Unexpected Synthesis of Novel Condensed Heteromacrocycles

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Abstract: Alkylation of 4-amino-1,2,4-triazol-3(2*H*)-thiones **9a**–**d** with 2,3-bis(bromomethyl)quinoxaline (**8**) in absolute ethanol containing potassium hydroxide gave the corresponding bis(amines) **10a**–**d**. Condensation of the latter with the appropriate aromatic aldehydes in refluxing acetic acid afforded the corresponding benzylideneamino derivatives **12a,b**. On the other hand, reaction of the bis(amines) **10a**–**d** with the bis(aldehydes) **13a**–**c** in refluxing acetic acid under high dilution conditions did not lead to the formation of the corresponding macrocyclic Schiffs bases **14**. Instead, the reaction gave the corresponding novel condensed heteromacrocycles **15a**–**f**.

Key words: alkylation, bis(bromomethyl)quinoxaline, heteromacrocycles, bis(amines), bis(aldehydes)

For the past three decades much work has been directed towards the synthesis of new macrocyclic ligands and the systematic determination of the parameter that affect their complex stability with different cations in terms of thermodynamic and kinetic data.[1–3] Since the discovery of crown ethers which represent the first class of the macrocyclic ligands, various structure changes have been made to the basic crown ether structure in an attempt to enhance the selectivity of these ligands and the stability of complexes formed with both metal and organic cations. Some of these modifications involved the substitutions of ligand polyether oxygen atoms by sulfur and/or nitrogen atoms. Other substitution have involved the insertion of aromatic and/or heterocyclic ring system into the macroring.[2–4] Heterocyclic groups provide rigidity and are able to participate, in some cases, in complexation through their soft donor atoms. Although many macrocyclic compounds containing heterocyclic rings such as pyridine, bipyridine, pyrimidine, triazole, pyrazole, imidazole, and thiophene have been synthesized and studied,[5–12] very little is known[13,14] about using benzoheterocycles as a subunit of macrocyclic compounds. As part of an ongoing investigation aimed at the synthesis of new macrocyclic ligands fused with benzoheterocycles, we report herein our attempts to synthesize novel macrocycles, which are fused to quinoxaline units. Our object in this project is to study the effect of rigidity provided by these groups on the ability of the ligands to form stable complexes compared to other macrocyclic analogues. In this respect, we recently[15] described the synthesis of some quinoxaline containing crown ethers, azacrown ethers, and macrocyclic diamides and their corresponding dithiodiamides **1**–**3** (Figure 1).

We have also investigated the reactivity of the bis(aldehydes) **4**[15] towards the bis(aminotriazoles) **5**[16] in an attempt to obtain the corresponding novel macrocycles **6** in which two triazole rings are fused to the macrocycles in addition to the quinoxaline moiety (Scheme 1). Unfortunately the reaction of **4** with **5** in refluxing acetic acid under high dilution conditions did not lead to the formation of **6**. Instead the reaction gave 2,3-bis(benzo[*b*]furan-2-yl)quinoxaline (**7**) via intramolecular cyclocondensation of the active methylene with the aldehyde groups. Although we were not able to get the target molcule **6**, this reaction provided a new and easy access to novel dibenzofuranylquinoxaline derivatives.

