Synthesis of Mixed-donor Azaoxathia Macrocyclic Tetraamides, Acyclic Polyether di/and Tetraamides and Their C-Pivot Lariat Derivatives

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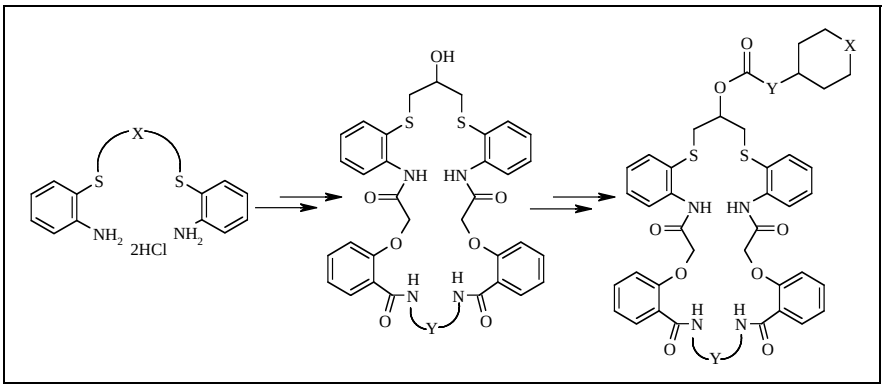

The macrocyclic tetraamides **11a-e** and 15-hydroxy macrocyclic tetraamides **23a-c** were prepared in good yields by the nucleophilic reaction of the potassium salts of the bis-phenoles **10a-c** with the appropriate dihalo compounds **5a-d** and **15**. Moreover, the acyclic diamides **7, 9, 17-21** and bis-acyclic tetraamide **22** were obtained in high yields by the reaction of the appropriate dichloro compounds with different phenoxides and secondary amines. Acylation of **23a-c** with different acid chlorides gave the corresponding esters **24a-c**. Compounds **24a-c** reacted with different secondary amines to afford the corresponding novel lariat macrocycles **25a-d** in high yields.

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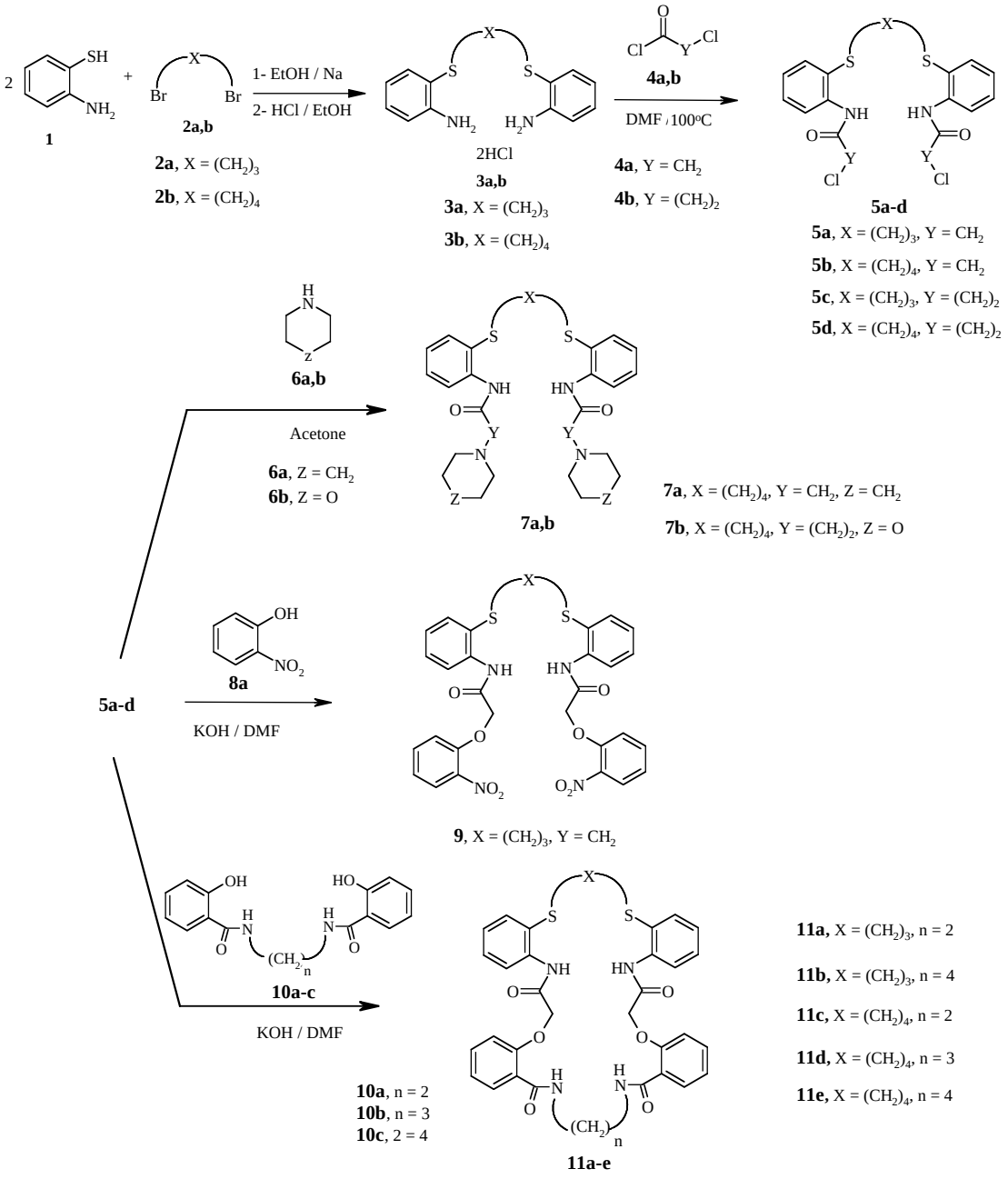
INTRODUCTION

Control of the cation binding ability of crown ethers has been the subject of several investigations since discovery by Pedersen [1,2]. For this reason, many different modifications 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 a wide variety of metal ions. These modifications involved substitution of ligand polyether oxygen donor atoms by sulfur and/or nitrogen atoms [3,4]. Macrocycles containing nitrogen and/or sulfur donor atoms are of interest as they exhibit high affinities towards heavy transition metal ions and their selectivity is readily tunable by altering the composition of the donor-atom set and ring size [5,6]. Mixed N, O, and S-donor crowns, form an interesting class of compounds, which are used to selectively extract soft metal cations [7,8] and as models for the active sites of some enzymes [9]. Other changes involved the development of functional groups in the macrocyclic ring. For example, incorporation of an amide linkage in a polyether macrocyclic has been reported to modify the binding properties of crown ether compounds to favor alkali and alkaline earth cations [10-14] where an amide group offers two potential binding atoms, oxygen and nitrogen. It has also been reported that macrocyclic ligands with amide functional groups as binding sites form strong and selective complexes with noble [15-17] and transition [18] metals. Moreover, macrocyclic tetraamides are of increasing interest in several fields such as valuable synthetic intermediates of azacrown [19], azaparacyclophanes [20] or macropolycyclic polyethers (cages) [21], artificial receptors of biological substrate [22], enzyme model [23] or synthetic enzymes (synzymes) [24], neutral ionophores for selective alkaline-earth ions extraction [25], transport through a bulk membrane [26] or ion-selective electrode incorporated membrane [27], luminescent lanthanide probes [28], ligands for highly oxidizing transition metal complexes [29], linkers for distribution of donor chelating sites in binuclear complexes [30] and interlocking moieties in neutral catenanes [31]. Further modification involved the attachment of a flexible side arm, with extra potential metal ion coordination sites, to a crown-ether framework producing complexing agents known as lariat crown ethers [32]. Unlike their crown ether analogues, lariat ethers possess three-dimensional cavities for coordination of metal cations, which can mimic the naturally occurring ionophores like valinomycin [33]. With this class of compounds, the guest cation can be wrapped in such a way that additional donor groups on the flexible arms would provide further coordination to the guest cation

Scheme 1



trapped in the parent macroring, which leads to higher cation-binding affinities for these new compounds compared with the parent macrocycle containing no extra donor sites [34,35]. Furthermore, the strong complexation of alkali metal cations by acyclic, naturally occurring antibiotics, such as nigericin and monensin, has prompted the systematic study of synthetic acyclic polyethers, which possess certain advantages over their cyclic analogues. Complex stability and ion selectivity can often be achieved with the synthetically more accessible acyclic polyethers [36]. Complexation and decomplexation processes are generally faster in the acyclic system and the pseudocavity usually has greater conformational flexibility [36]. Some acyclic polyethers are effective and selective ligands for the extraction of UO_2^{2+} and alkaline earth cations [37]. Others exhibited fairly good Ca^{2+} selectivity in solvent extraction and Ba^{2+} selectivity in transport across synthetic membranes [38,39]. Some acyclic diamide ligands are also known to show high ion selectivity towards lithium over sodium and other alkali metal ions [40-42].

