A Facile and Efficient Synthetic Approach to Novel Lariat Macrocyclic Diamides and Bis Macrocyclic Diamides

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The hydroxy macrocycles **8**, **19a-c** were prepared in 40-55% yields by reacting the dipotassium salts **2a-c** with each of epichlorohydrin (**7**) and bis(chloromethyl) derivative **18**. Acylation of the hydroxyl group of each of **8**, **19a-c** with 2-chloroacetylchloride (**9**) in DMF gave the corresponding esters **10**, **20a,b**. Reaction of the latter with different amines as well as phenoxides furnished exclusively the target lariat macrocycles **13a-c**, **22a-c** and **23a-c** in 60-63% and 50-55% yields, respectively. Amination of two equivalents of the chloroacetyloxy derivative **10** and **2a,b** with 1 equiv. of piperazine (**12c**) afforded the corresponding bis-macrocycles **14** and **26a,b** respectively, in 60-65% yields. Moreover, the novel bis(macrocycles) **27-29** were prepared in 45-50% yields, respectively, by reacting each of **20a,b** with the dipotassium salts **2b**, **24** and **25** respectively, in DMF.

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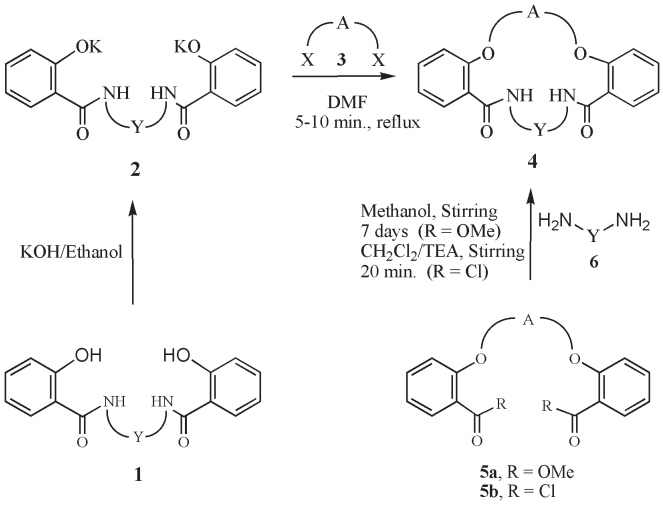
Introduction.

Since Pedersen [1,2] reported the synthesis and complexing properties of crown ethers, the influence of structure variation within such ligands have received much attention [3,4]. One of such structural variation is the replacement of oxygen with nitrogen and/or sulfur [5,6]. Another is the development of functional groups in the macrocyclic receptors, for example, incorporation of an amide linkage in a polyether macrocycle has been reported to modify the binding properties of crown ether compounds to favor alkali and alkaline earth cations [6-8]. Moreover macrocyclic amides are precursors in the preparation of azacrown compounds, which are used for the synthesis of cryptands [9,10]. Furthermore, insertion of aromatic rings into the macrocyclic ring was reported to facilitate the modification of macrocyclic hosts with various UV and/or fluorescent active groups [11], proton ionizable fragments [12] and functional groups, which can be attached to proteins to provide radionuclide carriers for medicals diagnosis and therapy [13]. In addition, attachment of a functional side arm to the ligand framework which provides the potential for three dimentional complexation of metal ions have attracted much interest in the last decades [14-19]. If the side arm attached site is a carbon atom of the macrocycle, the ligand is called a *C*-pivot lariat ether. If it is a nitrogen atom of an azacrown ether, the ligand is identified as *N*-pivot lariat ether. Moreover, recent attention has also been given to bis(macrocycles) which are capable of binding simultaneously to two or more metal ions [20-22]. One interest in such systems have reflected their potential for exhibiting cooperative behavior of the type found in particular metaloenzymes incorporating two metal centres [23]. A number of such compounds have been observed to act as anti-HIV agents, which exhibiting low cytotoxicity [24]. Many other linked mixed-donor macrocycles are also known and open possibilities in cooperative receptors and switching materials [25-31]. In connection with these findings and in continuation of our interest in synthesizing macrocyclic di- and tetralactams [32-38], and bis macrocycles [39-41] we report here on the synthesis of novel lariat macrocyclic diamides as well as bis(macrocyclic diamides) with enhanced cation binding properties compared with their corresponding precursors.