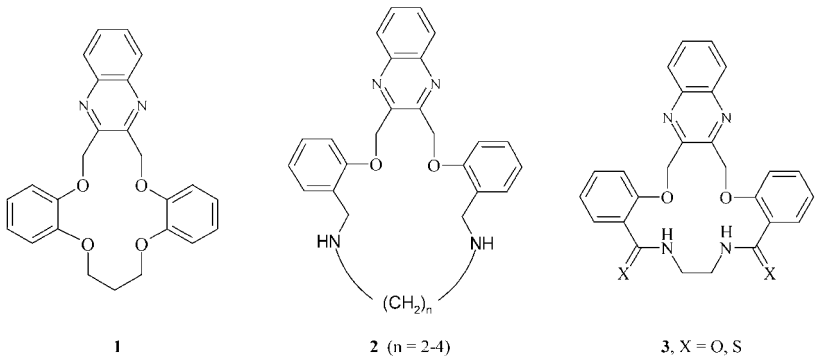

Figure 1 Chemical structures of quinoxaline macrocycles **1**–**3**

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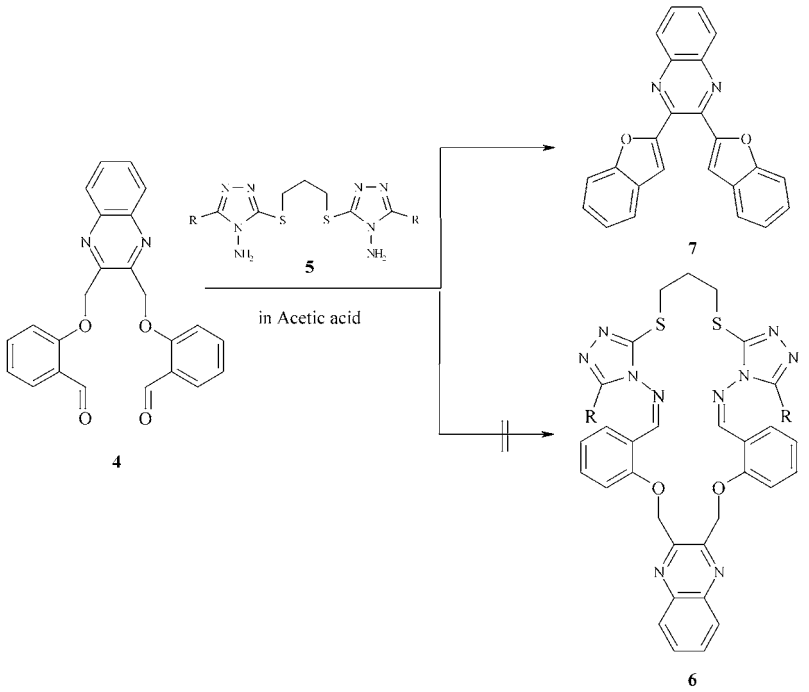
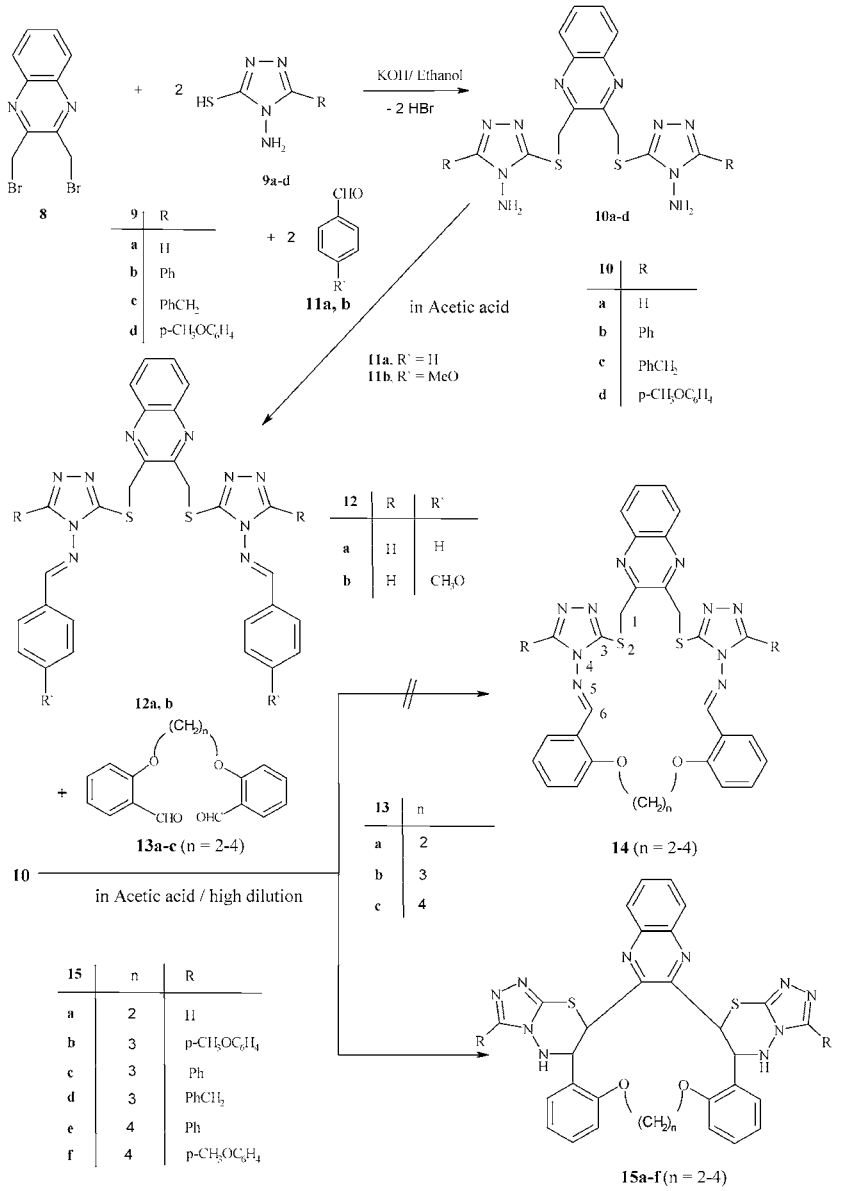