Thus, continuing our course for the preparation of macrocycles with amide functional groups [43-47], lariat macrocycles and bis-macrocycles [48-51], we describe herein a simple and efficient route for the synthesis of mixed N, O, and S-donor 27-30 membered macrocyclic tetraamides, polyacyclic di-and tetra-amides as well as their lariat derivatives with strong donor heteroatoms in the side arm in good yields. In this way, we hope to achieve a higher level of cation binding than generally observed with simple monocyclic crown compounds.

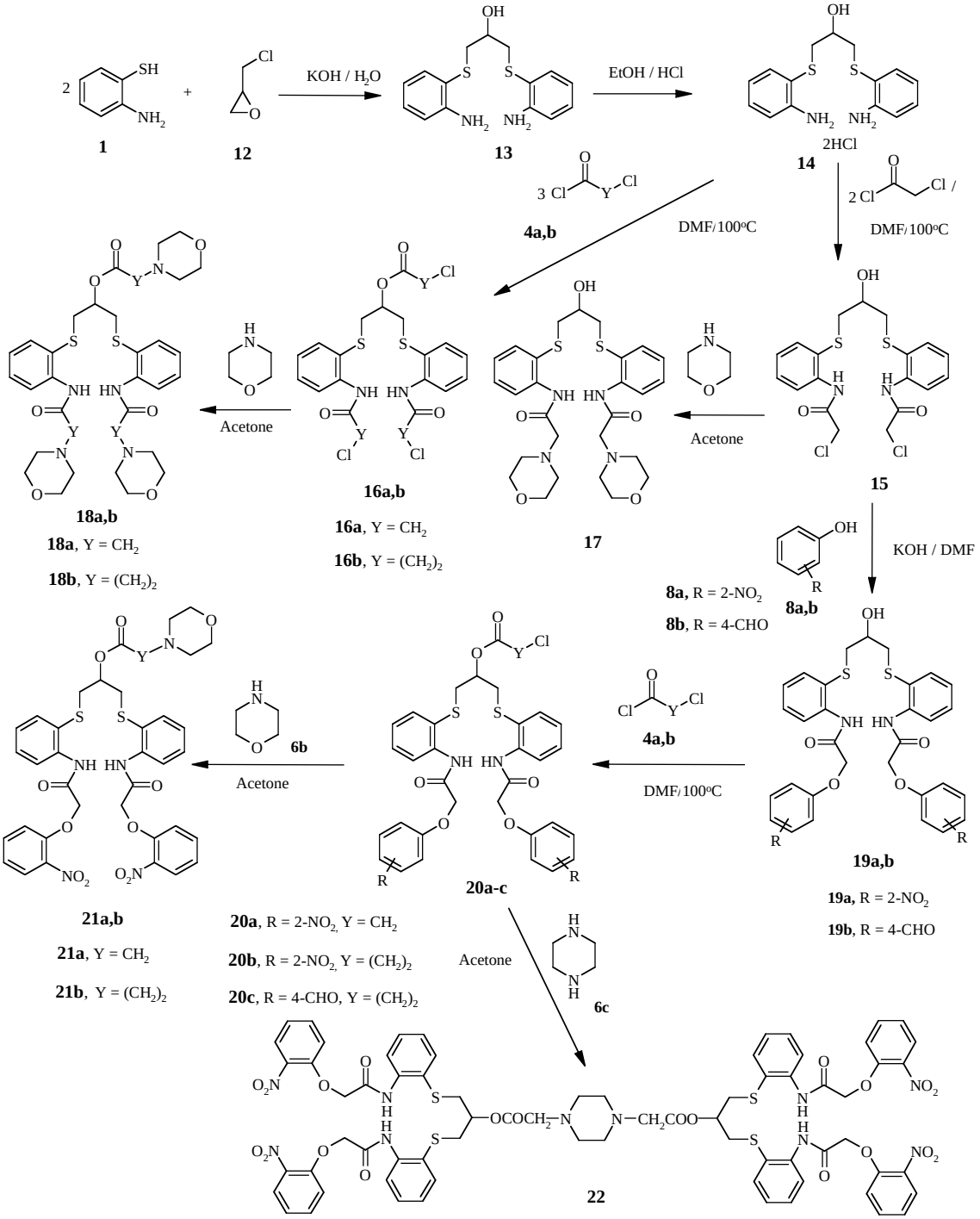
RESULTS AND DISCUSSION

In the present investigation, 1,ω-bis(2-aminothiophenoxy)alkanes **3a,b** or its 2-hydroxy derivative **13** were chosen as starting materials as well as a source of soft donor sulfur atoms. Thus, reaction of 2-aminothiophenole (**1**) with 1,ω-dibromoalkanes **2a,b**, in sodium ethoxide solution, furnished after treatment with ethanolic hydrochloric acid solution the corresponding bis(amine) hydrochloride salts **3a,b** in reasonable yields [52]. Reaction of the latter products with different acid chlorides namely, 2-chloroacetyl chloride (**4a**) and 3-chloropropanoyl chloride (**4b**) afforded the highly reactive 1,ω-bis[2-chloro(acteamido or propanoylamino)-thiophenoxy]alkanes **5a-d** in 55-76% yields (Scheme 1). The reactivity of compounds **5a-d** towards different nucleophiles (*e.g.* amines and phenoxides) is depicted in Scheme 1.

The reaction of **5a,d** with different secondary amines *e.g.* piperidine (**6a**), and morpholine (**6b**) gave the target acyclic polyether diamides *N*-piperidino, and *N*-morpholino derivatives **7a,b**, respectively in good yields. Furthermore, treatment of one equivalent of **5a** with two equivalents of the potassium salt of *o*-nitrophenol (**8**) gave the corresponding 1,3-bis-[2-(2-nitrophenoxy)acetamidothiophenoxy]propane (**9**) in a good yield. Similarly, when bis(chloro) compounds **5a,b** were treated with the appropriate bis-potassium salts of the bis-phenols **10a-c** furnished the novel 27-30 membered azaoxathia macrocyclic tetraamides **11a-e** in reasonable yields (Scheme 1). The structures of all new compounds were established and confirmed through spectroscopic (IR, NMR) and elemental analyses data (*c.f.* experimental part). The present study was extended to include the synthesis of new acyclic polyether diamides, their lariat analogue as well as novel acyclic polyether tetraamides as outlined in Scheme 2. To achieve our goal we choose 2-hydroxy-1,3-bis(2-aminothiophenoxy)propane hydrochloride (**14**) as a starting material, having pendant hydroxyl group to synthesize the key intermediate compounds **15** and **16a,b**. Thus, reaction of two equivalents of *o*-aminothiophenol (**1**) with one equivalent of epichlorohydrine (**2**) afforded successfully the bis(amine) **13** which gave the bis(amine) dihydrochloride salt **14** in high yield after treatment of **13** with ethanolic hydrochloric acid solution. Reaction of bis(amine) dihydrochloride salt **14** with two equivalents of chloroacetyl chloride in DMF at -10°C (to avoid the acylation of OH group) afforded the dichloroacyl product **15** in 52% yield, whereas reaction of **14** with three equivalents of the appropriate acid chlorides **4a,b** in DMF at 100°C furnished exclusively the desired trichloroacyl product **16a,b** (Scheme 2).

Having now available the dicloro and trichloro derivatives **15** and **16a,b**, their reactivates towards different nucleophiles were investigated aiming at the preparation of the target acyclic di/and tetraamides polyether compounds. Thus, compounds **15** and **16a,b** were reacted with morpholine as a typical example of secondary amines to give the corresponding dimorpholino and trimorpholino derivatives **17** and **18a,b**, respectively. Moreover, the reaction of **15** with the potassium salts of *o*-nitrophenol and *p*-hydroxybenzaldehyde in boiling DMF afforded the corresponding 2-nitrophenoxy and 4-formylphenoxy derivatives **19a,b**, respectively. The latter products contain hydroxy group as a reactive site for further transformation. Consequently, acylation of **19a,b** with acid chlorides **4a,b** in DMF furnished the corresponding 2-chloroacetoxy derivative **20a** and 2-(3-chloropropanoyl) derivatives **20b,c**, respectively in 55-75% yields. Compounds **20a-c** showed high reactivity towards different secondary amines, such as morpholine (**6b**) and piperazine (**6c**) to give the corresponding 2-(*N*-morpholino) **21a,b** and 1,4-bispiperazino derivative **22**, respectively in 50-60% yields as depicted in Scheme 2. The successful synthesis of novel compounds **18**, **21** and **22** prompted us to extend our synthetic methodology to prepare the main target lariat macrocyclic compounds containing mixed donor atoms (O, N and S) and four amide groups **25a-d**. For this purpose, compound **15** was chosen as a key intermediate for preparing the macrocycles **23a-c** with pendant hydroxy group as precursor for synthesis of lariat macrocycles as outlined in Scheme 3. Thus, reaction of **15** with the bis-potassium salts of **10a-c** gave 15-hydroxy macrocyclic tetraamides **23a-c** as expected in good yields (Scheme 3). Consequently, acylation of **23a** with chloroacetyl chloride (**4a**) in DMF furnished the corresponding 15-(chloroacetoxy) macrocyclic **24a** in 80% yield.

