Convenient Method for the Synthesis of Macrocyclic Teteraamides, Acyclic Diamides, their Lariat Derivatives and Bis-macrocyclic Tetraamides

Ashraf A. Abbas*

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt
Fax +20(2)5727556; E-mail: ashraf@chem-sci.cairo.eun.eg; E-mail: ashrafaa50@hotmail.com

Received 6 December 2003

Abstract: The macrocyclic tetraamides **8a**–**e** were obtained in good yields by bis-alkylation of the potassium salts of the appropriate bis-phenols **7a**–**c** with the dihalo compounds **2a**,**b**. Similarly, macrocyclic tetraamides with pendant hydroxy group **18a**,**b** were prepared by the nucleophilic reaction of the potassium salts of **7a**,**b** with the dihalo compound **10**. Acylation of **18a**,**b** with chloroacetyl chloride gave the corresponding ester **19a**,**b**. Compounds **19a**,**b** reacted with different secondary amines to afford the corresponding lariat macrocycles **20a**–**d** and novel bis-macrocycle **21** in 50–65% yield.

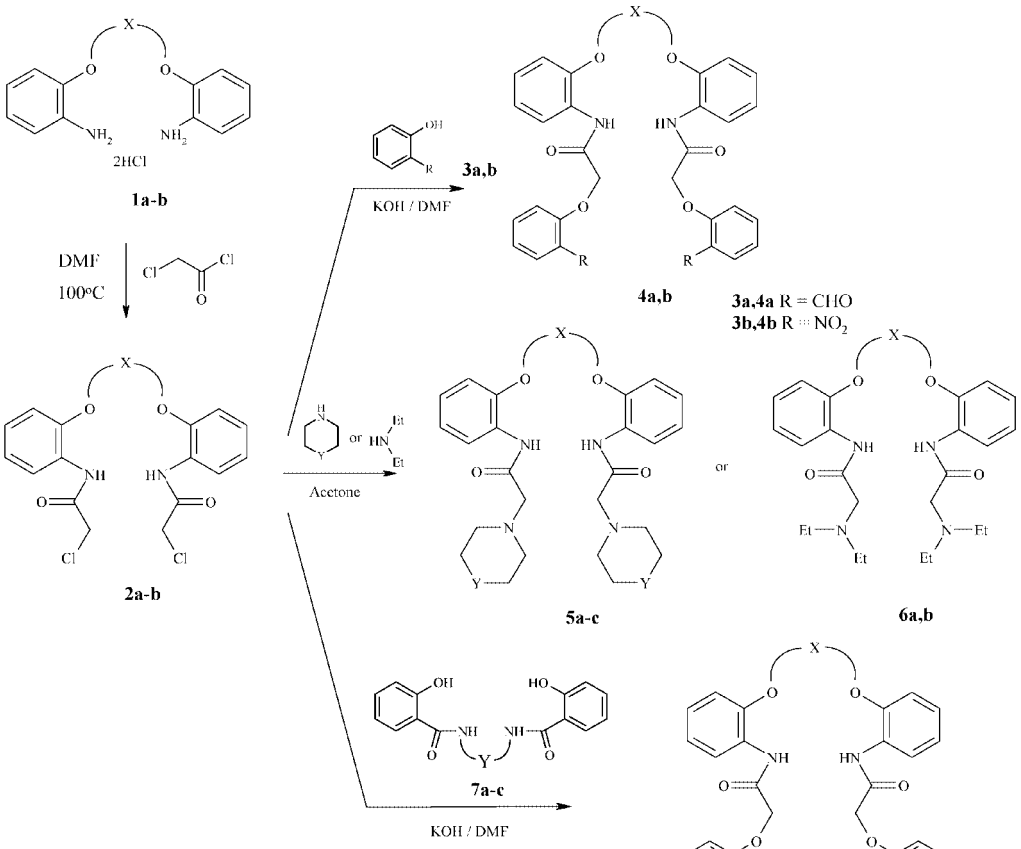
Key words: macrocyclic teteraamides, acyclic diamides, lariat macrocycles, bis-macrocyclic tetraamides

Much attention has been paid to the development of functional groups in the ring of crown ethers in an attempt to enhance the selectivity and the stability of complexes of these ligands.[1–4] For example, incorporation of an amide linkage in a polyether macrocycle has been reported to modify the binding properties of the crown ether compounds to favor alkali and alkaline earth cations.[5–12] Also, it was reported that, macrocyclic ligands with amide functional groups as binding sites show strong and selective complexation towards noble metals,[13–15] and transition metals.[16] Some substituted macrocyclic tetraamides showed high selectivity for Ag^{+}/Pd^{2+}.[17,18] Moreover, macrocyclic amides were originally regarded as valuable intermediates for the synthesis of aza-crown ethers and related compounds.[19–21] In addition, some acyclic diamide ligands are known to show high ion selectivity towards lithium over sodium and other alkali metal ions.[22–24] Furthermore, there is an intensive development of the lariat crown ethers concept[25] which led to the synthesis of large numbers of side-armed crown compounds, designed for uses ranging from routine (polymer-supported PTC catalysts, separation/extraction reagents, etc.) to sophisticated (application as redox switches for membrane transport, synthetic cation-conducting channels, etc.).[26] Lariat crown compounds can mimic the cation binding behavior of naturally occurring ionophores such as valinomycin,[27] where the side arm can effectively participate in the coordination and lead to higher cation-binding affinities for the new compounds compared with the parent macrocycle containing no extra donor sites.[28,29]

Keeping the above facts in mind, and in continuation of my interest in the synthesis of macrocyclic ligands with amide functional groups[30–33] and bis-macrocycles,[34] I am now engaged in a project directed towards the synthesis of 27–29-membered macrocyclic tetramides, acyclic diamides and their lariat derivatives with strong donor heteroatoms in the side arm as well as the bis-macrocyclic tetraamides aiming at the increase of their cation binding affinities. In this project a new methodology for the synthesis of the target macrocycles from activated bis(chloroacetamidophenoxy)alkanes and bis-phenolic compounds was used which are easily prepared from commercially available starting materials. Thus, reaction of 1, ω-bis(2-aminophenoxy)alkane hydrochlorides **1a**,**b** with chloroacetyl chloride in DMF at 100 °C afforded exclusively the corresponding 1,ω-bis(2-chloroacetamidophenoxy)alkanes **2a**,**b** in 70–76% yields. The latter compounds exhibit high reactivity towards different nucleophiles as shown in Scheme 1. Reaction of **2a**,**b** with the potassium salts of **3a**,**b** [obtained upon treatment of salicyaldehyde (**3a**) and *o*-nitrophenol (**3b**) with methanolic potassium hydroxide solution] in boiling DMF gave the corresponding bis-{2-[2-formyl or (2-nitrophenoxy)acetamidophenoxy]}alkanes **4a**,**b**, respectively, in moderate yields (50–60%). Moreover, compounds **2a**,**b** reacted with different secondary amines (namely, piperidine, morpholine, and *N*,*N*-diethylamine) to furnish the corresponding *N*-morpholino, *N*-piperidino, and *N*,*N*-diethylamino derivatives **5a**–**c** and **6a**,**b**, respectively, in 59–70% yields. The structures of compounds **4a**,**b**, **5a**–**c** and **6a**,**b** were inferred from the different spectroscopic and analytical data. These results prompted a study of the reactivity of **2a**,**b** towards bis-phenolic compounds aiming at preparing novel macrocycles tetraamides. Thus, treatment of **2a** with the potassium salt of bis-phenol **7a** (obtained upon treatment of **7a** with methanolic potassium hydroxide solution) under the same reaction conditions used for preparing **4a**,**b** afforded the corresponding 27-membered macrocyclic tetraamide **8a** in 30% yield. Similarly, the 27–29-membered macrocyclic **8b**–**d** were easily obtained in 26–35% yield by reacting the potassium salts of the appropriate bis-phenols **7a**–**c** with **2a**,**b** in refluxing DMF.