Scheme 1

We now attempted to prepare new quinoxaline containing macrocycles **14** which are isomeric with compound **6** using a new strategy as outlined in Scheme 2.

Thus, 4-amino-1,2,4-triazole-3(2*H*)-thiones **9a**–**d**[17] was reacted with 2,3-bis(bromomethyl)quinoxaline (**8**) in absolute ethanol containing KOH to give 61–74% of the corresponding 1,2-bis(4-amino-1,2,4-triazole-3-ylsulfanylmethyl)quinoxalines **10a**–**d**. The reactivity of the latter towards aromatic aldehydes was now investigated. Thus, reaction of **10a** with each of benzaldehyde and anisaldehyde in refluxing acetic acid afforded 30–35% yields of the corresponding benzylideneamino derivatives **12a**,**b**. We now studied the reaction of **10a** with 1,2-bis(2-formylphenoxy)ethane (**13a**)[18] in refluxing acetic acid under high dilution conditions aiming at the synthesis of the target molecule **14**. Unfortunately the reaction did not lead to the formation of the expected macrocyclic schiff base **14**. Instead the reaction gave another product, which could be characterized as the condensed heteromacrocycle **15a**. Similarly, were prepared the novel macrocycles **15b**–**f** by reacting the appropriate bis(aldehydes) **13a**–**c**[18,19] with the corresponding bis(amines) **10b**–**d**. The molecular structure proposed for the new compounds **15a**–**f** was confirmed by the presence of the correct molecular ion peak in their mass spectra. Based on the absence of the characteristic ^{1}H NMR signal for the aldimine H-atom HC=N at δ = 8–9,[16] the structure **14** was completely ruled out. The appearance of the OCH_2 signal as multiplet in compound **15a**–**f** together with the fact that its precursors **13a**–**c** exhibit singlet or triplet signals for these protons assumes the generation of asymmetric center in these molecules which is close enough to this CH_2 group to affect such splitting. Recently, we discussed the effect of the generation of asymmetric center on the ^{1}H NMR spectra of some related compounds.[20,21] Additional evidence for structure **15a**–**f** comes from studying the ^{13}C-{^{1}H} NMR spectra of compounds **15d**–**f** which indicate their existence as one stable conformer. Moreover, the presence of two signals at δ = 34.4–36.6 and 54.7–57.4, respectively, characteristic for the sp^3 CHNH and CHS carbons in the ^{13}C-{^{1}H} NMR spectra (APT) of compounds **15a**–**f** provide additional proof for the suggested structure. Furthermore, the presence of an absorption band at 3421–3363 cm^{-1} characteristic for NH group adds also another evidence for the proposed structures.