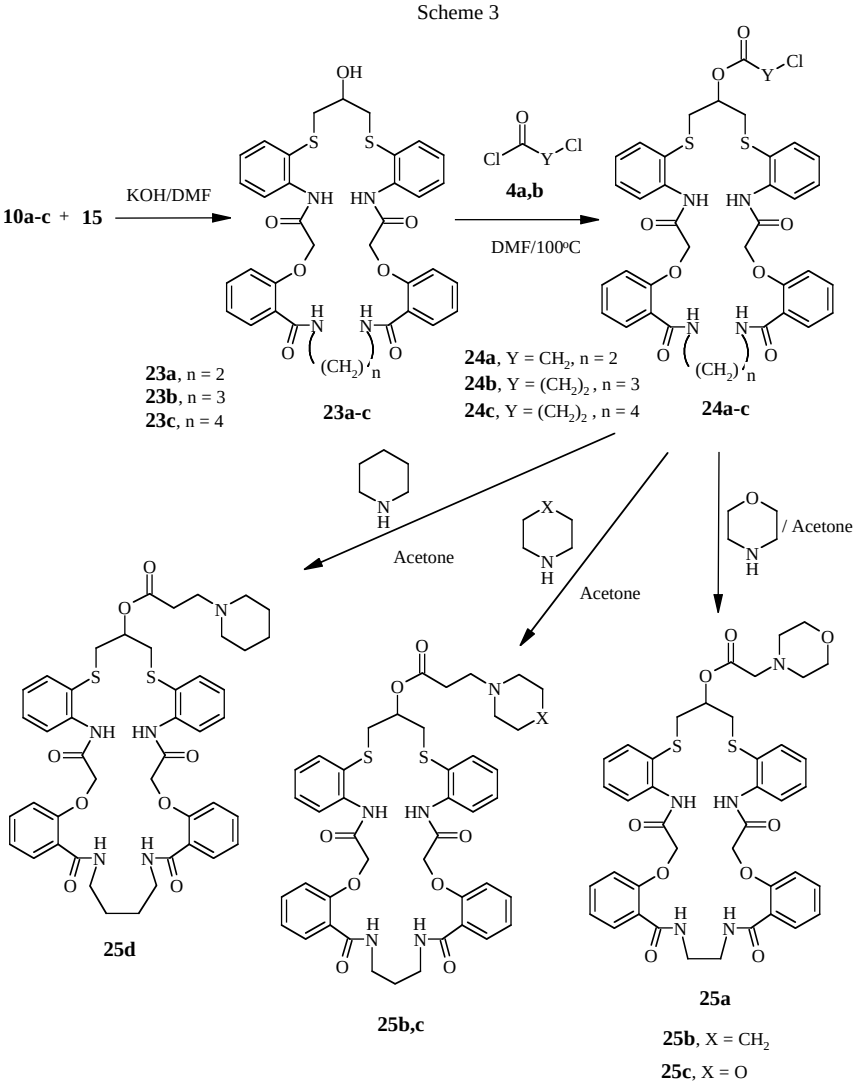
Scheme 2



In an attempt to extend the spacing between the macrocyclic ring and the soft donor atoms in the side arm of the lariat macrocycles, we report also the reaction of 3-chloropropanoyl chloride (**4b**) with 15-hydroxy macrocyclic tetraamides **23b,c**. Thus, reaction of **23b,c** with **4b** in DMF gave the desired macrocycles **24b,c** in 64-71% yield. Finally, treatment of esters **24a-c** with piperidine and morpholine afforded the corresponding lariat macrocyclic derivatives 15-(*N*-piperidino) **25b,d** and 15-(*N*-morpholino) **25a,c** respectively in high yields, where the length of the side arms were varied to investigate the optimal distance between the crown ether unit and soft donor atoms in the side arms.

The structures of all the new compounds were confirmed by IR, ^{1}H NMR and elemental analyses data. From the ^{1}H NMR spectra of the hydroxyl substituted side arm with different lengths. In addition, we believe that these new series of compounds could exhibit potential diverse application in supramolecular chemistry.

Scheme 3



macrocycles **23a-c**, the chloroacetoxy or (propanoyloxy) macrocycles **24a-c**, and the lariat macrocycles **25a-d** we can conclude that all these macrocycles are evidently present in one stable conformer or in slowly (on the time scale of NMR) interconvertible conformers. This is indicated by the presence of geminal coupling and non-equivalence of all OCH_2 and NCH_2 protons. Evidence for the existence of the new macrocycles entirely as one stable non-convertible conformer comes from ^{13}C NMR data (*cf.* experimental part. for compounds **23b** and **25a**).

In conclusion, the present work describes an efficient synthetic access towards acyclic polyether di/and tetra-amides, mixed N, O, and S-donor 27-30 membered macrocyclic tetraamides, and their lariat derivatives with soft donor atoms as a supporting ligand at the end of the Furthermore, development of the above synthetic methodology will lead to synthesis of a wide variety of useful acyclic polyethers, as well as novel lariat macrocycles with different ring sizes and having a variety of donor end groups and varying length side arms. Moreover, our synthetic methodology offers an advantage of their easy use on a large scale in a simple procedure using inexpensive starting materials.

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. ^{13}C NMR spectra were recorded using APT and DEPT pulse sequences. Mass spectra were recorded on HP 5988A (EI, 15 eV, for compounds **11a-e** and **23a-c**). 1,3-dibromopropane, 1,4-dibromobutane, 2-chloroacetyl chloride and 3-chloropropanoyl chloride were used as purchased from Aldrich. The starting compounds **3a,b** [52], **10a** [53], **10b,c** [54] were prepared as reported.

Synthesis of 2-Hydroxy-1,3-bis(2-aminothiophenoxy)-propane (13). A solution of *o*-aminothiophenol (**1**) (20 mmol) in aqueous solution containing KOH (20 mmol) was heated under reflux for 30 min. Epichlorohydrine (**12**) (10 mmol) was added to the latter solution dropwise with stirring within 30 min. After complete addition, the reaction mixture was heated in a water bath for 2 h. Then, the reaction mixture was poured into ice-cold water (500 ml), extracted with CH_2Cl_2, washed with aqueous NaOH solution. The separated oily mass was collected, dried to give **13**, which can be used in the next step without further purification. (70%), ^{1}H nmr ($CDCl_3$) δ 2.74-3.0 (m, 4H, SCH_2), 3.60-3.67 (m, 1H, C*H*-OH), 4.15 (brs, 1H, OH), 4.41 (brs, 4H, $2NH_2$), 6.62-7.39 (m, 8H, ArH's) ppm. *Anal.* Calcd. for $C_{15}H_{18}N_2OS_2$ (306.452): C, 58.79; H, 5.92; N, 4.19. Found: C, 58.60; H, 5.99; N, 4.30.

Synthesis of 2-Hydroxy-1,3-bis(2-aminothiophenoxy)-propane dihydrochlorides (14). Compound **13** was dissolved in absolute ethanol (100 ml) and acidified with conc. HCl to give the corresponding dihydrochloride salt **14**. The separated colourless solid was collected, washed with diethyl ether and used as it is in the next steps without further purification. (72%), mp. 220-222°C; ir: OH 3417 cm^{-1}; ^{1}H nmr (D_2O) δ 3.09 (dd, *J*=7.8, 14.1 Hz, 2H, upfield of SCH_2), 3.27 (dd, *J*=4.2, 14.1 Hz, 2H, downfield of SCH_2), 3.78-3.83 (m, 1H, C*H*-OH), 7.49-7.68 (m, 8H, ArH's) ppm. *Anal.* Calcd. for $C_{15}H_{20}N_2OS_2Cl_2$ (343.92): C, 52.39; H, 5.86; N, 8.15. Found: C, 52.22; H, 5.80; N, 8.20.

Reaction of bis-amine hydrochlorides 3a,b and 14 with acid chlorides (Synthesis of compounds 5a-d, 15 and 16a,b). (General procedure): To a solution of each of **3a,b** and **14** (5 mmol) in DMF (10 ml) were added the appropriate acid chlorides **4a,b** [(10 mmol) for synthesis of **5a-d** and **15** or (15 mmol) for synthesis of **16a,b**]. The reaction mixture was stirred at 100°C [(for compounds **5a-d** and **16a,b**) and at -10°C (for compound **15**)] for 2 h. The reaction mixture was poured on cursed ice. The solid obtained was collected by filtration and crystallized from the proper solvent to afford **5a-d**, **15** and **16a,b**.