Next, the study was extended to include the synthesis of some new acyclic diamides, lariat macrocyclic tertaamides as well as bis-macrocyclic tetraamide as outlined in Schemes 2 and 3. For this purpose, our strategy was based on using 2-hydroxy-1,3-bis(2-aminophenoxy)propane hydrochloride (**9**) as a starting material to synthesize the

SYNTHESIS 2004, No. 3, pp 0419–0428
Advanced online publication: 29.01.2004
DOI: 10.1055/s-2004-815938; Art ID: Z17403SS



1a, 2b; X = $(CH_2)_3$
1b, 2b; X = $(CH_2)_4$
3a, R = CHO
3b, R = NO_2
4a; R = CHO, X = $(CH_2)_3$
4b; R = NO_2, X = $(CH_2)_4$
5a; Y = CH_2, X = $(CH_2)_3$
5b; Y = O, X = $(CH_2)_3$
5c; Y = O, X = $(CH_2)_4$
6a; X = $(CH_2)_3$
6b; X = $(CH_2)_4$

7a; Y = $(CH_2)_2$
7b; Y = $(CH_2)_3$
7c; Y = $(CH_2)_4$
8a; X = $(CH_2)_3$, Y = $(CH_2)_2$
8b; X = Y= $(CH_2)_3$
8c; X = $(CH_2)_3$, Y = $(CH_2)_4$
8d; X = $(CH_2)_4$, Y = $(CH_2)_2$
8e; X = $(CH_2)_4$, Y = $(CH_2)_3$

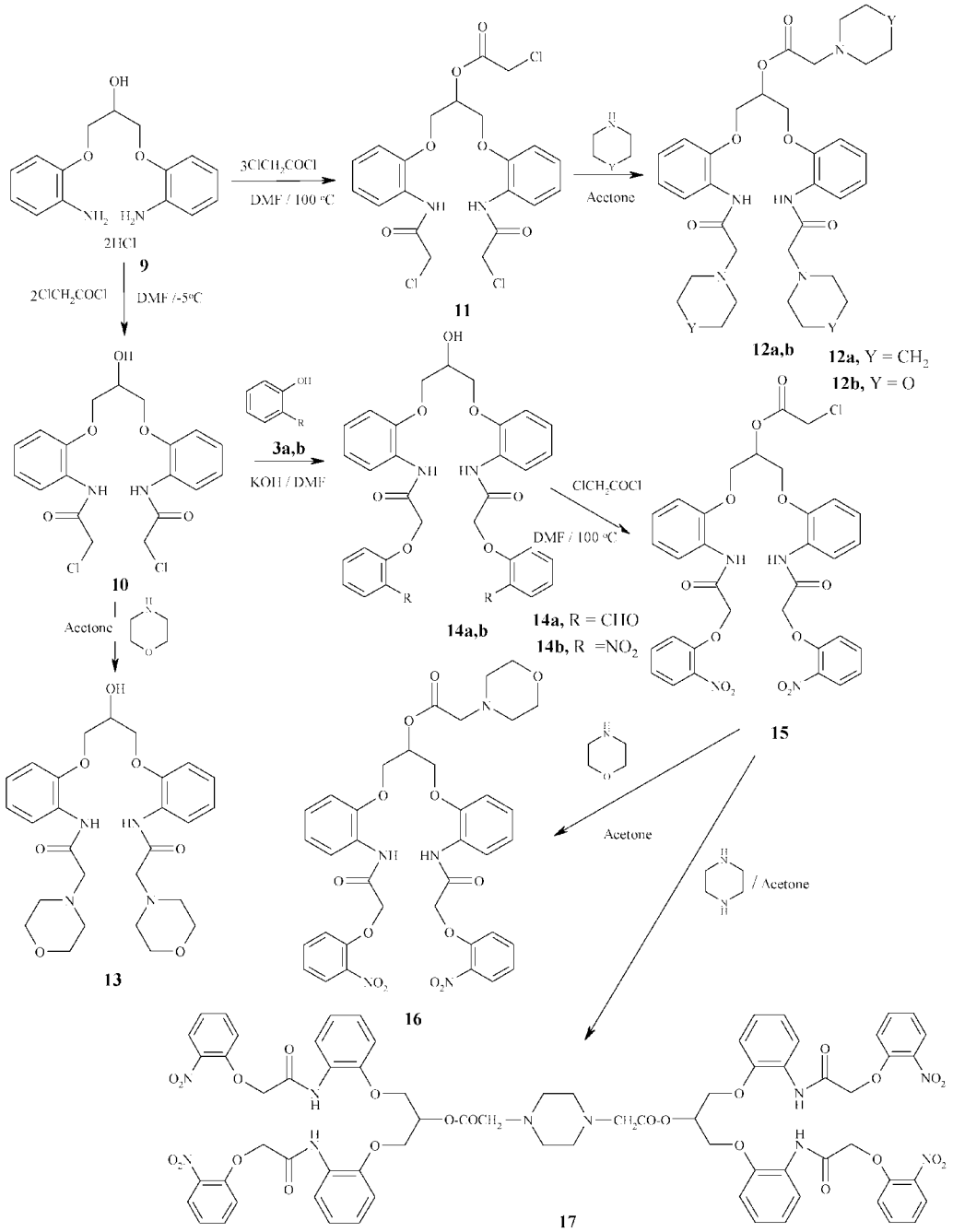
Scheme 1

key intermediate compound **10**. Thus, reaction of two equivalents of chloroacetyl chloride with one equivalent of **9** in DMF at 100 °C afforded the trichloroacyl product **11** in 40% yield and not the desired dichloroacyl product **10** (<2%) as expected with recovery of about 30% of starting material (TLC and ^{1}H NMR spectrum). As a result of the low yield of the target dichloroacyl product **10**, the reaction was repeated using different reaction conditions and solvents. Surprisingly, compound **10** could be obtained as the major product (70% yield) by reacting one equivalent of **9** with two equivalents of chloroacetyl chloride in DMF at –5 °C with the formation of traces of **11** (<2%). It is noteworthy that compound **11** could be obtained in 90% yield by reaction of **9** with three equivalents of chloroacetyl chloride in DMF at 100 °C.

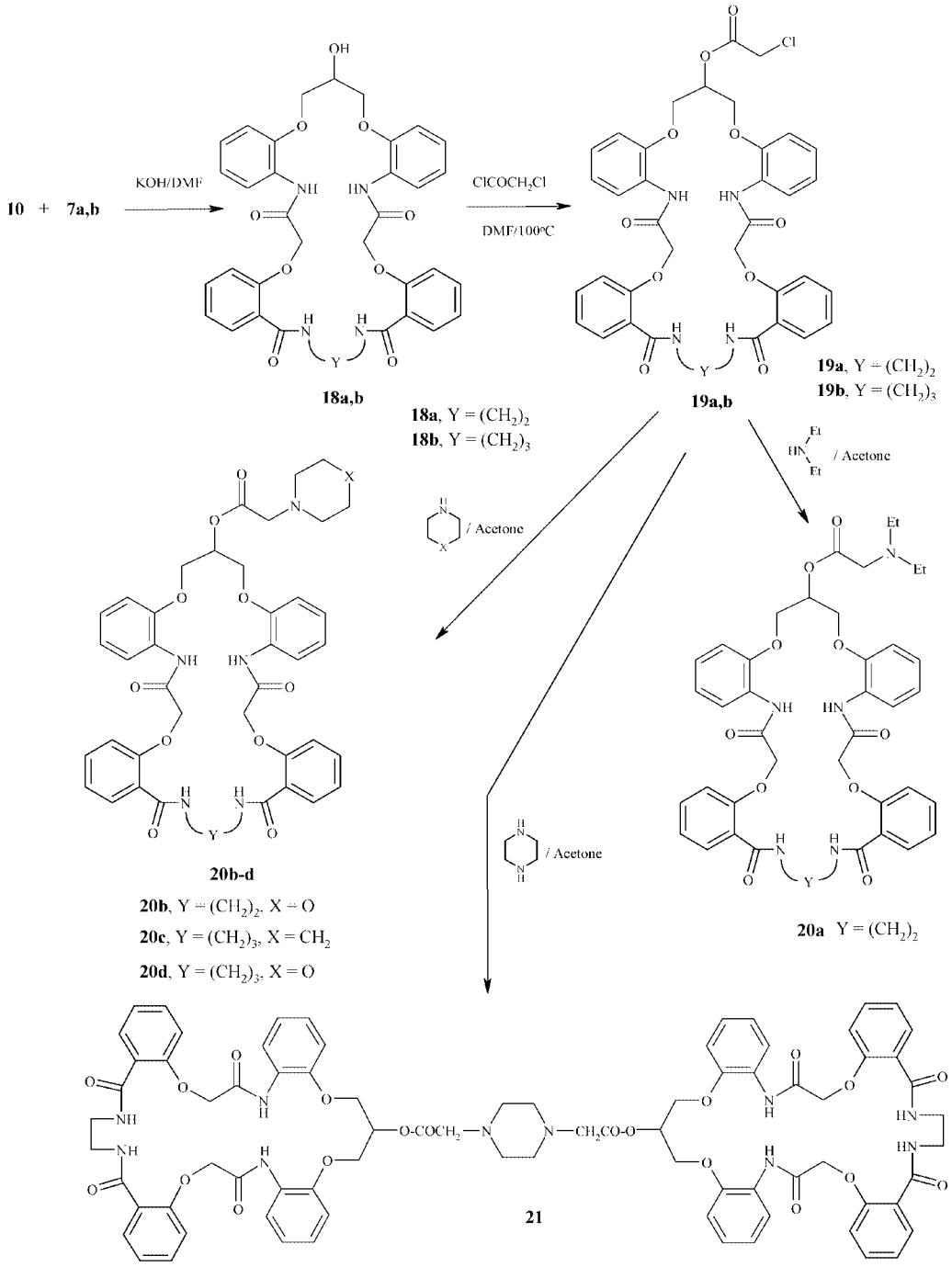
The reactivities of **10** and **11** towards different nucleophiles were investigated aimed at the preparation of new acyclic diamides, their lariat analogues and bis-acyclic diamides. Thus, compound **11** reacts exclusively with piperidine and morpholine to give the corresponding triamino derivatives **12a**,**b** in 70% and 75% yields, respectively. Similarly, reaction of **10** as a representative example with morpholine gave the corresponding 2-hydroxy-1,3-bis(2-*N*-morpholinoacetamidophenoxy)propane (**13**) in 65% yield. Moreover, compound **10** reacted with the potassium salt of salicyaldehyde and *o*-nitrophenol in boiling DMF to afford the corresponding 2-formylphenoxy or 2-nitrophenoxy derivatives **14a**,**b** in 55% and 60% yields, respectively. Consequently, **14b** reacted with chloroacetyl chloride in DMF to afford the corresponding *O*-acyl product **15** which reacted with morpholine and piperazine in

acetone to furnish the corresponding 2-(*N*-morpholinoacetoxy) **16** and 1,4-bispiperazino derivative **17** in 70% and 60% yields, respectively as depicted in Scheme 2. The structure of the novel bis-product **17** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses data.