The reaction can proceed via initial formation of the corresponding macrocyclic Schiffs base **14**. Under the reaction conditions the acid catalyst affords small amounts of the tautomeric methylene form **A**[22] (Figure 2), which could then react with the benzylideneamino carbon that act as an electrophile to give **15**. The reaction was faciliated by the enhanced electrophilicity of C-1 caused by protonation of N-2 under the acidic conditions. The reaction can also proceed by an intermolecular ene-reaction with the azomethine group as ene part and the eneamine group as enophile part in the proposed intermediate A. In both cases, the formation of the six-membered ring is the driving force for the formation of **15**. We expect also the restricted rotational freedom in the cyclic precursor **14** caused by the rigidity provided by the heterocycles and the aromatic groups together with the presence of the two reacting species in close proximity in the same molecule may assist the intramolecular ring closure of **14** to **15** to occur in relatively moderate yield.[23,24] On the other hand, the absence of such rigidity in the acyclic schiff bases **12** did not allow the cyclization of the latter to the cor-



Scheme 2

responding 2,3-bis(6,7-dihydro-5*H*-1,2,4-triazolo(4,3-*b*)-thiadiazine-7-yl)quinoxaline **16a** (Figure 2). It is noteworthy to mention that we were unable to separate pure sample of the corresponding schiff base **12** (R = Ph, R' = OMe) by condensing **10b** with anisaldehyde. The ^{1}H NMR of the reaction products indicate the presence of a mixture of each of the corresponding schiff base and the corresponding cyclic product **16b** but we are still unable to isolate pure samples of each of them. The presence of phenyl group in the 3-position of the triazole ring may add some restriction to the rotational freedom in these molecules allowing the formation of some of the cyclic product.

In conclusion, we have provided a new access to novel condensed heteromacrocycles, which represent an important point of departure from traditional heterocyclic chemistry and would add another dimension to this difference. Studying the incorporation of a range of heteroatoms into the new macrocycles to enhance their potential as ligands is now in progress.

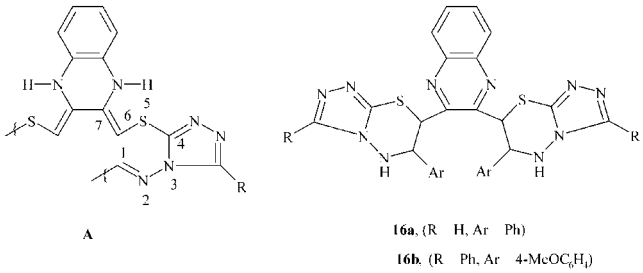


Figure 2 Chemical structures of tautomeric methylene form A and compounds **16a**,**b**

1,2-Bis(4-amino-1,2,4-triazole-3-yl-sulfanylmethyl)quinoxalines 10a–d; General Procedure

To a stirred solution of KOH (0.12 g, 20 mmol) in absolute EtOH (15 mL) was added the appropriate triazole **9a–d** (20 mmol). To the formed potassium salt was added 2,3-bis(bromomethyl)quinoxaline (**8**; 10mmol). The mixture was heated under reflux for 1 h during which time a crude solid was precipitated. The product was collected and recrystallized to give colorless crystals of **10a–d**.

1,2-Bis(4- amino-1,2,4-triazole-3-yl-sulfanylmethyl)quinoxaline (10a)

By using the general procedure, compounds **8** and **9a** gave **10a** which was recrystallized from EtOH; brown crystals (71%); mp 170 °C.

IR (KBr): 3256.5, 3343.1 (NH_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.96 (s, 4 H, SCH_2), 6.21 (s, 4 H, NH_2), 7.8–8.1 (m, 4 H, ArH), 8.51 (s, 2 H, triazole-H).

Anal. Calcd for $C_{14}H_{14}N_{10}S_2$ (386.5): C, 43.50; H, 3.65; N, 36.24. Found: C, 43.30; H, 3.50; N, 36.20.

1,2-Bis(4-amino-5-phenyl-1,2,4-triazole-3-yl-sulfanylmethyl)-quinoxaline (10b)

By using the general procedure, compounds **8** and **9b** gave **10b** which was recrystallized from HOAc; brown crystals (73%); mp 250 °C.

IR (KBr): 3280.5, 3354.4 (NH_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 5.06 (s, 4 H, CH_2S), 6.3 (s, 4 H, NH_2), 7.5–8.1 (m, 14 H, ArH).

Anal. Calcd for $C_{26}H_{22}N_{10}S_2$ (538.7): C, 57.97; H, 4.12; N, 26.00. Found: C, 57.70; H, 4.10; N, 26.10.

1,2-Bis(4-amino-5-benzyl-1,2,4-triazole-3-yl-sulfanylmethyl)-quinoxaline (10c)

By using the general procedure, compounds **8** and **9c** gave **10c** which was recrystallized from EtOH, pale brown crystals (61%); mp 192 °C.