1,3-Bis[(2-chloroacetamido)thiophenoxy]propane (5a). With the use of the general procedure **3a** and **4a** gave crude **5a** which was crystallized from benzene as colorless crystals (70%), mp. 136-8°C; ir: NH 3321, CO 1681 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.77 (quintet, *J*=7.1 Hz, 2H, SCH_2CH_2), 2.86 (t, *J*=7.1 Hz, 4H, SCH_2), 4.23 (s, 4H, CH_2Cl), 7.03-8.43 (m, 8H, ArH's), 9.71 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{19}H_{20}N_2O_2S_2Cl_2$ (443.417): C, 51.47; H, 4.55; N, 6.32. Found: C, 51.55; H, 4.45; N, 6.43.

1,4-Bis[(2-chloroacetamido)thiophenoxy]butane (5b). With the use of the general procedure **3b** and **4a** gave crude **5b** which was crystallized from benzene as colorless crystals (76%), mp. 120-2°C; ir: NH 3286, CO 1681 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.63-1.68 (m, 4H, SCH_2CH_2), 2.71-2.76 (m, 4H, SCH_2), 4.22 (s, 4H, CH_2Cl), 7.05-8.4 (m, 8H, ArH's), 9.66 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{20}H_{22}N_2O_2S_2Cl_2$ (457.44): C, 52.51; H, 4.85; N, 6.12. Found: C, 52.60; H, 4.90; N, 5.95.

1,3-Bis[2-(3-chloropropanoylamino)thiophenoxy]propane (5c). With the use of the general procedure **3a** and **4b** gave crude **5c** which was crystallized from benzene/petroleum ether (40-60°C) as colorless crystals (55%), mp. 118-20°C; ir NH 3294, CO 1662 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.76 (quintet, *J*=5.8 Hz, 2H, SCH_2CH_2), 2.79-2.87 (m, 8H, SCH_2 & CH_2CO), 3.88 (t, *J*=6.3 Hz 4H, CH_2Cl), 7.13-8.50 (m, 8H, ArH's), 8.64 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{21}H_{24}N_2O_2S_2Cl_2$ (471.471): C, 53.50; H, 5.13; N, 5.94. Found: C, 53.60; H, 5.25; N, 6.2.

1,4-Bis[2-(3-chloropropanoylamino)thiophenoxy]butane (5d). With the use of the general procedure **3b** and **4b** gave crude **5**d which was crystallized from benzene as colorless crystals (57%), mp. 94-96°C; ir NH 3298, CO 1662 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.62-1.66 (brs, 4H, SCH_2CH_2), 2.68-2.78 (brs, 4H, SCH_2), 2.86 (t, *J*=6.3 Hz, 4H, CH_2CO), 3.89 (t, *J*=6.3 Hz, 4H, CH_2Cl), 7.03-8.39 (m, 8H, ArH's), 8.54 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{22}H_{26}N_2O_2S_2Cl_2$ (485.497): C, 54.43; H, 5.40; N, 5.77. Found: C, 54.35; H, 5.32; N, 5.85.

2-Hydroxy-1,3-bis[(2-chloroacetamido)thiophenoxy]-propane (15). With the use of the general procedure **14** and **4a** gave crude **15** which was crystallized from benzene as colorless crystals (52%), mp. 120-22°C; ir: NH 3440, OH 3294, CO 1689 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.79 (d, *J*=3.7 Hz, 1H, OH), 2.83 (dd, *J*=7.5, 13.6 Hz, 2H, upfield of SCH_2), 2.98 (dd, *J*=4.5, 13.6 Hz, 2H, downfield of SCH_2), 3.6-3.64 (m, 1H, C*H*-OH), 4.21 (s, 4H, CH_2Cl), 7.02-8.36 (m, 8H, ArH's), 9.26 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{19}H_{20}N_2O_3S_2Cl_2$ (459.416): C, 49.67; H, 4.39; N, 6.10. Found: C, 49.59; H, 4.29; N, 5.90.

2-(2-Chloroacetoxy-1,3-bis[(2-chloroacetamido)thiophenoxy]propane (16a). With the use of the general procedure **14** and **4a** gave crude **16a** which was crystallized from methanol as colorless crystals (65%), mp. 108-110°C; ir NH 3282, CO 1751, 1678 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.09 (d, *J*=5.74 Hz, 4H, SCH_2), 3.74 (s, 2H, $OCOCH_2$), 4.24 (s, 4H, CH_2Cl), 3.07 (quintet, *J*=5.8, 1H, CH-O), 7.05-8.39 (m, 8H, ArH's), 9.53 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{21}H_{21}N_2O_4S_2Cl_3$ (535.899): C, 47.07; H, 3.95; N, 5.23. Found: C, 46.92; H, 4.12; N, 5.39.

2-(3-Chloropropanoyloxy)-1,3-bis[2-(3-chloropropanoyl-amino)thiophenoxy]propane (16b). With the use of the general procedure **14** and **4b** gave crude **16b** which was purified by column chromatography using ethyl acetate/petroleum ether (40-60°C) as an eluent to give oily product (70%); ir: NH 3290, CO 1725, 1650 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.62 (t, *J*=6.3 Hz, 2H, $OCOCH_2CH_2Cl$), 2.87-3.01 (m, 8H, SCH_2 & CH_2CONH), 3.66 (t, *J*=6.3 Hz 2H, $ClCH_2CH_2COO$), 3.88 (t, *J*=6.3 Hz, 4H, $ClCH_2CH_2CONH$), 5.08 (quintet, *J*=6 Hz, 1H, CH-O), 7.01-8.24 (m, 8H, ArH's), 8.42 (brs, 2H, NH) ppm. *Anal. Calcd.* for $C_{24}H_{27}N_2O_4S_2Cl_3$ (577.979): C, 49.87; H, 4.71; N, 4.85. Found: C, 49.79; H, 4.62; N, 4.99.

Preparation of the potassium salts of compounds 8a,b and 10a-c. To a solution of KOH (1.14 g, 10 mmol) in methanol (10 ml) was added each of 2-nitrophenol (**8a**), 4-hydroxybenz-aldehyde (**8b**), (10 mmol) or bis-phenols **10a-c** (5 mmol). The mixture was stirred at room temperature for 10 min. The solvent was then removed in vacuo. The remaining solid was triturated with dry ether, collected, dried, and used in the next step without further purification.

Synthesis of compounds 9, 19a,b and macrocyclic tetraamides 11a-e and 23a-c. (General procedure): A solution of the appropriate potassium salts of each of **8a,b** (20 mmol) or **10a-c** (10 mmol) and the appropriate dichloro compounds **5a**,**b**, and **15** (10 mmol) in DMF (20 ml) was heated under reflux for 10 min. during which KCl was precipitated. The solvent was then removed *in vacuo* and the remaining material was washed

with water (50 ml) and crystallized from the proper solvent to give compounds **9**, **19a**,**b**, **11a-e** and **23a-c**.

1,3-Bis[2-(2-nitrophenoxy)acetamidothiophenoxy]propane (9). With the use of the general procedure the potassium salt of **8a** and **5a** gave crude **9** which was crystallized from ethanol as pale yellow crystals (50%), mp. 138-40°C; ir: NH 3305, CO 1681, NO_2 1523, 1350 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.75 (quintet, *J*=7.2 Hz, 2H, SCH_2CH_2), 2.79 (t, *J*=7.2 Hz, 4H, SCH_2), 4.75 (s, 4H, $COCH_2$), 6.98-8.33 (m, 16H, ArH's), 9.52 (brs, 2H, NH) ppm. *Anal*. Calcd. for $C_{31}H_{28}N_4O_8S_2$ (648.716): C, 57.40; H, 4.35; N, 8.64. Found: C, 57.55; H, 4.30; N, 8.50.

2-Hydroxy-1,3-bis[2-(2-nitrophenoxy)acetamidothiophenoxy]propane (19a). With the use of the general procedure the potassium salt of **8a** and **15** gave crude **19a** which was crystallized from ethanol as pale yellow crystals (55%), mp. 160-2°C; ir: OH 3444, NH 3298, CO 1678, NO_2 1527, 1350 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.87 (dd, *J*=7.5, 13.5 Hz, 2H, upfield of SCH_2), 3.0 (dd, *J*=4.5, 13.5 Hz, 2H, downfield of SCH_2), 3.21 (d, *J*=4.2 Hz, 1H, OH), 3.69-3.74 (m, 1H, C*H*OH), 4.75 (s, 4H, $COCH_2$), 7.0-8.29 (m, 16H, ArH's), 9.51 (s, 2H, NH) ppm. *Anal*. Calcd. for $C_{31}H_{28}N_4O_9S_2$ (664.715): C, 56.02; H, 4.25; N, 8.43. Found: C, 55.90; H, 4.17; N, 8.38.