In continuation of the study and due to the success in the synthesis of the novel acyclic diamide **16** and bis-piperazino derivative **17**, the strategy was extended to the synthesis of the target lariat and bis-macrocycles containing four amide groups. For this purpose, compound **10** was chosen as a key intermediate for preparing the macrocycles with a pendant hydroxy group **18a**,**b**, as precursors for synthesis of lariat and bis-macrocycles as outlined in Scheme 3. Thus, reaction of **10** with the bis-potassium salt of **7a**,**b** gave 15-hydroxy macrocyclic tetraamides **18a**,**b** as expected in 40–45% yields. The latter compounds reacted with chloroacetyl chloride in DMF to furnish 15-(chloroacetoxy) macrocycles **19a**,**b** in 70–85% yields. Treatment of esters **19a**,**b** with *N*,*N*-diethylamine, morpholine, and piperazine afforded the corresponding 15-(*N*,*N*-diethylaminoacetoxy), 15-(*N*-morpholinoacetoxy) and 1,4-bis-macrocycles **20a**–**d** and **21** in 50–65% yields, respectively. The structures of the compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses data.



Scheme 2



Scheme 3

From the ^{1}H NMR and ^{13}C NMR data of the new macrocyclic tetraamides **8a–e**, **18a**,**b**, **19a**,**b** and **20a**–**d**, the following conclusions were obtained:

a) The magnetic equivalence of the OCH_2 and NCH_2 protons in **8a**–**e** indicates rapid change in all macrocycles.

b) Contrary to compounds **8a**–**e**, the 15-substituted macrocycles **18a**,**b**, **19a**,**b** and **20a**–**d** show in their ^{1}H NMR a geminal coupling and nonequivalence in all OCH_2 and NCH_2 protons. This indicates that the 15-substituted macrocycles are evidently present in one stable conformer or as slow (on the time scale of NMR) interconverting conformers. Evidence for the existence of the lariat derivatives entirely as one stable nonconvertible conformer comes from ^{13}C NMR data (cf. experimental). Similar results were reported by Ibrahim et al.[35] for some *N*-alkyl derivatives **A** (R = Me, Et, $PhCH_2$ and PhCO (Figure 1).

c) The ^{1}H NMR of all macrocyclic tetraamides in $CDCl_3$ or DMSO-d_6 showed a triplet or a broad singlet for NH in $NHCH_2$ group indicating a reduced rate of exchange in these compounds. This behavior may be attributed to the intermolecular hydrogen bonded structure **B** (Figure 1).

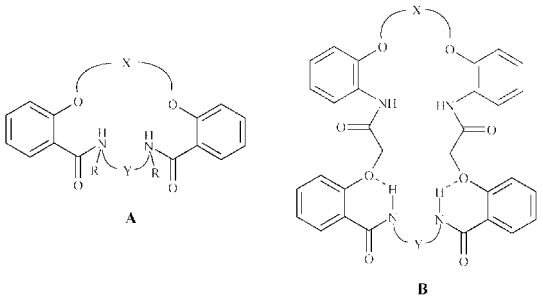


Figure 1 *N*-Alkyl derivatives **A** and intermolecular hydrogen bonded structure **B**

In conclusion, a new series of acyclic diamides and 27–29-membered tetrabenzosubstituted macrocyclic tetraamides and their 15-hydroxy derivatives have been synthesized as precursors for the synthesis of novel lariat macrocycles containing strong donor group as supporting ligand at the end of the side arm. The development of the present reactions will provide a new way for the synthesis of a new and wide variety of useful lariat macrocycles having a variety of donar/acceptor end groups with side arms of different lengths. In addition this project succeeded to offer a facile method for a novel bis-macrocyclic having two crown units connected by flexible bridge which might form 'sandwich complex' (complex with two crown moieties per cation).[36–37] A study of the complexing properties of the new macrocycles and their lariat derivatives will be described in detail when the work is completed. Further studies to develop new routes to introduce new and different side arms and synthesis of bis-macrocycles are in progress.

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 pulse sequence for compounds **17** and **20b**. Mass spectra were recorded on HP 5988A (EI, 15 eV). 1,2-Diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, 1,3-dibromopropane and 1,4-dibromobutane were used as purchased from Aldrich. The starting compounds **1a**,[38] **1b**,[39] **7a**,[35] **7b**,**c**[40] and **9**[39] were prepared as reported.

Reaction of Bis-amines 1a,b and 9 with Chloroacetyl Chloride; Synthesis of Compounds 2a,b, 10 and 11; General Procedure

To each solution of **1a**,**b**, and **9** (5 mmol) in DMF (10 mL) was added chloroacetyl chloride [1.123 g (10 mmol) for the preparation of **2a**,**b**, and **10** or 1.69 g (15 mmol) for the preparation of **11**]. The reaction mixture was stirred at 100 °C [(for compounds **2a**,**b**, and **11**) and at –5 °C (for compound **10**)] for 2 h. The mixture was then poured onto crushed ice. The solid obtained was collected by filtration and crystallized from the appropriate solvent to afford **2a**,**b**, **10** and **11**.

1,3-Bis[(2-chloroacetamido)phenoxy]propane (2a)

With the use of the general procedure, **1a** gave crude **2a** which was crystallized from toluene to give colorless crystals (70%); mp 182–184 °C.

IR (KBr): 3287 (NH), 1679 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 2.27 (quintet, J = 6.2 Hz, 2 H, OCH_2CH_2), 4.28 (t, J = 6.2 Hz, 4 H, OCH_2), 4.37 (s, 4 H, CH_2Cl), 6.90–7.96 (m, 8 H, ArH), 9.35 (s, 2 H, NH).

Anal. Calcd for $C_{19}H_{20}Cl_2N_2O_4$ (411.28): C, 55.49; H, 4.90; N, 6.81; Cl, 17.24. Found: C, 55.51; H, 4.85; N, 6.85; Cl, 17.12.

1,4-Bis[(2-chloroacetamido)phenoxy]butane (2b)

By the general procedure, **1b** gave crude **2b** which was crystallized from benzene to give colorless crystals (76%); mp 152–154 °C.

IR (KBr): 3396 (NH), 1647 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 2.1 (br s, 4 H, OCH_2CH_2), 4.15 (br s, 4 H, OCH_2), 4.18 (s, 4 H, CH_2Cl), 6.88–8.35 (m, 8 H, ArH), 9.03 (s, 2 H, NH).

Anal. Calcd for $C_{20}H_{22}Cl_2N_2O_4$ (425.31): C, 56.48; H, 5.21; N, 6.59; Cl, 16.67. Found: C, 56.52; H, 5.30; N, 6.40; Cl, 16.72.

2-Hydroxy-1,3-bis(2-chloroacetamidophenoxy)propane (10)

By the general procedure, **9** gave crude **10** which was crystallized from benzene to give colorless crystals (70%); mp 144–146 °C.

IR (KBr): 3533 (NH), 3287 (OH), 1668 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 3.04 (br s, 1 H, OH), 4.15 (s, 4 H, CH_2Cl), 4.28 (d, J = 4.5 Hz, 4 H, OCH_2), 4.47 (quintet, J = 4.8 Hz, 1 H, CHO), 6.93–8.24 (m, 8 H, ArH), 8.93 (br s, 2 H, NH).

Anal. Calcd for $C_{19}H_{20}Cl_2N_2O_5$ (427.28): C, 53.41; H, 4.72; N, 6.56; Cl, 16.59. Found: C, 53.49; H, 4.59; N, 6.65; Cl, 16.66.

2-Chloroacetoxy-1,3-bis(2-chloroacetamidophenoxy)propane (11)

By the general procedure, **9** gave crude **11** which was crystallized from benzene to give colorless crystals (90%); mp 138–140 °C.

IR (KBr): 3382 (NH), 1760, 1682 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 4.14 (s, 2 H, $OCOCH_2$), 4.21 (s, 4 H, CH_2Cl), 4.42 (m, 4 H, OCH_2), 5.76 (quintet, J = 5.1 Hz, 1 H, CHO), 6.89–8.36 (m, 8 H, ArH), 8.86 (br s, 2 H, NH).

