100). *Anal.* Calcd for $C_{42}H_{36}N_8O_3S_2$ (764.94): C, 65.95; H, 4.74; N, 14.65. Found: C, 65.70; H, 4.50; N, 14.60.

13,17,32,36-Dimetheno-15-methyl-37-methoxy-12*H*,18*H*,27*H*,31*H*-bis[1,2,4-]triazolo[4,3-*f*:3,4-*q*]dibenzo[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacyclotricontin (35a). With the use of the general procedure **6a** and **29** gave crude **35a** which was crystallized from acetic acid/ethanol (1:1) as colorless crystals (61%), mp 186 °C; ^{1}H nmr (DMSO-d_6): δ 2.03

(s, 3H, $CH_3C_6H_2$), 3.70 (s, 3H, OCH_3), 4.21 (s, 4H, SCH_2), 5.19 (s, 4H, OCH_2), 7.09-7.77 (m, 14H, ArH's), 8.81 (s, 2H, CH=N), 9.04 ppm (s, 2H, triazole H' s); ms: m/z (%) 689 (M^++1, 0.7), 685 (0.8), 632 (1.2), 551 (13.2), 323 (6.8), 313 (62), 239 (41), 171 (30), 129 (77), 72 (100). *Anal.* Calcd for $C_{36}H_{32}N_8O_3S_2$ (688.84): C, 62.77; H, 4.68; N, 16.27. Found: C, 63.00; H, 4.60; N, 16.40.

13,17,32,36-Dimetheno-3,27-diphenyl-15-methyl-37-methoxy-12*H*,-18*H*,27*H*,31*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*q*]dibenzo-[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacyclotricontin (35b). With the use of the general procedure **6b** and **29** gave crude **35b** which was crystallized from ethanol as colorless crystals (76%), mp 155-157 °C; ^{1}H nmr (DMSO-d_6): δ 2.03 (s, 3H, $CH_3C_6H_2$), 3.71 (s, 3H, OCH_3), 4.32 (s, 4H, S-CH_2), 5.24 (s, 4H, OCH_2), 7.13-7.98 (m, 24H, ArH's), 9.15 ppm (s, 2H, CH=N); ^{13}C nmr (DMSO-d_6): δ 20.27 ($CH_3C_6H_2$), 37.72 (S-CH_2), 62.50 (O-CH_3), 65.30 (O-CH_2), 113.75, 120.24, 121.49, 126.66, 127.13, 127.84, 128.02, 128.56, 128.64, 128.72, 128.89, 129.48, 129.89, 133.42, 134.89, 136.62, 145.73, 151.92, 153.52, 158.53, 161.18 ppm (Aromatic C's, triazole C's, CH=N); ms: m/z (%) 840 (M^+, 0.7), 837 (0.9), 811 (0.7), 797 (0.8), 558 (15.9), 381 (25.6), 280 (100). *Anal.* Calcd for $C_{48}H_{40}N_8O_3S_2$ (841.04): C, 68.55; H, 4.79; N, 13.32. Found: C, 68.70; H, 4.80; N, 13.10.

13,17,32,36-Dimetheno-3,27-diphenyl-34-methyl-38-methoxy-12*H*,18*H*,31*H*,37*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*q*]dibenzo-[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacyclotricontin (36). With the use of the general procedure **2** and **31** gave crude **36** which was crystallized from ethanol as colorless crystals (71%), mp 210-212 °C; ^{1}H nmr (DMSO-d_6): δ 1.99 (s, 3H, $CH_3C_6H_2$), 3.63 (s, 3H, OCH_3), 4.42 (s, 4H, S-CH_2), 5.22 (s, 4H, OCH_2), 7.07-7.94 (m, 24H, ArH's), 8.98 ppm (s, 2H, CH=N); ^{13}C nmr (DMSO-d_6): δ 19.89 ($CH_3C_6H_2$), 32.12 (S-CH_2), 62.29 (O-CH_3), 69.65 (O-CH_2), 113.65, 119.97, 121.49, 126.52, 127.07, 127.78, 128.07, 128.61, 128.71,129.89, 129.89, 131.77, 133.64, 134.88, 136.20, 136.26, 136.77, 145.68, 151.88, 154.73, 158.28, 160.45 ppm (Aromatic C's, triazole C's, CH=N); ms: m/z (%) 841 (M^++1, 3.1), 656 (4%), 604 (12), 578 (49), 481 (8.6), 367 (20.8), 313(100), 239 (40.7), 69 (73). *Anal.* Calcd for $C_{48}H_{40}N_8O_3S_2$ (841.04): C, 68.55; H, 4.79; N, 13.32. Found: C, 68.50; H, 4.50; N, 13.00.

13,17,32,36-Dimetheno-3,27-diphenyl-15,34-dimethyl-37,38-dimethoxy-12*H*,18*H*,31*H*,37*H*-bis[1,2,4]triazole[4,3-*f*:3,4-*q*]-dibenzo[*b*,*u*]-1,23-dioxa-5,6,18,19-tetraaza-8,16-dithiacyclotricontin (37). With the use of the general procedure **29** and **31** gave crude **37** which was crystallized from benzene/*n*-pentane as colorless crystals (78%), mp 154 °C; ^{1}H nmr (DMSO-d_6): δ 1.93, 2.09 (2s, 6H, $CH_3C_6H_2$), 3.41, 3.70 (2s, 6H, OCH_3), 4.32 (s, 4H, SCH_2), 5.20 (s, 4H, OCH_2), 7.16-7.99 ppm (m, 22H, ArH's), 9.14 (s, 2H, CH=N); ms: m/z (%) 884 (M^+, 0.1), 799 (0.1), 652 (0.1), 554 (0.1), 480 (0.1), 386 (0.5), 279 (11.9), 167 (27.8), 149 (100). *Anal.* Calcd for $C_{50}H_{44}N_8O_4S_2$ (885.09): C, 67.85; H, 5.01; N, 12.66. Found: C, 68.10; H, 4.90; N, 12.50.

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