2-Hydroxy-1,3-bis[2-(4-formylphenoxy)acetamidothiophenoxy]propane (19b). With the use of the general procedure the potassium salt of **8b** and **15** gave crude **19b** which was purified by column chromatography using ethyl acetate/ petroleum ether (40-60°C) as an eluent to give semisolid product (53%); ir: OH 3425, NH 3313, CO 1689, 1600 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.61-2.84 (m, 5H, SCH_2 & OH), 3.49 (brs, 1H, C*H*OH), 4.67 (s, 4H, $COCH_2$), 6.96-8.41 (m, 16H, ArH's), 9.61 (brs, 2H, NH), 9.90 (s, 2H, CHO) ppm. *Anal*. Calcd. for $C_{33}H_{30}N_2O_7S_2$ (630.741): C, 62.84; H, 4.79; N, 4.44. Found: C, 62.75; H, 4.60; N, 4.55.

6,14,15,24,32,33-Hexahydro-16*H*-tetrabenzo[*e,l,r,z*][1,17]-dioxa[7,11]dithia[4,14,21,24]tetraaza-cycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (11a). With the use of the general procedure the potassium salt of **10a** and **5a** gave crude **11a** which was purified by column chromatography using ethyl acetate/petroleum ether (40-60°C) as an eluent, to give colorless crystals of 11a, (50%), mp. 130-32°C; ir: NH 3321, CO 1689, 1643 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.23 (quintet, *J*=6.7 Hz, 2H, SCH_2CH_2), 2.25 (t, *J*=6.7 Hz, 4H, SCH_2), 3.84 (brs, 4H, CH_2N), 4.99 (s, 4H, $COCH_2$), 6.78-8.36 (m, 16H, ArH's), 8.67 (brs, 2H, CH_2NHCO), 9.33 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 670 (M^+, 5%). *Anal*. Calcd. for $C_{35}H_{34}N_4O_6S_2$ (670.808): C, 62.67; H, 5.11; N, 8.35. Found: C, 62.55; H, 5.01; N, 8.23.

6,14,15,24,32,33,34,35-Octahydro-16*H*-tetrabenzo[e,l,r,b$_1$]-[1,17]dioxa[7,11]dithia- [4,14,21,26]tetra-azacyclononacosin-7,23,30,37-(8*H*,22*H*,31*H*,36*H*)tetraone (11b). With the use of the general procedure the potassium salt of **10c** and **5a** gave crude **11b** which was crystallized from ethanol as colorless crystals (40%), mp. 218-20°C; ir: NH 3267, CO 1681, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.46 (quintet, *J*=6.6 Hz, 2H, SCH_2CH_2), 1.81 (s, 4H, CH_2CH_2N), 2.49 (t, *J*=6.6 Hz, 4H, SCH_2), 3.57 (d, *J*=5.7 Hz, 4H, CH_2N), 4.88 (s, 4H, $COCH_2$), 6.89-8.34 (m, 16H, ArH's), 7.66 (brs, 2H, CH_2NHCO), 9.30 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 698 (M^+, 4%). *Anal*. Calcd. for $C_{37}H_{38}N_4O_6S_2$ (698.862): C, 63.59; H, 5.48; N, 8.02. Found: C, 63.65; H, 5.39; N, 7.90.

6,14,15,16,17,25,33,34-Octahydrotetrabenzo[*e,m,s,*a$_1$][1,18]-dioxa[7,12]dithia[4,15,22,25]tetraazacyclooctacosin-7,24,31,36-(8*H*,23*H*,32*H*,35*H*)-tetraone (11c). With the use of the general procedure the potassium salt of **10a** and **5b** gave crude **11c** which was crystallized from toluene as colorless crystals (53%), mp. 162-164°C; ir: NH 3329, CO 1697, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.15-1.21 (m, 4H, SCH_2CH_2), 2.28-2.34 (m, 4H, SCH_2), 3.81 (brs, 4H, CH_2NH), 4.97 (s, 4H, $COCH_2$), 6.77-8.37 (m, 16H, ArH's), 8.65 (brs, 2H, CH_2NHCO), 9.36 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 684 (M^+, 5%). *Anal*. Calcd. for $C_{36}H_{36}N_4O_6S_2$ (684.835): C, 63.14; H, 5.30; N, 8.18. Found: C, 63.25; H, 5.40; N, 7.95.

6,14,15,16,17,25,33,34-Octahydro-35*H*-tetrabenzo[*e,m,s,*b$_1$]-[1,18]dioxa[7,12]dithia[4,15,22,26]-tetraazacyclononacosin-7,24,31,37-(8*H*,23*H*,32*H*,36*H*)tetraone (11d). With the use of the general procedure the potassium salt of **10b** and **5b** gave crude **11d** which was purified by column chromatography using ethyl acetate/petroleum ether (40-60°C) as an eluent, to give colorless crystals of **11d**, (45%), mp. 174-76°C; ir: NH 3336, CO 1693, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.20-1.26 (m, 4H, SCH_2CH_2), 1.89 (brs, 2H, CH_2CH_2N), 2.42 (brs, 4H, SCH_2), 3.63-3.69 (m, 4H, CH_2NH), 4.99 (s, 4H, $COCH_2$), 6.89-8.43 (m, 16H, ArH's), 8.49 (brs, 2H, CH_2NHCO), 9.49 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 698 (M^+, 6%). *Anal*. Calcd. for $C_{37}H_{38}N_4O_6S_2$ (698.862): C, 63.59; H, 5.48; N, 8.02. Found: C, 63.66; H, 5.30; N, 7.92.

6,14,15,16,17,25,33,34,35,36-Decahydrotetrabenzo[*e,m,s,*c$_1$]-[1,18]dioxa[7,12]dithia[4,15,22,27]-tetraazacyclodecacosin-7,24,31,38-(8*H*,23*H*,32*H*,37*H*)tetraone (11e). With the use of the general procedure the potassium salt of **10c** and **5b** gave crude **11e** which was crystallized from ethanol as colorless crystals (38%), mp. 216-218°C; ir: NH 3267, CO 1681, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.25 (brs, 4H, SCH_2CH_2), 1.80 (brs, 4H, CH_2CH_2N), 2.44 (brs, 4H, SCH_2), 3.57 (d, *J*=5.7 Hz, 4H, CH_2NH), 4.89 (s, 4H, $COCH_2$), 6.91-8.4 (m, 16H, ArH's), 7.67 (brs, 2H, CH_2NHCO), 9.37 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 712 (M^+, 5%). *Anal*. Calcd. for $C_{38}H_{40}N_4O_6S_2$ (712.889): C, 64.02; H, 5.66; N, 7.86. Found: C, 64.15; H, 5.74; N, 7.92.

15-Hydroxy-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo-[*e,l,r,z*][1,17]dioxa[7,11]dithia-[4,14,21,24]tetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (23a). With the use of the general procedure the potassium salt of **10a** and **15** gave crude **23a** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as colorless crystals (45%), mp. 127-75°C; ir: OH, NH 3321, 3066, CO 1689, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.55-2.72 (m, 5H, SCH_2 & OH), 3.42-3.49 (m, 1H, C*H*-OH), 3.81 (brs, 4H, CH_2N), 4.70 (d, *J*=15 Hz, 2H, upfield of $COCH_2$), 4.81 (d, *J*=15.5 Hz, 2H, downfield of $COCH_2$), 6.70-8.23 (m, 18H, ArH's & $NHCH_2$), 9.51 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 686 (M^+, 5%). *Anal*. Calcd. for $C_{35}H_{34}N_4O_7S_2$ (686.808): C, 61.21; H, 4.99; N, 8.16. Found: C, 61.30; H, 5.03; N, 8.29.

15-Hydroxy-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*e,l,r,a*$_1$][1,17]dioxa[7,11]dithia-[4,14,21,25]tetraaza-cyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (23b). With the use of the general procedure the potassium salt of **10b** and **15** gave crude **23b** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as colorless crystals (40%), mp. 172-5°C; ir: OH, NH, 3321, 3066, CO 1689, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.95 (brs, 2H, NCH_2CH_2), 2.54 (dd, *J*=8.1, 13 Hz, 2H, upfield of SCH_2), 2.64 (dd, *J*=4.0, 13.1 Hz, 2H, downfield of SCH_2), 3.43-3.46 (m, 1H, C*H*-OH), 3.61-3.75 (m, 4H, NCH_2), 4.54 (d, *J*=4.8 Hz, 1H, OH), 4.87 (d, *J*=15.9 Hz, 2H, upfield of $COCH_2$), 4.97 (d, *J*=15.9 Hz, 2H, downfield of $COCH_2$), 6.96-8.38 (m, 16H, ArH's), 7.98 (t, *J*=5.7 Hz, 2H, CH_2NHCO), 9.59 (s, 2H, $NHCOCH_2$) ppm; ^{13}C NMR (APT & DEPT pulse sequences,

DMSO) δ 29.08, 36.82, 39.93, 67.89 (CH_2's), 67.99 (aliphatic CH), 113.42, 121.42, 123.76, 125.61, 127.32, 130.18, 131.91 (aromatic CH's), 124.17, 128.65, 136.63, 155.02 (aromatic C's), 165.22, 166.7 (carbonyl C's); ms: m/z 700 (M^+, 6%). *Anal.* Calcd. for $C_{36}H_{36}N_4O_7S_2$ (700.835): C, 61.70; H, 5.18; N, 7.99. Found: C, 61.59; H, 5.22; N, 8.18.