Anal. Calcd for $C_{21}H_{21}Cl_3N_2O_6$ (503.77): C, 50.07; H, 4.20; N, 5.56; Cl, 21.11. Found: C, 50.22; H, 4.12; N, 5.64; Cl, 21.04.

Potassium Salts of Compounds 3a,b and 7a-c; General Procedure

To a solution of KOH (1.14 g, 10 mmol) in MeOH (10 mL) was added salicylaldehyde (**3a**), *o*-nitrophenol (**3b**) (10 mmol), or bisphenols **7a**–**c** (5 mmol). The mixture was stirred at r.t. for 10 min. The solvent was then removed in vacuo. The remaining solid was triturated with anhyd Et_2O, collected, dried, and used in the next step without further purification.

Compounds 4a,b, 14a,b and Macrocyclic Tetraamides 8a–e and 18a,b; General Procedure

A solution of the appropriate potassium salt of **3a**,**b** (20 mmol), or **7a**–**c** (10 mmol) and the appropriate dichloro compound **2a**,**b**, or **10** (10 mmol) in DMF (20 mL) was heated under reflux for 10 min during which time KCl precipitated. The solvent was then removed in vacuo and the remaining material was washed with H_2O (50 ml) and crystallized from the appropriate solvent to give compounds **4a**,**b**, **14a**,**b**, **8a**–**e** and **18a**,**b**.

1,3-Bis[2-(2-formaylphenoxy)acetamidophenoxy]propane (4a)

By the general procedure, the potassium salt of **3a** and **2a** gave crude **4a** which was crystallized from dioxane to give pale yellow crystals (50%); mp 222–224 °C.

IR (KBr): 3404 (NH), 1687, 1600 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 2.2 (quintet, J = 5.6 Hz, 2 H, OCH_2CH_2), 4.17 (t, J = 5.4 Hz, 4 H, OCH_2), 4.89 (s, 4 H, $COCH_2$), 6.85–8.01 (m, 16 H, ArH), 9.23 (s, 2 H, NH), 10.48 (s, 2 H, CHO).

Anal. Calcd for $C_{33}H_{30}N_2O_8$ (582.61): C, 68.03; H, 5.19; N, 4.81. Found: C, 68.20; H, 5.25; N, 4.71.

1,4-Bis[2-(2-nitrophenoxy)acetamidophenoxy]butane (4b)
By the general procedure, the potassium salt of **3b** and **2b** gave crude **4b** which was crystallized from AcOH to give colorless crystals (60%); mp 204–205 °C.

IR (KBr): 3372 (NH), 1673 (C=O), 1526, 1346 cm^{-1} (NO_2).

^{1}H NMR (DMSO-d_6): δ = 1.89 (br s, 4 H, OCH_2CH_2), 4.09 (br s, 4 H, OCH_2), 4.88 (s, 4 H, $COCH_2$), 8.87–8.15 (m, 16 H, ArH), 9.04 (s, 2 H, NH).

Anal. Calcd for $C_{32}H_{30}N_4O_{10}$ (630.61): C, 60.95; H, 4.79; N, 8.88. Found: C, 61.06; H, 4.85; N, 8.78.

2-Hydroxy-1,3-bis[2-(2-formylphenoxy)acetamidophenoxy]-propane (14a)
By the general procedure, the potassium salt of **3a** and **10** gave crude **14a** which was crystallized from dioxane–EtOH to give pale yellow crystals (55%); mp 190–192 °C.

IR (KBr): 3396 (NH), 1647 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 4.21 (d, J = 4.1 Hz, 4 H, OCH_2), 4.45 (br s, 1 H, C*H*OH), 4.72 (s, 4 H, $COCH_2$), 5.10 (d, J = 5.7 Hz, 1 H, OH), 6.86–8.36 (m, 16 H, ArH), 9.34 (s, 2 H, NH), 10.22 (s, 2 H, CHO).

Anal. Calcd for $C_{33}H_{30}N_2O_9$ (598.61): C, 66.21; H, 5.05; N, 4.68. Found: C, 66.40; H, 4.99; N, 4.52.

2-Hydroxy-1,3-bis[2-(2-nitrophenoxy)acetamidophenoxy]propane (14b)
By the general procedure, the potassium salt of **3b** and **10** gave crude **14b** which was crystallized from dioxane to give pale yellow crystals (60%); mp 209–211 °C.

IR (KBr): 3359 (NH), 3340 (OH), 1691 (C=O), 1520, 1342 cm^{-1} (NO_2).

^{1}H NMR (DMSO-d_6): δ = 4.18 (m, 4 H, OCH_2), 4.37 (br s, 1 H, C*H*OH), 4.95 (s, 4 H, $COCH_2$), 5.42 (d, J = 5.6 Hz, 1 H, OH), 6.91–8.09 (m, 16 H, ArH), 9.23 (s, 2 H, NH).

Anal. Calcd for $C_{31}H_{28}N_4O_{11}$ (632.58): C, 58.86; H, 4.46; N, 8.86. Found: C, 58.99; H, 4.31; N, 8.99.

6,14,15,24,32,33-Hexahydro-16*H*-tetrabenzo[*b,h,p,v*]-[1,7,18,24,4,11,14,21]tetraoxatetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (8a)
By the general procedure, the potassium salt of **7a** and **2a** gave crude **8a** which was crystallized from EtOH to give colorless crystals (30%); mp 172–173 °C.

IR (KBr): 3528, 3472 (NH), 1692, 1634 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.6 (quintet, J = 6.6 Hz, 2 H, OCH_2CH_2), 3.48 (t, J = 6.6 Hz, 4 H, OCH_2), 3.78 (br s, 4 H, CH_2N), 4.92 (s, 4 H, $COCH_2$), 6.49–8.39 (m, 16 H, ArH), 8.75 (br s, 2 H, CH_2NHCO), 8.85 (s, 2 H, N*H*$COCH_2$).

MS: *m*/*z* (%) = 638 (M^+, 12.1), 504 (11), 462 (7.2), 353 (11.2), 284 (38.8), 258 (10.5), 175 (28.8), 150 (15.1), 133 (100), 108 (28.7).

Anal. Calcd for $C_{35}H_{34}N_4O_8$ (638.68): C, 65.82; H, 5.37; N, 8.77. Found: C, 65.91; H, 5.25; N, 8.71.

6,14,15,24,32,33-Hexahydro-16*H*,34*H*-tetrabenzo[*b,h,q,w*]-[1,7,19,25,4,11,15,22]tetraoxatetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (8b)
By the general procedure, the potassium salt of **7b** and **2a** gave crude **8b** which was crystallized from AcOH to give colorless crystals (35%); mp 258–260 °C.

IR (KBr): 3389, 3343 (NH), 1688, 1652 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 1.74 (quintet, J = 5.8 Hz, 2 H, NCH_2CH_2), 2.03 (quintet, J = 6.4 Hz, 2 H, OCH_2CH_2), 3.43 (m, 4 H, CH_2N), 4.07 (t, J = 6.4 Hz, 4 H, OCH_2), 4.81 (s, 4 H, $COCH_2$), 6.80–7.99 (m, 16 H, ArH), 8.72 (t, 2 H, J = 5 Hz, CH_2NHCO), 9.31 (s, 2 H, *NH*$COCH_2$).

MS: *m*/*z* (%) = 652 (M^+, 8.8), 518 (8.7), 418 (11.2), 284 (45.7), 258 (14.2), 133 (100), 118 (25.1), 105 (10.4).

Anal. Calcd for $C_{36}H_{36}N_4O_8$ (652.70): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.09; H, 5.49; N, 8.49.

6,14,15,24,32,33,34,35-Octahydro-16*H*-tetrabenzo[*b,h,r,x*]-[1,7,20,26,4,11,16,23]tetraoxatetraazacyclononacosin-7,23,30,37-(8*H*,22*H*,31*H*,36*H*)tetraone (8c)
By general procedure, the potassium salt of **7c** and **2a** gave crude **8c** which was crystallized from EtOH to give colorless crystals (25%); mp 248–250 °C.

IR (KBr): 3310 (NH), 1710, 1633 cm^{-1} (C=O).

^{1}H NMR (DMSO): δ = 1.58 (br s, 4 H, CH_2CH_2N), 2.13 (quintet, J = 6.2 Hz, 2 H, OCH_2CH_2), 3.25 (m, 4 H, CH_2N), 4.17 (t, J = 6.2 Hz, 4 H, OCH_2), 4.72 (s, 4 H, $COCH_2$), 6.79–7.90 (m, 16 H, ArH), 8.53 (t, 2 H, J = 5.2 Hz, CH_2NHCO), 9.32 (s, 2 H, N*H*$COCH_2$).

MS: *m*/*z* (%) = 666 (M^+, 4.8), 532 (3.3), 418 (7.1), 284 (32.8), 258 (8.3), 133 (100), 118 (18.8), 108 (28.6).