IR (KBr): 3306, 3334 (NH_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.10 (s, 4 H, PhCH_2), 4.9 (s, 4 H, CH_2S), 6.03 (s, 4 H, NH_2), 7.1–8.0 (m, 14 H, ArH).

Anal. Calcd for $C_{28}H_{26}N_{10}S_2$ (566.7): C, 59.34; H, 4.62; N, 24.72. Found: C, 59.30; H, 4.50; N, 24.50.

1,2-Bis[4-amino-5-(*p*-methoxyphenyl)-1,2,4-triazole-3-yl-sulfanylmethyl]quinoxaline (10d)

By using the general procedure, compounds **8** and **9d** gave **10d** which was recrystallized from HOAc; colorless crystals (65%); mp 220 °C.

IR (KBr): 3162.1, 3276.6 (NH_2) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.83 (s, 6 H, OCH_3), 5.02 (s, 4 H, CH_2S), 6.25 (s, 4 H, NH_2), 7.0–8.1 (m, 12 H, ArH).

Anal. Calcd for $C_{28}H_{26}N_{10}O_2S_2$ (598.7): C, 56.17; H, 4.38; N, 23.39. Found: C, 56.30; H, 4.50; N, 23.50.

Acyclic Schiff Bases 12a,b and the Condensed Heteromacrocycles 15a–f; General Procedure

To a solution of each of **13a–c** or **11a,b** (10 mmol) in glacial HOAc (50 mL) was added a solution of the appropriate bis(amines) **10a–d** (10 mmol) in glacial HOAc (50 mL). The mixture was then refluxed for 2 h. The solution was then concentrated to a small volume (ca. 2 mL) and then cold water (ca. 15 mL) was added. The solid obtained was collected and recrystallized to give crystals of **12a,b** or **15a–f**.

1,2-Bis(4-benzylideneamino-1,2,4-triazole-3-yl-sulfanylmethyl)quinoxaline (12a)

By using the general procedure, compounds **10a** and **11a** gave **12a** which was recrystallized from EtOAc; pale green crystals (22%); mp 206–207 °C.

^1H NMR ($CDCl_3$): δ = 5.03 (s, 4 H, CH_2S), 7.2–8.0 (m, 14 H, ArH), 8.45 (s, 2 H, triazole-H), 8.45 (s, 2 H, CH=N).

Anal. Calcd for $C_{28}H_{22}N_{10}S_2$ (530.5): C, 63.39; H, 4.18; N, 26.24. Found: C, 63.30; H, 4.10; N, 26.20.

1,2-Bis[4-(*p*-methoxy)benzylideneamino-1,2,4-triazole-3-yl-sulfanylmethyl]quinoxaline (12b)

By using the general procedure, compounds **10a** and **11b** gave **12b** which was recrystallized from EtOAc; brown crystals (25%); mp 190 °C.

^1H NMR (DMSO-d_6): δ = 3.8 (s, 6 H, OCH_3), 5.02 (s, 4 H, CH_2S), 7.01–7.92 (m, 12 H, ArH), 8.81 (s, 2 H, triazole-H), 9.27 (s, 2 H, CH=N).

Anal. Calcd for $C_{30}H_{26}N_{10}S_2O_2$ (622.7): C, 57.86; H, 4.21; N, 22.49. Found: C, 57.70; H, 4.50; N, 22.50.

The Macrocycle 15a

By using the general procedure, compounds, **10a** and **13a** gave crude **15a** which was recrystallized from EtOAc; colorless crystals (30%); mp 244 °C.

IR (KBr): 3390.2 (NH) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.6–4.98 (m, 8 H, CHS, CHNH, OCH_2), 6.7–7.82 (m, 14 H, ArH, NH), 8.68 (s, 2 H, triazole-H).

MS: *m*/*z* (%) = 621 (M^+, 71.4), 342 (78.2), 228 (100), 144 (71.2), 131 (71.4).

Anal. Calcd for $C_{30}H_{24}N_{10}O_2S_2$ (620.7): C, 58.05; H, 3.90; N, 22.57. Found: C, 58.30; H, 4.10; N, 22.80.