15-Hydroxy-6,14,15,24,32,33,34,35-Octahydro-16*H*-tetrabenzo[*e*,*l*,*r*,*b*$_1$][1,17]dioxa[7,11]dithia-[4,14,21,26]tetraazacyclononacosin-7,23,30,37-(8*H*,22*H*,31*H*,36*H*)tetraone (23c). With the use of the general procedure the potassium salt of **10c** and **15** gave crude **23c** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as colorless crystals (38%), mp. 158-60°C; ir: OH, NH 3317, 3100, CO 1689, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.71-1.91 (m, 4H, NCH_2CH_2), 2.67 (dd, *J*=7.7, 13.6 Hz, 2H, upfield of SCH_2), 2.83 (dd, *J*=3.1, 13 Hz, 2H, downfield of SCH_2), 3.05 (brs, 1H, OH), 3.45-3.6 (m, 5H, CH_2N & CH-OH), 4.72 (d, *J*=15.8 Hz, 2H, upfield of $COCH_2$), 4.88 (d, *J*=15.3 Hz, 2H, downfield of $COCH_2$), 6.91-8.37 (m, 16H, ArH's), 7.42 (t, *J*=5.6 Hz, 2H, CH_2NHCO), 9.61 (s, 2H, $NHCOCH_2$) ppm; ms: m/z 714 (M^+, 6%). *Anal.* Calcd. for $C_{37}H_{38}N_4O_7S_2$ (714.861): C, 62.17; H, 5.36; N, 7.84. Found: C, 62.25; H, 5.25; N, 7.92.

Reaction of acid chlorides 4a,b with 19a,b and 23a-c. (Synthesis of compounds 20a-c and 24a-c). (General procedure): To a solution of each of **19a,b** and **23a-c** (5 mmol) in DMF (10 ml) was added 2-chloroacetyl chloride (**4a**) or 3-chloropropanoyl chloride (**4b**) (12 mmol). The reaction mixture was stirred at room temperature for 2h. then poured on cursed ice. The solid obtained was collected by filtration and crystallized from the proper solvent for each derivatives to afford **20a-c** and **24a-c**.

2(2-Chloroacetoxy)-1,3-bis[2-(2-nitrophenoxy)acetamidothiophenoxy]propane (20a). With the use of the general procedure **19a** and **4a** gave crude **20a** which was crystallized from benzene as colorless crystals (75%), mp. 138-40°C; ir: NH 3321, CO 1755, 1685, NO_2 1523, 1346 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.05 (d, *J*=5.2 Hz, 4H, SCH_2), 3.77 (s, 2H, CH_2Cl), 4.76 (s, 4H, OCH_2), 5.09 (quintet, *J*=5.7, 1H, CH-OCO), 7.04-8.35 (m, 16H, ArH's), 9.45 (brs, 2H, NH) ppm. *Anal.* Calcd. for $C_{33}H_{29}N_4O_{10}S_2Cl$ (741.198): C, 53.48; H, 3.94; N, 7.56. Found: C, 53.55; H, 3.82; N, 7.40.

2-(3-Chloropropanoyloxy)-1,3-bis[2-(2-nitrophenoxy)acetamidothiophenoxy]propane (20b). With the use of the general procedure **19a** and **4b** gave crude **20b** which was crystallized from benzene as colorless crystals (55%), mp. 127-29°C; ir: NH 3305, CO 1732, 1685, NO_2 1527, 1365 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.23 (t, *J*=6.9 Hz, 2H, CH_2CH_2Cl) 3.05 (d, *J*=5.7 Hz, 4H, SCH_2), 3.57 (t, *J*=6.9 Hz, 2H, CH_2Cl), 4.76 (s, 4H, OCH_2), 5.07 (quintet, *J*=5.7, 1H, CH-OCO), 7.02-8.34 (m, 16H, ArH's), 9.45 (s, 2H, NH) ppm. *Anal. Calcd.* for $C_{34}H_{31}N_4O_{10}S_2Cl$ (755.224): C, 54.07; H, 4.14; N, 7.42. Found: C, 53.95; H, 4.09; N, 7.25.

2-(3-Chloropropanoyloxy)-1,3-bis[2-(4-formaylphenoxy)-acetamidothiophenoxy]propane (20c). With the use of the general procedure **19b** and **4b** gave crude **20c** which was crystallized from benzene/petroleum ether (40-60) as pale yellow crystals (70%), mp. 90-2°C; ir: NH 3325, CO 1739, 1689 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.48 (t, *J*=6.6 Hz, 2H, CH_2CH_2Cl), 2.86 (d, *J*=5.7 Hz, 4H, SCH_2), 3.55 (t, *J*=6.6 Hz, 2H, CH_2Cl), 4.69 (s, 4H, OCH_2), 4.95 (quintet, *J*=5.7, 1H, CH-OCO), 7.02-8.48 (m, 16H, ArH's), 9.48 (s, 2H, NH), 9.92 (s, 2H, CHO) ppm. *Anal.* Calcd. for $C_{36}H_{33}N_2O_8S_2Cl$ (721.25): C, 59.95; H, 4.61; N, 3.88. Found: C, 59.80; H, 4.55; N, 3.75.

15-(2-Chloroacetoxy-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo[*e*,*l*,*r*,*z*][1,17]dioxa[7,11]dithia-[4,14,21,24]tetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (24a). With the use of the general procedure **23a** and **4a** gave crude **24a** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as colorless crystals (80%), mp. 115-8°C; ir: NH 3328, CO 1755, 1689; ^1H nmr ($CDCl_3$) δ 2.56-2.59 (m, 4H, SCH_2), 3.52 (s, 2H, CH_2Cl), 2.80-3.91 (m, 4H, CH_2N), 4.71 (quintet, *J*=5.3 Hz, 1H, CH-OCO), 4.96 (s, 4H, OCH_2), 6.84-8.29 (m, 16H, ArH's), 8.52 (brs, 2H, CH_2NHCO), 9.25 (s, 2H, $NHCOCH_2$) ppm. *Anal.* Calcd. for $C_{37}H_{35}N_4O_8S_2Cl$ (763.291): C, 58.22; H, 4.62; N, 7.34. Found: C, 58.32; H, 4.50; N, 7.45.

15-(3-Chloropropanoyloxy)-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*e*,*l*,*r*,*a*$_1$][1,17]-dioxa[7,11]dithia[4,14,21,25]tetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (24b). With the use of the general procedure **23b** and **4b** gave crude **24b** which was crystallized from ethanol as colorless crystals (71%), mp. 118-20°C; ir: NH 3329, CO 1693, 1643 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.89 (brs, 2H, CH_2CH_2N), 2.29 (t, *J*=6.6 Hz, 2H, $COCH_2CH_2Cl$), 2.63 (d, *J*=5.4 Hz, 4H, SCH_2), 3.43 (t, *J*=6.6 Hz, 2H, CH_2Cl), 3.54-3.64 (m, 2H, upfield of $NHCH_2$), 3.83-3.91 (m, 2H, downfield of $NHCH_2$), 4.75 (quintet, *J*=5.4 Hz, 1H, CH-OCO), 4.97-5.1 (m, 4H, OCH_2CO), 6.99-8.38 (m, 16H, ArH's), 8.47 (t, *J*=6 Hz, 2H, CH_2NHCO), 9.37 (s, 2H, $NHCOCH_2$) ppm. *Anal.* Calcd. for $C_{39}H_{39}N_4O_8S_2Cl$ (791.344): C, 59.19; H, 4.97; N, 7.08. Found: C, 59.35; H, 4.84; N, 7.25.