Anal. Calcd for $C_{37}H_{38}N_4O_8$ (666.73): C, 66.65; H, 5.74; N, 8.40. Found: C, 66.55; H, 5.69; N, 8.22.

6,14,15,16,17,25,33,34-Octahydrotetrabenzo[*b,h,p,v*]-[1,7,18,24,4,11,14,21]tetraoxatetraazacyclooctacosin-7,24,31,36-(8*H*,23*H*,32*H*,35*H*)tetraone (8d)
By the general procedure, the potassium salt of **7a** and **2b** gave crude **8d** which was crystallized from dioxane to give colorless crystals (30%); mp 215–217 °C.

IR (KBr): 3394, 3356 (NH), 1682, 1653 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 1.58 (br s, 4 H, CH_2CH_2O), 3.50 (m, 4 H, CH_2N), 3.85 (br s, 4 H, OCH_2), 4.81 (s, 4 H, $COCH_2$), 6.88–7.99 (m, 16 H, ArH), 8.79 (br s, 2 H, CH_2NHCO), 9.17 (s, 2 H, N*H*$COCH_2$).

MS: *m*/*z* (%) = 652 (M^+, 13.3), 518 (12.2), 432 (10.8), 387 (28), 324 (21.8), 272 (13.5), 188 (58.7), 183 (63), 147 (17.6), 133 (100).

Anal. Calcd for $C_{36}H_{36}N_4O_8$ (652.70): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.33; H, 5.49; N, 8.65.

6,14,15,16,17,25,33,34-Octahydro-35*H*-tetrabenzo[*b,h,q,w*]-[1,7,19,25,4,11,15,22]tetraoxatetraazacyclononacosin-7,24,31,37-(8*H*,23*H*,32*H*,36*H*)tetraone (8e)
By the general procedure, the potassium salt of **7b** and **2b** gave crude **8e** which was crystallized from AcOH to give colorless crystals (26%); mp 220–222 °C.

IR (KBr): 3406, 3341 (NH), 1685, 1648 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 1.62 (m, 6 H, CH_2CH_2N + CH_2CH_2O), 3.36 (m, 4 H, CH_2N), 3.88 (s, 4 H, OCH_2), 4.86 (s, 4 H, $COCH_2$), 6.89–8.02 (m, 16 H, ArH), 8.62 (t, J = 5.4 Hz, 2 H, CH_2NHCO), 9.22 (s, 2 H, N*H*$COCH_2$).

MS: *m*/*z* (%) = 666 (M^+, 8.3), 532 (4.9), 432 (9.5), 298 (29.5), 272 (12.4), 233 (2.4), 188 (58.9), 163 (52.6), 143 (10), 133 (100), 104 (52.5);

Anal. Calcd for $C_{37}H_{38}N_4O_8$ (666.73): C, 66.65; H, 5.74; N, 8.40. Found: C, 66.70; H, 5.85; N, 8.50.

15-Hydroxy-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo-[*b,h,p,v*][1,7,18,24,4,11,14,21]tetraoxatetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (18a)
By the general procedure, the potassium salt of **7a** and **10** gave crude **18a**, which was purified by column chromatography using EtOAc–petroleum ether (bp 40–60 °C) as an eluent, to give colorless crystals (40%); mp 94–96 °C.

IR (KBr): 3387, 3071 (OH, NH), 1682, 1643 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.69 (d, *J* = 4.8 Hz, 4 H, OCH_2), 3.78 (br s, 4 H, CH_2N), 3.81 (quintet, *J* = 4.8 Hz, 1 H, C*H*OH), 4.01 (br s, 1 H, OH), 4.81 (d, *J* = 15.9 Hz, 2 H, upfield of $COCH_2$), 4.89 (d,, *J* = 15.9 Hz, 2 H, downfield of $COCH_2$), 6.64–8.33 (m, 16 H, ArH), 8.10 (br s, 2 H, CH_2NHCO), 8.99 (s, 2 H, $NHCOCH_2$).

MS: *m*/*z* (%) = 654 (M^+, 6.8), 520 (3.5), 461 (3), 359 (1.5), 300 (16.2), 134 (100), 105 (4), 77 (3.2).

Anal. Calcd for $C_{35}H_{34}N_4O_9$ (654.68): C, 64.21; H, 5.23; N, 8.56. Found: C, 64.29; H, 5.43; N, 8.40.

15-Hydroxy-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo-[*b,h,q,w*][1,7,19,25,4,11,15,22]tetraxatetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (18b)
By the general procedure, the potassium salt of **7b** and **10** gave crude **18b**, which was purified by column chromatography using EtOAc–petroleum ether (bp 40–60 °C) as an eluent, to give colorless crystals (45%); mp166–168 °C.

IR (KBr): 3400, 3347 (NH), 1686, 1639 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.92 (m, 2 H, NCH_2CH_2), 3.5–3.95 (m, 9 H, CH_2N, OCH_2, C*H*OH), 4.63 (d, *J* = 4.2 Hz, 1 H, OH), 4.81 (d, *J* = 15.6 Hz, 2 H, upfield of $COCH_2O$), 4.95 (d, *J* = 15.5 Hz, 2 H, downfield of $COCH_2O$), 6.65–8.36 (m, 16 H, ArH), 7.83 (t, *J* = 5.5 Hz, 2 H, CH_2NHCO), 9.06 (s, 2 H, $NHCOCH_2$).

MS: *m*/*z* (%) = 668 (M^+, 8.9), 592 (8.2), 491 (8.1), 383 (10), 285 (100), 133 (84.8).

Anal. Calcd for $C_{36}H_{36}N_4O_9$ (668.70): C, 64.66; H, 5.43; N, 8.38. Found: C, 64.50; H, 5.55; N, 8.19.

Reaction of Chloroacetyl Chloride with 14b and 18a,b; Synthesis of Compounds 15 and 19a,b; General Procedure
To a solution of each of **14b** and **18a**,**b** (5 mmol) in DMF (10 mL) was added chloroacetyl chloride (1.36 g, 12 mmol). The reaction mixture was stirred at r.t. for 2 h and then poured onto crushed ice. The solid obtained was collected by filtration and crystallized from the appropriate solvent for each derivative to afford **15** and **19a**,**b**.

2-Chloroacetoxy-1,3-bis[2-(2-nitrophenoxy)acetamidophenoxy]propane (15)
By the general procedure, **14b** gave crude **15**, which was crystallized from benzene to give colorless crystals (65%); mp 150–152 °C.

IR (KBr): 3375 (NH), 1761, 1688 (C=O), 1526, 1345 cm^{-1} (NO_2).

^1H NMR ($CDCl_3$): δ = 4.04 (s, 2 H, CH_2Cl), 4.43 (m, 4 H, OCH_2), 4.71 (s, 4 H, CH_2CO), 5.76 (quintet, 1 H, *J* = 5.1, CHO), 6.88–8.29 (m, 16 H, ArH), 9.07 (s, 2 H, NH).

Anal. Calcd for $C_{33}H_{29}ClN_4O_{12}$ (709.06): C, 55.90; H, 4.12; N, 7.90; Cl, 5.00. Found: C, 55.81; H, 3.98; N, 7.85; Cl, 4.90.

15-Chloroacetoxy-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo[*b,h,p,v*][1,7,18,24,4,11,14,21]tetraoxatetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (19a)
By the general procedure **18a,** gave crude **19a**, which was crystallized from EtOH to give colorless crystals (85%); mp 218–220 °C.

IR (KBr): 3348, 3248 (NH), 1759, 1682, 1643 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.70 (s, 2 H, CH_2Cl), 3.76 (m, 4 H, CH_2N), 3.95 (d, 4 H, *J* = 5.8 Hz, 4 H, OCH_2), 4.80 (d, *J* = 15.5 Hz, 2 H, upfield of $COCH_2O$), 4.92 (d, *J* = 15.5 Hz, 2 H, downfield of $COCH_2O$), 5.44 (quintet, *J* = 5.7 Hz, 1 H, CHO), 6.72–8.32 (m, 16 H, ArH), 8.35 (br s, 2 H, CH_2NHCO), 8.85 (s, 2 H, $NHCOCH_2$).

MS: *m*/*z* (%) = 731 (M^+, 1.5), 671 (1.6), 577 (6.5), 524 (5.4), 368 (57), 236 (100), 152 (18.4), 98 (9.5).

Anal. Calcd for $C_{37}H_{35}ClN_4O_{10}$ (731.16): C, 60.78; H, 4.82; N, 7.66; Cl, 4.85. Found: C, 60.88; H, 4.94; N, 7.71; Cl, 4.93.

15-Chloroacetoxy-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*b,h,q,w*][1,7,19,25,4,11,15,22]tetraoxatetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (19b)
By the general procedure, **18b** gave crude **19b**, which was crystallized from AcOH–EtOH, to give colorless crystals (70%); mp 244–246 °C.