The Macrocycle 15b

By using the general procedure, compounds, **10d** and **13a** gave crude **15b** which was recrystallized from EtOAc; colorless crystals (30%); mp 280 °C.

IR (KBr): 3382.4 (NH) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.72 (s, 6 H, OCH_3), 4.6–5.1 (m, 8 H, CHS, CHNH, OCH_2), 6.8–8.2 (m, 22 H, ArH, NH).

MS: *m*/*z* (%) = 833 (M^+, 64.3), 748 (92.8), 491 (100), 288 (64.3), 244 (78.5), 136 (78.5).

Anal. Calcd for $C_{44}H_{36}N_{10}O_4S_2$ (833.0): C, 63.45; H, 4.36; N, 16.82. Found: C, 63.40; H, 4.50; N, 16.80.

The Macrocycle 15c

By using the general procedure, compounds, **10b** and **13b** gave crude **15c** which was recrystallized from EtOAc; pale yellow crystals (29%); mp 255 °C.

IR (KBr): 3385.4 (NH) cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 2.45 (br, 2 H, C$H_2$$CH_2$O), 4.3–5.1 (m, 8 H, CHS, C*H*NH, OCH_2), 6.7–8.23 (m, 24 H, ArH, NH).

MS: *m*/*z* (%) = 787 (M^+, 78.5), 516 (78.5), 379 (71.9), 318 (100), 52 (71.4).

Anal. Calcd for $C_{43}H_{34}N_{10}O_2S_2$ (786.9): C, 65.63; H, 4.35; N, 17.8. Found: C, 65.40; H, 4.50; N, 16.80.

The Macrocycle 15d

By using the general procedure, compounds **10c** and **13b** gave crude **15d** which was recrystallized from EtOAc; colorless crystals (35%); mp 260 °C.

IR (KBr): 3372.2 (NH) cm^{-1}

^1H NMR ($CDCl_3$): δ = 2.3 (br, 2 H, CH_2CH_2O), 4.0–5.9 (m, 12 H, CHS, CHNH, CH_2O, PhCH_2), 6.1–7.7 (m, 24 H, ArH, NH).

^{13}C-{^1H} NMR: ($CDCl_3$): δ = 34.43, 56.80 (aliphatic CH), 26.8, 30.74, 63.47 (aliphatic CH_2), 112.35, 122.24, 124.5, 127.08, 128.7, 128.8, 130.69, 131.04 (ArCH), 122.98, 136.41, 140.14, 141.4, 152.5, 152.99, 154.15 (ArC).

MS: *m*/*z* (%) = 814 (M^+, 62.5), 762 (93.7), 544 (87.5), 403 (100), 238 (93), 191 (81), 125 (75).

Anal. Calcd for $C_{45}H_{38}N_{10}O_2S_2$ (814.5): C, 66.32; H, 4.70; N, 17.19. Found: C, 66.40; H, 4.50; N, 17.60.

The Macrocycle 15e

By using the general procedure, compounds **10b** and **13c** gave crude **15e** which was recrystallized from EtOAc; pale yellow crystals (30%); mp 240 °C.

IR: ν = 3363.5 (NH) cm^{-1}.

^1H NMR: (DMSO-d_6): δ = 2.1 (s, 4 H, CH_2CH_2O), 4.6–5.07 (m, 8 H, CHS, C*H*NH, OCH_2), 6.8–8.3 (m, 24 H, ArH, NH).

^{13}C-{^1H} NMR (DMSO-d_6): δ = 36.58, 57.48 (aliphatic CH), 30.2, 67.85 (aliphatic CH_2), 111.55, 120.95, 125.85, 127.34, 127.34, 128.12, 128.12, 129.24, 130.18 (ArCH), 123.32, 126.51, 140.18, 141.43, 150.70, 150.85, 154.88 (ArC).

MS: *m*/*z* (%) = 800 (M^+, 69.23), 712 (92.3), 627 (76.9), 586 (84.6), 512 (69.2), 390 (76.9), 200 (100), 110 (92.3).

Anal. Calcd for $C_{44}H_{36}N_{10}O_2S_2$ (800.3): C, 65.98; H, 4.53; N, 17.49. Found: C, 66.10; H, 4.50; N, 17.60.