15-(3-Chloropropanoyloxy)-6,14,15,24,32,33,34,35-Octahydro-16*H*-tetrabenzo[*e*,*l*,*r*,*b*$_1$][1,17]-dioxa[7,11]dithia-[4,14,21,26]tetraazacyclononacosin-7,23,30,37-(8*H*,22*H*,31*H*, 36*H*)-tetraone (24c). With the use of the general procedure **23c** and **4b** gave crude **24c** which was crystallized from benzene/ petroleum ether (40-60) as colorless crystals (65%), mp. 110-12°C; ir: NH 3329, CO 1712, 1639 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.82 (brs, 4H, CH_2CH_2N), 2.37 (t, *J*=6.6 Hz, 2H, $COCH_2CH_2Cl$), 2.75 (d, *J*=5.5 Hz, 4H, SCH_2), 3.59 (brs, 4H, $NHCH_2$), 3.74 (t, *J*=6.6 Hz, 2H, CH_2Cl), 4.66-4.91 (m, 5H, OCH_2CO & CH-OCO), 6.92-8.32 (m, 16H, ArH's), 7.64 (brs, 2H, CH_2NHCO), 9.23 (s, 2H, $NHCOCH_2$) ppm. *Anal.* Calcd. for $C_{40}H_{41}N_4O_8S_2Cl$ (805.371): C, 59.65; H, 5.13; N, 6.96. Found: C, 59.55; H, 5.05; N, 7.05.

Reaction of compounds 5b,d, 15, 16a,b, 20a,b and 24a-c with secondary amines (synthesis of compounds 7a,b, 17, 18a,b, 21a,b, 22 and 25a-d). (General procedure): A mixture of each of **5b,d, 15, 16a,b, 20a,b** and **24a-c** (5 mmol) and excess of the appropriate secondary amines [piperidine (**6a**) and morpholine (**6b**)] or [(6 mmol) of compounds **20a** and (3 mmol) of piperazine (**6c**) and a few drops of triethylamine for synthesis of compounds **22**] in acetone (50 ml) was heated under reflux for 10 min, then stirring at r.t over night. [In case of synthesis of compound **22** the reaction mixture was heated under reflux for 24h.]. The solvent was then removed *in vacuo*. The solid obtained was washed with cold water and crystallized from the proper solvent to give compounds **7a,b, 17, 18a,b, 21a,b, 22** and **25a-d).**

1,4-Bis[2-(*N*-piperidino)acetamidothiophenoxy]butane (7a). With the use of the general procedure **5b** and piperidine (**6a**) gave crude **7a** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as oily product (60%); ir: NH 3224, CO 1650 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.48 (brs, 4H, $CH_2CH_2CH_2N$), 1.66 (brs, 12H, $CH_2CH_2CH_2N$ & SCH_2CH_2), 2.54 (t, *J*=4.8 Hz,8H, CH_2N), 2.73 (brs, 4H, SCH_2), 3.09 (s, 4H, CH_2CO), 6.97-8.5 (m, 8H, ArH's), 10.41 (s, 2H, NH)

ppm. *Anal*. Calcd. for $C_{30}H_{42}N_4O_2S_2$ (554.819): C, 64.95; H, 7.63; N, 10.10. Found: C, 64.82; H, 7.60; N, 10.21.

1,4-Bis[2-(3-*N*-morpholino)propanoylaminothiophenoxy]-butane (7b). With the use of the general procedure **5d** and morpholine (**6b**) gave crude **7b** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as oily product (55%); ir: NH 3350, CO 1645 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.61 (brs, 4H, CH_2CH$_2$S), 2.54-2.75 (m, 20H, SCH_2 & NCH_2 & CH_2CO), 3.76 (t, *J*=4.2 Hz, 8H, OCH_2), 7.02-8.17 (m, 8H, ArH's), 9.99 (brs, 2H, NH) ppm. *Anal*. Calcd. for $C_{30}H_{42}N_4O_4S_2$ (562.796): C, 61.40; H, 7.21; N, 9.55. Found: C, 61.58; H, 7.32; N, 9.45.

2-Hydroxy-1,3-bis[2-(*N*-morpholino)acetamidothiophenoxy]-propane (17). With the use of the general procedure **15** and morpholine (**6b**) gave crude **17** which was crystallized from ethanol as colorless crystals (83%), mp. 139-40°C; ir: OH 3440, NH 3228, CO 1678 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.61 (t, *J*=4.6 Hz, 8H, NCH_2CH$_2$O), 2.83 (dd, *J*=7.4, 13.5 Hz, 2H, upfield of SCH_2), 2.96 (dd, *J*=4.6, 13.5 Hz, 2H, downfield of SCH_2), 3.16 (s, 4H, $COCH_2$), 3.32 (brs, 1H, OH), 3.56-3.66 (m, 1H, C*H*-OH), 3.76 (t, *J*=4.6 Hz, 8H, OCH_2CH$_2$N), 6.96-8.45 (m, 8H, ArH's), 10.27 (brs, 2H, NH) ppm. *Anal*. Calcd. for $C_{27}H_{36}N_4O_5S_2$ (560.737): C, 57.83; H, 6.47; N, 9.99. Found: C, 57.75; H, 6.36; N, 10.16.

2-(*2*-*N*-Morpholinoacetoxy)-1,3-bis[2-(*N*-morpholino)acetamidothiophenoxy]propane (18a). With the use of the general procedure **16a** and morpholine (**6b**) gave crude **18a** which was crystallized from ethanol as colorless crystals (80%), mp. 148-50°C; ir: NH 3240, CO 1720, 1685; ^1H nmr ($CDCl_3$) δ 2.48 (t, *J*=4.4 Hz, 4H, $OCOCH_2NCH_2$) 2.62 (t, *J*=4.4 Hz, 8H, NCH_2) 2.88 (s, 2H, $OCOCH_2N$), 3.05 (d, *J*=5.8 Hz, 4H, SCH_2), 3.17 (s, 4H, NCH_2CONH), 3.70 (t, *J*=4.5 Hz, 4H, OCH_2), 3.77 (t, *J*=4.5 Hz, 8H, $OCH_2CH_2NCH_2CONH$), 5.19 (quintet, *J*=5.8 Hz, 1H, O-CH), 6.99-8.48 (m, 8H, ArH's), 10.24 (brs, 2H, NH) ppm. *Anal*. Calcd. for $C_{33}H_{45}N_5O_7S_2$ (687.879): C, 57.62; H, 6.59; N, 10.18. Found: C, 57.80; H, 6.68; N, 10.30.

2-(*3*-*N*-Morpholinopropanoyloxy)-1,3-bis[2-(3-*N*-morpholino)propanoylaminothiophenoxy]-propane (18b). With the use of the general procedure **16b** and morpholine (**6b**) gave crude **18b** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as oily product (60%); ir: NH 3350, CO 1737, 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.26-2.34 (m, 6H, NCH_2CH_2CO), 2.39 (brs, 4H, OCH_2CH_2N), 2.66 (brs, 8H, OCH_2CH_2N), 2.67 (d, *J*=5.7 Hz, 4H, SCH_2), 2.83-2.95 (m, 6H, NCH_2CH_2CO), 3.63 (brs, 4H, OCH_2CH_2N), 3.72 (brs, 8H, OCH_2CH_2N), 5.0 (quintet, *J*=5.4 Hz, 1H, CH-O), 6.96-8.21 (m, 8H, ArH's), 9.97 (s, 2H, NH) ppm. *Anal*. Calcd. for $C_{36}H_{51}N_5O_7S_2$ (729.960): C, 59.24; H, 7.04; N, 9.59. Found: C, 59.40; H, 6.92; N, 9.45.

2-(2-*N*-Morpholinoacetoxy)-1,3-bis[2-(2-nitrophenoxy)acetamidothiophenoxy]propane (21a). With the use of the general procedure **20a** and morpholine (**6b**) gave crude **21a** which was purified by column chromatography using ethyl acetate and petroleum ether (40-60) as an eluent as oily product (60%); ^1H nmr ($CDCl_3$) δ 2.46 (t, *J*=4.5 Hz, 4H, NCH_2), 2.96 (s, 2H, $COCH_2N$), 3.0 (d, *J*=5.9 Hz, 4H, SCH_2), 3.67 (t, *J*=4.5 Hz, 4H, OCH_2CH_2N), 4.73 (s, 4H, OCH_2CO), 5.28 (quintet, *J*=5.7 Hz, 1H, O-CH), 7.0-8.32 (m, 16H, ArH's), 9.44 (s, 2H, NH) ppm. *Anal*. Calcd. for $C_{37}H_{37}N_5O_{11}S_2$ (791.858): C, 56.12; H, 4.71; N, 8.84. Found: C, 56.00; H, 4.85; N, 8.90.