IR (KBr): 3387, 3347 (NH), 1765, 1692, 1635 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.84 (m, 2 H, CH_2CH_2N), 3.22–3.29 (m, 2 H, CH_2N), 3.71–3.82 (m, 4 H, CH_2Cl, CH_2N), 3.90–4.0 (m, 4 H, OCH_2), 4.63 (d, *J* = 15 Hz, 2 H, upfield of $COCH_2O$), 4.95 (d, *J* = 15.3 Hz, 2 H, downfield of $COCH_2O$), 5.43 (quintet, *J* = 5.7 Hz, 1 H, CHO), 6.69–8.23 (m, 16 H, ArH), 8.14 (t, *J* = 5.7 Hz 2 H, CH_2NHCO), 8.97 (s, 2 H, $NHCOCH_2$).

MS: *m*/*z* (%) = 745 (M^+, 12), 581 (11), 488 (11.5), 314 (85), 224 (23), 177 (100), 120 (52).

Anal. Calcd for $C_{38}H_{37}ClN_4O_{10}$ (745.18): C, 61.25; H, 5.00; N, 7.52; Cl, 4.76. Found: C, 61.40; H, 4.93; N, 7.75; Cl, 4.60.

Reaction of Compounds 2a,b, 10, 11, 15 and 19a,b with Secondary Amines; Synthesis of Compounds 5a–c, 6a,b, 12a,b, 13, 16, 17, 20a–d and 21); General Procedure
A mixture of each of **2a**,**b**, **10**, **11**, **15** and **19a**,**b** (5 mmol) and excess of the appropriate secondary amines (*N*,*N*-diethylamine, morpholine and piperidine) or [6 mmol of compounds **15**, **19a** and 3 mmol of piperazine and few drops of Et_3N for synthesis of compounds **17** and **21**] in acetone (50 mL) was heated under reflux for 10 min, and then stirred at r.t overnight. (For the synthesis of compounds **17** and **21**, the reaction mixture was heated under reflux for 24 h). The solvent was then removed in vacuo. The solid obtained was washed with cold H_2O and crystallized from the proper solvent to give compounds **5a–c**, **6a**,**b**, **12a**,**b**, **13**, **16**, **17**, **20a–d** and **21**.

1,3-Bis[2-(*N*-piperidino)acetamidophenoxy]propane (5a)
By the general procedure, **2a** and piperidine gave crude **5a**, which was crystallized from EtOH to give colorless crystals (65%); mp 150–152 °C.

^1H NMR ($CDCl_3$): δ = 1.38 (quintet, *J* = 5.4 Hz, 4 H, $CH_2CH_2CH_2N$), 1.55 (quintet, *J* = 5.1 Hz, 8 H, $CH_2CH_2CH_2N$), 2.41–2.52 (m, 10 H, CH_2N, CH_2CH_2O), 3.08 (s, 4 H, $COCH_2$), 4.31 (t, *J* = 6.3 Hz, 4 H, OCH_2), 6.80–8.46 (m, 8 H, ArH), 9.81 (s, 2 H, NH).

Anal. Calcd for $C_{29}H_{40}N_4O_4$ (508.66): C, 68.48; H, 7.93; N, 11.01. Found: C, 68.40; H, 7.91; N, 11.21.

1,3-Bis[2-(*N*-morpholino)acetamidophenoxy]propane (5b)
By the general procedure, **2a** and morpholine gave crude **5b**, which was crystallized from EtOH to give colorless crystals (70%); mp 176–178 °C.

IR (KBr): 3301 (NH), 1685 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 2.49 (quintet, *J* = 6.2 Hz, 2 H, C$H_2$$CH_2O$), 2.57 (t, *J* = 4.4 Hz, 8 H, CH_2N), 3.15 (s, 4 H, $COCH_2N$), 3.68 (t, *J* = 4.6 Hz, 8 H, OC$H_2$$CH_2N$), 4.32 (t, *J* = 6.4 Hz, 4 H, OCH_2), 6.87–8.47 (m, 8 H, ArH), 9.69 (s, 2 H, NH).

Anal. Calcd for $C_{27}H_{36}N_4O_6$ (512.60): C, 63.26; H, 7.08; N, 10.93. Found: C, 63.11; H, 7.27; N, 10.75).

1,4-Bis[2-(*N*-morpholino)acetamidophenoxy]butane (5c)
By the general procedure, **2b** and morpholine gave crude **5c,** which was crystallized from EtOH to give colorless crystals (65%); mp 140–142 °C.

IR (KBr): 3357 (NH), 1679 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 2.15 (br s, 4 H, C$H_2$$CH_2O$), 2.60 (t, *J* = 4.5 Hz, 8 H, OC$H_2$$CH_2N$), 3.16 (s, 4 H, $COCH_2N$), 3.74 (t, *J* = 4.4 Hz, 8 H, OC$H_2$$CH_2N$), 4.17 (br s, 4 H, OCH_2), 6.87–8.47 (m, 8 H, ArH), 9.65 (br s, 2 H, NH).

Anal. Calcd for $C_{28}H_{38}N_4O_4$ (494.63): C, 67.99; H, 7.74; N, 11.33. Found: C, 67.85; H, 7.69; N, 11.16.

1,3-Bis[2-(*N*,*N*-diethylamino)acetamidophenoxy]propane (6a)
By the general procedure, **2a** and *N*,*N*-diethylamine gave crude **6a**, which was crystallized from EtOH to give colorless crystals (60%); mp 140–142 °C.

IR (KBr): 3305 (NH), 1685 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.07 (t, *J* = 6.9 Hz, 12 H, CH_3), 2.42 (quintet, *J* = 6.3 Hz, 2 H, $OCH_2C$$H_2$), 2.60 (q, 8 H, *J* = 6.9 Hz, CH_2N), 3.18 (s, 4 H, $COCH_2$), 4.31 (t, *J* = 6.3 Hz, 4 H, OCH_2), 6.88–8.49 (m, 8 H, ArH), 9.96 (s, 2 H, NH).

Anal. Calcd for $C_{27}H_{40}N_4O_4$ (484.64): C, 66.92; H, 8.32; N, 11.56. Found: C, 66.81; H, 8.21; N, 11.45.

1,4-Bis[2-(*N*,*N*-diethylamino)acetamidophenoxy]butane (6b)
By the general procedure, **2b** and *N*,*N*-diethylamine gave crude **6b**, which was crystallized from EtOH to give colorless crystals (59%); mp 160–162 °C.

IR (KBr): 3321 (NH), 1682 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.07 (t, *J* = 6.9 Hz, 12 H, CH_3), 2.10 (br s, 4 H, $OCH_2C$$H_2$), 2.61 (q, *J* = 6.9 Hz, 8 H, CH_2N), 3.17 (s, 4 H, $COCH_2$), 4.12 (br s, 4H, OCH_2), 6.86–8.47 (m, 8 H, ArH), 9.45 (s, 2 H, NH).

Anal. Calcd for $C_{28}H_{42}N_4O_4$ (498.66): C, 67.44; H, 8.49; N, 11.24. Found: C, 67.39; H, 8.31; N, 11.39.

2-(*N*-Piperidinoacetoxy)-1,3-bis[2-(*N*-piperidinoacetamido)phenoxy]propane (12a)
By the general procedure, **11** and piperidine gave crude **12a**, which was crystallized from benzene–petroleum ether (bp 40–60 °C) to give colorless crystals (75%); mp 108–110 °C.

IR (KBr): 3319 (NH), 1738, 1689 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.39 (m, 6 H, $NCH_2CH_2C$$H_2$), 1.55 (m, 12 H, $CH_2C$$H_2CH_2N$), 2.48 (m, 12 H, NC$H_2$$CH_2CH_2$), 3.08 (s, 4 H, NCH_2CO), 3.22 (s, 2 H, $OCOCH_2N$), 4.43 (d, *J* = 5.1 Hz, 4 H, OCH_2), 5.61 (quintet, *J* = 5.1 Hz, 1 H, OCH), 6.91–8.45 (m, 8 H, ArH), 9.62 (s, 2 H, NH).

Anal. Calcd for $C_{36}H_{51}N_5O_6$ (649.83): C, 66.54; H, 7.91; N, 10.78. Found: C, 66.66; H, 7.99; N, 10.65.

2-(*N*-Morpholinoacetoxy)-1,3-bis[2-(*N*-morpholinoacetamido)phenoxy]propane (12b)
By the general procedure, **11** and morpholine gave crude **12b**, which was purified using short column of silica gel using EtOAc–*n*-hexane as an eluent to give an oil (70%).

^1H NMR ($CDCl_3$): δ = 2.55 (m, 12 H, NC$H_2$$CH_2O$), 3.04, 3.12 (2 s, 4 H, 2 $COCH_2N$), 3.25 (s, 2 H, $OCOCH_2N$), 3.67 (m, 12 H, OC$H_2$$CH_2N$), 4.42 (d, *J* = 4.9 Hz, 4 H, CH_2O), 5.71 (quintet, *J* = 4.9 Hz, 1 H, OCH), 6.84–8.43 (m, 8 H, ArH), 9.48 (s, 2 H, NH).