The Macrocycle 15f

By using the general procedure, compounds **10d** and **13c** gave crude **15f** which was recrystallized from EtOAc; pale green crystals (32%); mp 263 °C.

IR (KBr): 3395.4 (NH) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.15 (br, 4 H, CH_2CH_2O), 3.77(s, 6 H, OCH_3), 4.15–5.1 (m, 8 H, CHS, C*H*NH, OCH_2), 6.25–8.13 (m, 22 H, ArH, NH).

^{13}C-{^1H} NMR (DMSO-d_6): δ = 36.45, 54.79, 56.55 (aliphatic CH, OCH_3), 28.3, 67.5 (aliphatic CH_2), 111.09, 113.48, 113.48, 120.41, 125.8, 128.9, 129.37, 130.12 (ArCH), 118.85, 123.27,139.68, 141.09, 150.84, 151.31, 155.77, 160.06 (ArC).

MS: *m*/*z* (%) = 860 (M^+, 60), 781 (73), 644 (73), 408 (80), 341 (100), 114 (93.3).

Anal. Calcd for $C_{46}H_{40}N_{10}O_4S_2$ (860.0): C, 64.17; H, 4.68; N, 16.27. Found: C, 64.40; H, 4.50; N, 16.40.

References

(1) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313.
(2) Bradshaw, J. S.; Izatt, R. M. *Acc. Chem. Res.* **1997**, *30*, 338.
(3) Izatt, J. S. *J. Incl. Phenom.* **1997**, *29*, 197.
(4) Bradshaw, J. S. *J. Incl. Phenom.* **1997**, *29*, 221.
(5) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
(6) Weber, E.; Kohler, H. J.; Reuter, H. *J. Prakt. Chem.* **1995**, *337*, 451.
(7) Radd, J. T.; Bradshaw, J. S.; Huszthy, P.; Izatt, R. M. *J. Heterocycl. Chem.* **1994**, *31*, 1047.
(8) Radd, J. T.; Bradshaw, J. S.; Huszthy, P.; Izatt, R. M.; Dally, N. K. *J. Heterocycl. Chem.* **1998**, *35*, 1.
(9) Li, Y.; Thiemann, T.; Sawada, T.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2323.
(10) Kim, H. S.; Koh, Y. K.; Choi, J. H. *J. Heterocycl. Chem.* **1998**, *35*, 177.
(11) Elshani, S.; Apgar, P.; Wang, S.; Wai, C. M. *J. Heterocycl. Chem.* **1994**, *31*, 1271.
(12) Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **2000**, *56*, 885.
(13) Foerster, S.; Niclas, H. J.; Lukyanenko, N. J. *Z. Chem.* **1985**, *25*, 102.
(14) Mtay, M. M.; Cohn, O. M. *Tetrahedron Lett.* **1976**, 79.
(15) Elwahy, A. H. M. *Tetrahedron* **2000**, *56*, 897.
(16) (a) Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. *J. Chem. Res. (S)* **1996**, 183. (b) Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. *J. Chem. Res. (M)* **1996**, 1066.
(17) Hoggarth, E. *J. Chem. Soc.* **1952**, 4811.
(18) (a) Ibrahim, Y. A.; Elwahy, A. H. M.; El-Kareish, G. M. M. *J. Chem. Res. (S)* **1994**, 414. (b) Ibrahim, Y. A.; Elwahy, A. H. M.; El-Kareish, G. M. M. *J. Chem. Res. (M)* **1994**, 2321.
(19) (a) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *J. Chem. Res. (S)* **1998**, 548. (b) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *J. Chem. Res. (M)* **1998**, 2501.
(20) (a) Elwahy, A. H. M. *J. Chem. Res. (S)* **1995**, 88. (b) Elwahy, A. H. M. *J. Chem. Res. (M)* **1995**, 653.
(21) (a) Elwahy, A. H. M. *J. Chem. Res. (S)* **1999**, 602. (b) Elwahy, A. H. M. *J. Chem. Res. (M)* **1999**, 2582.
(22) Katarítzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, **1985**.
(23) Shaw, B. L. *J. Am. Chem. Soc.* **1975**, *97*, 3856.
(24) Rasshofer, W.; Vogtle, F. *Liebigs Ann. Chem.* **1978**, 552.