2-(3-*N*-Morpholinopropanoyloxy)-1,3-bis[2-(2-nitrophenoxy)-acetamidothiophenoxy)]propane (21b). With the use of the general procedure **20b** and morpholine (**6b**) gave crude **21b** which was crystallized from benzene/petroleum ether (40-60) as colorless crystals (55%), mp. 121-23°C; ir: NH 3321, CO 1728, 1689, NO_2 1527, 1357 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.28 (t, *J*=7.2 Hz, 2H, $COCH_2CH_2N$), 2.38 (t, *J*=4.5 Hz, 4H, NCH_2CH_2O), 2.53 (t, *J*=7.5 Hz, 2H, $COCH_2CH_2N$), 3.02 (d, *J*=6 Hz, 4H, SCH_2), 3.63 (t, *J*=4.5 Hz, 4H, OCH_2CH_2N), 4.75 (s, 4H, OCH_2CO), 5.03 (quintet, *J*=5.7 Hz, 1H, O-CH), 7.0-8.34 (m, 16H, ArH's), 9.46 (s, 2H, NH) ppm. *Anal*. Calcd. for $C_{38}H_{39}N_5O_{11}S_2$ (805.885): C, 56.64; H, 4.88; N, 8.69. Found: C, 56.59; H, 4.92; N, 8.52.

1,4-Bis{1,3-bis[2-(2-nitophenoxy)acetamidothiophenoxy]-propane-2-yloxycarbonylmethyl}-piperazine (22). With the use of the general procedure **20a** and piperazine (**6c**) gave crude **22** which was crystallized from ethanol as colorless crystals (50%), mp. 93-5°C; ir: NH 3317, CO 1747, 1689, NO_2 1523, 1350 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.75 (s, 8H, CH_2N), 3.03-3.06 (m, 12H, SCH_2 & $COCH_2N$), 4.77 (s, 8H, OCH_2CO), 5.09 (quintet, *J*=5.7 Hz, 2H, COO-CH), 7.03-8.32 (m, 32H, ArH's), 9.45 (s, 4H, NH) ppm. *Anal*. Calcd. for $C_{70}H_{66}N_{10}O_{20}S_4$ (1495.61): C, 56.22; H, 4.45; N, 9.37. Found: C, 56.10; H, 4.52; N, 9.42.

15-(2-N-morpholinoacetoxy)-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo[*e*,*l*,*r*,*z*][1,17]dioxa[7,11]dithia[4,14,21,24]tetraaza-cycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (25a). With the use of the general procedure **24a** and morpholine (**6b**) gave crude **25d** which was crystallized from benzene/petroleum ether (40-60°C) to give colorless crystals of **25a**, (61%), mp. 118-20°C; ir: NH 3329 , CO 1743, 1689 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.39 (t, *J*=4.5 Hz, 4H, N-CH_2CH$_2$-O), 2.54 (d, *J*=5.4 Hz, 4H, SCH_2), 2.34 (s, 2H, $COCH_2N$), 3.67 (t, *J*=4.5 Hz, 4H, OCH_2CH_2N), 3.72-3.8 (m, 2H, upfield of $NHCH_2$), 3.82-3.96 (m, 2H, downfield of $NHCH_2$), 4.71 (quintet, *J*=5.4 Hz, 1H, CH-OCO), 4.91 (d, *J*=15.6 Hz, 2H, upfield of OCH_2CO), 4.99 (d, *J*=15.6 Hz, 2H, downfield of OCH_2CO), 6.84-8.28 (m, 16H, ArH's), 8.51 (brs, 2H, CH_2NHCO), 9.26 (s, 2H, $NHCOCH_2$) ppm; ^{13}C NMR (APT pulse sequence, $CDCl_3$) δ 36.94, 41.21, 52.99, 58.52, 66.57, 68.61, 121.97, 124.23, 137.36, 155.36, 166.02, 166.28, 168.94 (C's and CH_2's), 70.80, 112.16, 121.47, 122.40, 125.24, 129.23, 132.20, 133.15, 133.71(CH's). *Anal*. Calcd. for $C_{41}H_{43}N_5O_9S_2$ (813.95): C, 60.50; H, 5.32; N, 8.60. Found: C, 60.39; H, 5.22; N, 8.71.

15-(3-N-piperidinopropanoyloxy)-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*e*,*l*,*r*,a_1]-[1,17]dioxa[7,11]dithia-[4,14,21,25]tetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (25b). With the use of the general procedure **24b** and piperidine (**6a**) gave crude **25b** which was crystallized from ethanol as colorless crystals (85%), mp. 200-202°C; ir: NH 3358, CO 1693, 1638 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.38-1.42 (m, 2H, $NCH_2CH_2CH_2$), 1.51 (quintet, *J*=5.4 Hz, 4H, N-$CH_2CH_2CH_2$), 1.87-1.92 (m, 2H, $CONHCH_2CH_2$), 2.08 (t, *J*=7.5 Hz, 2H, $OCOCH_2CH_2N$), 2.27 (t, *J*=5.1 Hz, 4H, $NCH_2CH_2CH_2$), 2.40 (t, *J*=7.5 Hz, 2H, $OCOCH_2CH_2N$), 2.57 (d, *J*=5.1 Hz, 4H, SCH_2), 3.55-3.61 (m, 2H, upfield of $CONHCH_2$), 3.55-3.61 (m, 2H, downfield of $CONHCH_2$), 4.69 (quintet, *J*=5.4 Hz, 1H, CH-OCO), 4.99 (d, *J*=15.9 Hz, 2H, upfield of OCH_2CO), 5.05 (d, *J*=15.9 Hz, 2H, downfield of OCH_2CO), 6.98-8.38 (m, 16H, ArH's), 8.51 (t, *J*=6.3 Hz, 2H, CH_2NHCO), 9.40 (s, 2H, $NHCOCH_2$) ppm. *Anal*. Calcd. for $C_{44}H_{49}N_5O_8S_2$ (840.032): C, 62.91; H, 5.88; N, 8.34. Found: C, 63.01; H, 5.90; N, 8.24.

15-(3-N-morpholinopropanoyloxy)-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*e*,*l*,*r*,a_1]-[1,17]dioxa[7,11]dithia-[4,14,21,25]tetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (25c). With the use of the general procedure **24b** and morpholine (**6b**) gave crude **25c** which was crystallized from ethanol as colorless crystals (92%), mp. 193-95°C; ir: NH 3337,

CO 1693, 1643 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.86-1.94 (m, 2H, $CONHCH_2CH_2$), 2.09 (t, *J*=7.2 Hz, 2H, $OCOCH_2CH_2N$), 2.33 (t, *J*=4.5 Hz, 4H, OCH_2CH_2N), 2.43 (t, *J*=7.2 Hz, 2H, $OCOCH_2CH_2N$), 2.58 (d, *J*=5.4 Hz, 4H, SCH_2), 3.53-3.63 (m, 2H, upfield of $CONHCH_2$), 3.61 (t, *J*=4.5 Hz, 4H, OCH_2CH_2N), 3.85-3.94 (m, 2H, downfield of $CONHCH_2$), 4.72 (quintet, *J*=5.4 Hz, 1H, CH-OCO), 4.99 (d, *J*=15.6 Hz, 2H, upfield of OCH_2CO), 5.05 (d, *J*=15.6 Hz, 2H, downfield of OCH_2CO), 6.97-8.38 (m, 16H, ArH's), 8.46 (t, *J*=6.3 Hz, 2H, CH_2NHCO), 9.40 (s, 2H, $NHCOCH_2$) ppm. *Anal*. Calcd. for $C_{43}H_{47}N_5O_9S_2$ (842.004): C, 61.34; H, 5.63; N, 8.32. Found: C, 61.51; H, 5.55; N, 8.20.

15-(3-N-piperidinopropanoyloxy)-6,14,15,24,32,33,34,35-octahydro-16*H*-tetrabenzo[*e*,*l*,*r*,b_1][1,17]dioxa[7,11]dithia-[4,14,21,26]tetraazacyclononacosin-7,23,30,37-(8*H*,22*H*,31*H*,36*H*)tetraone (25d). With the use of the general procedure **24c** and piperidine (**6a**) gave crude **25a** which was crystallized from benzene/petroleum ether (40-60°C) to give colorless crystals of **25d**, (60%), mp. 108-110°C; ir: NH 3344, CO 1735, 1689 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.51 (quintet, *J*=4.8 Hz, 2H, $N-CH_2CH_2CH_2$), 1.82 (brs, 8H, $N-CH_2CH_2$ & $N-CH_2CH_2CH_2$), 2.19 (t, *J*=7.5 Hz, 2H, $COCH_2CH_2-N$), 2.30 (brs, 4H, $N-CH_2CH_2$), 2.45 (t, *J*=7.5 Hz, 2H, $COCH_2CH_2N$), 2.75 (d, *J*=5.7 Hz, 4H, SCH_2), 3.41-3.61 (m, 4H, $NH-CH_2$), 4.78-4.89 (m, 5H, OCH_2CO & CH-OCO), 6.93-8.31 (m, 16H, ArH's), 7.65 (brs, 2H, CH_2NHCO), 9.23 (s, 2H, $NHCOCH_2$) ppm. *Anal*. Calcd. for $C_{45}H_{51}N_5O_8S_2$ (854.058): C, 63.29; H, 6.02; N, 8.20. Found: C, 63.40; H, 5.97; N, 8.32.

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