Anal. Calcd for $C_{33}H_{45}N_5O_9$ (655.75): C, 60.44; H, 6.92; N, 10.68. Found: C, 60.39; H, 6.86; N, 10.59.

2-Hydroxy-1,3-bis[2-(*N*-morpholino)acetamidophenoxy]propane (13)
By the general procedure, **10** and morpholine gave crude **15**, which was crystallized from benzene to give colorless crystals (65%); mp 172–174 °C.

IR (KBr): 3408 (NH), 3300 (OH), 1684 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 2.55 (t, *J* = 4.5 Hz, 8 H, NC$H_2$$CH_2O$), 3.12 (s, 4 H, $COCH_2N$), 3.38 (br s, 1 H, OH), 3.68 (t, *J* = 4.5 Hz, 8 H, OC$H_2$$CH_2N$), 4.28 (m, 4 H, OCH_2), 4.53 (quintet, *J* = 4.5 Hz, 1 H, OCH), 6.89–8.32 (m, 8 H, ArH), 9.56 (s, 2 H, NH).

Anal. Calcd for $C_{27}H_{36}N_4O_7$ (528.60): C, 61.35; H, 6.86; N, 10.60. Found: C, 61.46; H, 6.91; N, 10.71.

2-(*N*-Morpholinoacetoxy)-1,3-bis[2-(nitrophenoxyacetamido-phenoxy]propane (16)
By the general procedure **15** and morpholine gave crude **16**, which was crystallized from EtOH to give pale yellow crystals (70%); mp 146–148 °C.

IR (KBr): 3364 (NH), 1745, 1688 (C=O), 1528, 1348 cm^{-1} (NO_2).

^1H NMR ($CDCl_3$): δ = 2.46 (m, 4 H, NC$H_2$$CH_2O$), 3.16 (s, 2 H, $COCH_2N$), 3.63 (m, 4 H, OC$H_2$$CH_2N$), 4.46 (m, 4 H, OCH_2), 4.68 (s, 4 H, OCH_2CO), 5.74 (quintet, *J* = 5.1 Hz, 1 H, OCH), 6.85–8.29 (m, 16 H, ArH), 9.01 (s, 2 H, NH).

Anal. Calcd for $C_{37}H_{37}N_5O_{13}$ (759.73): C, 58.50; H, 4.91; N, 9.22. Found: C, 58.45; H, 4.88; N, 9.09.

1,4-Bis{1,3-bis[2-(2-nitophenoxy)acetamidophenoxy]propane-2-yloxycarbonylmethyl}piperazine (17)
By the general procedure **15** and piperazine gave crude **17**, which was crystallized from dioxane–EtOH to give pale yellow crystals (65%); mp 194–196 °C.

IR (KBr): 3381 (NH), 1743, 1692 (C=O), 1526, 1346 cm^{-1} (NO_2).

^1H NMR ($CDCl_3$): δ = 2.43 (s, 8 H, CH_2N), 3.12 (s, 4 H, $COCH_2N$), 4.43 (m, 8 H, OCH_2), 4.69 (s, 8 H, OCH_2CO), 5.74 (quintet, *J* = 5.1 Hz, 2 H, OCH), 6.82–8.29 (m, 32 H, ArH), 9.09 (s, 4 H, NH).

^{13}C NMR (APT pulse sequence, $CDCl_3$): δ = 51.41, 57.83, 66.19, 66.82, 67.84, 126.35, 138.73, 147.77, 150.18, 164.85 (C and CH_2), 69.82, 71.55, 112.19, 115.52, 120.76, 121.33, 124.54, 125.23, 134.62 (CH).

Anal. Calcd for $C_{70}H_{66}N_{10}O_{24}$ (1431.34): C, 58.74; H, 4.65; N, 9.79. Found: C, 58.60; H, 4.70; N, 9.84.

15-[(*N*,*N*-Diethylamino)acetoxy]-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo[*b*,*h*,*p*,*v*][1,7,18,24,4,11,14,21]tetraoxatetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone(20a)
By the general procedure, **19a** and *N*,*N*-diethylamine gave crude **20a**, which was crystallized from $CHCl_3$–petroleum ether (bp 40–60 °C) to give colorless crystals (60%); mp 182–84 °C.

IR (KBr): 3391, 3350 (NH), 1743, 1688, 1644 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 6 H, CH_3), 2.42 (q, *J* = 7 Hz, 4 H, C*H*$_2$CH$_3$), 2.97 (s, 2 H, COC*H*$_2$N), 3.75 (m, 4 H, C*H*$_2$NH), 3.96 (d, *J* = 5.8 Hz, 4 H, OCH_2), 4.78 (d, *J* = 15.3 Hz, 2 H, upfield of OCH_2CO), 4.94 (d, *J* = 15.3 Hz, 2 H, downfield of OCH_2CO), 5.45 (quintet, *J* = 5.5 Hz, 1 H, CHO), 6.62–8.89 (m, 20 H, ArH + NH).

MS: *m*/*z* (%) = 768 (M + 1, 0.5), 665 (0.5), 521 (1), 413 (2.1), 326 (2), 300 (10), 140 (32), 85 (100).

Anal. Calcd for $C_{41}H_{45}N_5O_{10}$ (767.83): C, 64.14; H, 5.91; N, 9.12. Found: C, 64.34; H, 5.99; N, 9.24.

15-Morpholinoacetoxy-6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo[*b,h,p,v*][1,7,18,24,4,11,14,21]tetraoxatetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone (20b)

By the general procedure **19a** and morpholine gave crude **20b**, which was crystallized from MeOH to give colorless crystals (65%); mp 184–186 °C.

IR (KBr): 3384, 3335 (NH), 1729, 1692, 1636 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 2.33 (t, *J* = 4.5 Hz, 4 H, NC*H*$_2$CH$_2$O), 2.84 (s, 2 H, COC*H*$_2$N), 3.58 (t, *J* = 4.5 Hz, 4 H, OC*H*$_2$CH$_2$N), 3.74 (br s, 4 H, C*H*$_2$NHCO), 3.95 (d, *J* = 5.7 Hz, 4 H, OCH_2), 4.73 (d, *J* = 15 Hz, 2 H, upfield of OCH_2CO), 4.92 (d, *J* = 15 Hz, 2 H, downfield of OCH_2CO), 5.38 (quintet, *J* = 5.7 Hz, 1 H, CHO), 6.73–8.26 (m, 16 H, ArH), 8.33 (br s, 2 H, CON*H*CH$_2$), 8.85 (s, 2 H, CH$_2$CON*H*).

^{13}C NMR (APT pulse sequence, $CDCl_3$): δ = 41.12, 53.03, 58.9, 66.54, 66.87, 68.85, 122.29, 126.69, 145.35, 147.08, 155.41, 165.9, 166.09 (C and CH_2), 70.05, 111.42, 112.4, 121.12, 121.82, 122.29, 124.66, 131.84, 132.77 (CH).

MS: *m*/*z* (%) = 780 (M – 1, 7.1), 715 (7), 604 (13), 552 (17.2), 423 (15.4), 333 (11), 281 (23), 262 (100), 183 (24).

Anal. Calcd for $C_{41}H_{43}N_5O_{11}$ (781.82): C, 62.99; H, 5.54; N, 8.96. Found: C, 63.05; H, 5.50; N, 8.72.

15-Piperidinoacetoxy-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*b,h,q,w*][1,7,19,25,4,11,15,22]tetraoxatetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (20c)

By the general procedure **19b** and piperidine gave crude **20c**, which was crystallized from EtOH to give colorless crystals (60%); mp 192–194 °C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.34 (m, 2 H, C*H*$_2$CH$_2$CH$_2$N), 1.40–1.49 (m, 4 H, CH$_2$*CH*$_2$CH$_2$N), 1.9 (br s, 2 H, NCH$_2$C*H*$_2$CH$_2$N), 2.23 (t, *J* = 4.8 Hz, 4 H, NC*H*$_2$CH$_2$CH$_2$), 2.85 (s, 2 H, COC*H*$_2$N), 3.49–3.60 (m, 2 H, NCH_2), 3.70–3.79 (m, 2 H, NCH_2), 3.87–4.0 (m, 4 H, OCH_2), 4.82 (d, *J* = 15.3 Hz, 2 H, downfield of OCH_2CO), 4.97 (d, *J* = 15.3 Hz, 2 H, upfield of OCH_2CO), 5.36 (quintet, *J* = 5.4 Hz, 1 H, CHO), 6.71–8.25 (m, 18 H, ArH and CON*H*CH$_2$), 8.99 (s, 2 H, CH$_2$CON*H*).

^{13}C NMR ($CDCl_3$): δ = 23.23, 25.69, 30.09, 36.27, 54.03, 59.57, 67.01, 69.39, 69.75, 111.34, 112.64, 121.52, 121.73, 122.30, 122.77, 124.82, 126.65, 132.04, 132.66, 147.39, 155.41, 165.61, 166.19, 169.72.

Anal. Calcd for $C_{43}H_{47}N_5O_{10}$ (793.87): C, 65.06; H, 5.97; N, 8.82. Found: C, 64.90; H, 5.67; N, 8.75.

15-Morpholinoacetoxy-6,14,15,24,32,33-hexahydro-16*H*,34*H*-tetrabenzo[*b,h,q,w*][1,7,19,25,4,11,15,22]tetraoxatetraazacyclooctacosin-7,23,30,36-(8*H*,22*H*,31*H*,35*H*)tetraone (20d)

By the general procedure **19b** and morpholine gave crude **19b**, which was crystallized from EtOH to give colorless crystals (65%); mp 217–219 °C.

IR (KBr): 3389, 3335 (NH), 1769, 1697 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.83 (m, 2 H, *CH*$_2$CH$_2$N), 2.30 (t, *J* = 4.5 Hz, 4 H, NC*H*$_2$CH$_2$O), 2.84 (s, 2 H, COC*H*$_2$N), 3.50–3.58 (m, 6 H, 4 H of OC*H*$_2$CH$_2$N and 2 H of NC*H*$_2$), 3.70–3.85 (m, 2 H, NC*H*$_2$), 3.86–4.00 (m, 4 H, OCH_2), 4.84 (d, *J* = 15.3 Hz, 2 H, downfield of OCH_2CO), 4.99 (d, *J* = 15 Hz, 2 H, upfield of OCH_2CO), 5.34 (quintet, *J* = 5.7 Hz, 1 H, CHO), 6.71–8.27 (m, 16 H, ArH), 8.20 (t, *J* = 6 Hz, 2 H, CON*H*CH$_2$), 8.98 (s, 2 H, CH$_2$CON*H*).

MS: *m*/*z* (%) = 795 (M^+, 11), 777 (23), 584 (17), 337 (25), 186 (100), 113 (88).

Anal. Calcd for $C_{42}H_{45}N_5O_{11}$ (795.85): C, 63.39; H, 5.70; N, 8.80. Found: C, 63.45; H, 5.55; N, 8.70.

1,4-Bis{6,14,15,24,32,33-hexahydro-16*H*-tetrabenzo[*b,h,p,v*]-[1,7,18,24,4,11,14,21]tetraoxatetraazacycloheptacosin-7,23,30,35-(8*H*,22*H*,31*H*,34*H*)tetraone-15-yloxycarbonylmethyl}piperazine (21)

By the general procedure **19a** and piperazine gave crude **21**, which was crystallized from dioxane to give pale yellow crystals (50%); mp 248–250 °C.

IR (KBr): 3392, 3325 (NH), 1760, 1693, 1635 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 2.22 (br s, 8 H, CH_2N), 2.99 (br s, 4 H, COC*H*$_2$N), 3.51 (br s, 8 H, C*H*$_2$NHCO), 4.31 (br s, 8 H, OCH_2), 4.33 (s, 8 H, OCH_2CO), 5.55 (br s, 2 H, OCH), 6.94–7.89 (m, 32 H, ArH), 8.71 (br s, 4 H, CON*H*CH$_2$), 9.39 (s, 4 H, CH$_2$CON*H*).

^{13}C NMR (DMSO-d_6): δ = 51.46, 57.96, 67.42, 67.84, 69.85, 113.09, 113.36, 120.96, 121.33, 122.20, 124.17, 125.02, 126.59, 130.04, 131.82, 148.71, 154.94, 165.49, 166.29, 169.20.

Anal. Calcd for $C_{78}H_{78}N_{10}O_{20}$ (1475.53): C, 63.49; H, 5.33; N, 9.49. Found: C, 63.33; H, 5.29; N, 9.52.

References

(1) Irie, S.; Yamamoto, M.; Kishikawa, K.; Kohmoto, S.; Yamada, K. *Synthesis* **1995**, 1179.
(2) Fujita, T.; Lehn, J. M. *Tetrahedron Lett.* **1988**, *29*, 1122.
(3) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1035.
(4) Grammenudi, S.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1122.
(5) Pioget, T.; Duriez, M. C.; Picard, C.; Cazaux, L.; Tisnes, P. *Tetrahedron* **1992**, *48*, 4359.
(6) Cazaux, L.; Duriez, M. C.; Picard, C.; Tisnes, P. *Tetrahedron Lett.* **1989**, *30*, 1369.
(7) Cazaux, L.; Picard, C.; Pigot, T.; Tisnes, P. *Tetrahedron Lett.* **1991**, *32*, 919.
(8) Nakatsuji, Y.; Kobayashi, H.; Okahara, M.; Matsushima, K. *Chem. Lett.* **1982**, 1571.
(9) Maruizumi, T.; Wegmann, D.; Suter, G.; Ammann, D.; Simon, W. *Mikrochim. Acta* **1986**, *63*, 2271.
(10) Kataky, R.; Nicholson, P. E.; Paeker, D.; Covington, A. K. *The Analyst* **1991**, *116*, 135.
(11) Erne, D.; Stojanac, N.; Ammann, D.; Hofstetter, P.; Pretsch, E.; Simon, W. Helv. Chim. acta **1980**, *63*, 2271.
(12) Schefer, U.; Ammann, D.; Pretsch, E.; Oesch, U.; Simon, W. *Anal. Chem.* **1986**, *58*, 2282.
(13) Collins, T. J.; Kostka, K. L.; Munck, E.; Uffelman, E. S. *J. Am. Chem. Soc.* **1990**, *112*, 5637.
(14) Kimura, E. *Pure Appl. Chem.* **1989**, *61*, 823.
(15) Kimura, E.; Kurogi, Y.; Wada, S.; Shionoya, M. *J. Chem. Soc., Chem. Commun.* **1989**, 781.
(16) Gordon, W.; Scott, W.; Collins, T. J. US Patent 6051704, **2000**; *Chem. Abstr.* **2000**, *132*, 273412.
(17) Kumar, S.; Hundal, M. S.; Hundal, G.; Kaur, N.; Singh, H. *Tetrahedron* **1997**, *53*, 10841.
(18) Kumar, S.; Hundal, G.; Kaur, N.; Hundal, M. S.; Singh, H. *Tetrahedron Lett.* **1997**, *38*, 131.
(19) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.* **1989**, *89*, 929.

(20) Dietrich, B. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon: New York, **1996**, 153–212.
(21) Krakowiak, K. E.; Bradshaw, J. S.; Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3364.
(22) Metzger, E.; Ammann, D.; Schefer, U.; Pretsch, E.; Simon, W. *Chimia* **1984**, *38*, 440.
(23) Metzger, E.; Ammann, D.; Asper, R.; Simon, W. *Anal. Chem.* **1986**, *58*, 132.
(24) Kataky, R.; Nicholson, P. E.; Paeker, D. *Tetrahedron Lett.* **1989**, *30*, 4554.
(25) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1053.
(26) Gokel, G. W. *Chem. Soc. Rev.* **1992**, *21*, 39.
(27) Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6659.
(28) Gokel, G. W.; Arnold, K. A.; Cleary, T.; Friese, R.; Gatto, V.; Goli, D.; Hanlon, C.; Kim, M.; Miller, S.; Ouchi, M.; Posey, I.; Sandler, A.; Viscariello, A.; White, B.; Wolfe, J.; Yoo, H. In *ACS Symposium Series, 326: Phase-Transfer Cataysis - New Chemistry, Catalysts, and Applications*; Starks, C. M., Ed.; ACS: Washington DC, **1987**, 24.
(29) Goto, Y.; Kohno, Y.; Fukuda, W.; Tomoi, Y. *J. Polymer Science: Part A: Polymer Chemistry* **1994**, *32*, 1543.
(30) Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **2000**, *56*, 885.
(31) Ibrahim, Y. A.; Elwahy, A. H. M.; Abass, A. A. *J. Chem. Res., Synop.* **1998**, 548.
(32) Ibrahim, Y. A.; Elwahy, A. H. M.; Abass, A. A.; Kassab, R. M. *J. Chem. Res., Synop.* **1999**, 522.
(33) Elwahy, A. H. M.; Abass, A. A.; Kassab, R. M. *Heteroatom Chem.* **2003**, *14*, 551.
(34) Abbas, A. A. *Tetrahedron* **1997**, *54*, 12421.
(35) Ibrahim, Y. A.; Elwahy, A. H. M. *Synthesis* **1993**, 503.
(36) Wong, K. H.; Bourgoin, M.; Smid, J. *J. Chem. Soc., Chem. Commun.* **1974**, 715.
(37) Bourgoin, M.; Wong, K. H.; Hui, J. Y.; Smid, J. *J. Am. Chem. Soc.* **1975**, *97*, 3462.
(38) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **1994**, *50*, 11489.
(39) Ibrahim, Y. A.; Elwahy, A. H. M.; Barsom, B. N.; Abbas, A. A.; Khella, S. K. *Talanta* **1998**, *47*, 1199.
(40) Djurendic, E. A.; Sauranyj, T. M.; Miljkovic, D. A. *Coll. Czech. Chem. Commun.* **990**, *55*, 1763.