Results and Discussion.

Recently [32-36] we reported the synthesis of a series of benzo-substituted macrocyclic diamides of type **4** by reacting the appropriate dipotassium salt **2** (obtained upon treatment of the bis phenols **1** with the corresponding dihalo or ditosylate compounds **3** as outlined in Scheme 1. Other research groups [42-44] reported the synthesis of **4** by reacting the appropriate α,β-dicarboxylic acid derivatives (diester **5a**, or diacid dichloride **5b**) with various diamines **6**. Some macrocyclic diamide derivatives have also recently been used as new catalysts in the highly regioselective cleavage of epoxides with elemental halogens [44]. To improve the cation binding abilities of the macrocycles **4** our attention focused on functionalizing them with ligating side arms. We have also planned to study the connecting of two units of these macrocycles by a flexible bridge aiming at the synthesis of the first bis (macrocyclic diamides) which should show promising analytical uses on account of their capability of binding two or more metal ions. For this purpose macrocyclic diamide with pendant hydroxyl group **8** was prepared by reacting the potassium salt **2** (obtained upon treatment of **1** with methanolic potassium hydroxide solution) with epichlorohydrin (**7**) in aqueous media as depicted in Scheme 2.

Scheme 1

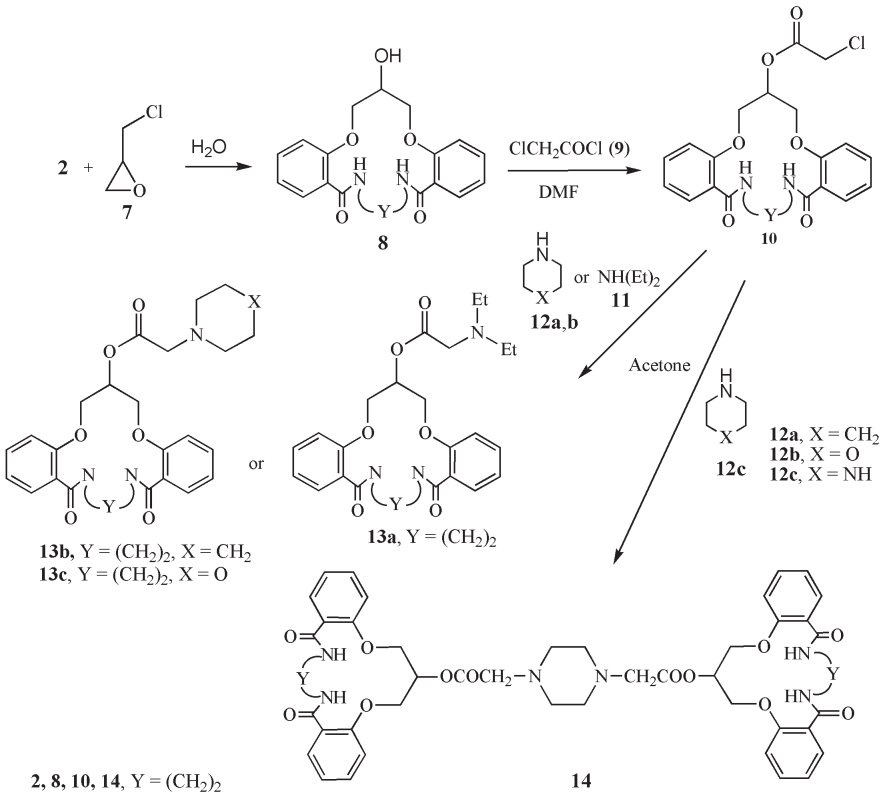


Acylation of the hydroxy group of compounds **8** with 2-chloroacetylchloride (**9**) in DMF afforded the corresponding chloroacetoxy macrocycles **10** in 70% yields. The latter compound could be used as a key intermediate for the synthesis of lariat macrocycles **13a-c**. Thus, reaction of compounds **10** with a series of secondary amines namely, diethyamine (**11**), piperidine (**12a**) and morpholine (**12b**) in acetone for 2 h furnished 60-65% yields of the corresponding lariat macrocycles **13a-c**. The novel bis macrocycles **14** were obtained in 60% yields by reacting 2 equiv. of **10** with 1 equiv. of piperazine (**12c**) in refluxing acetone (Scheme 2).

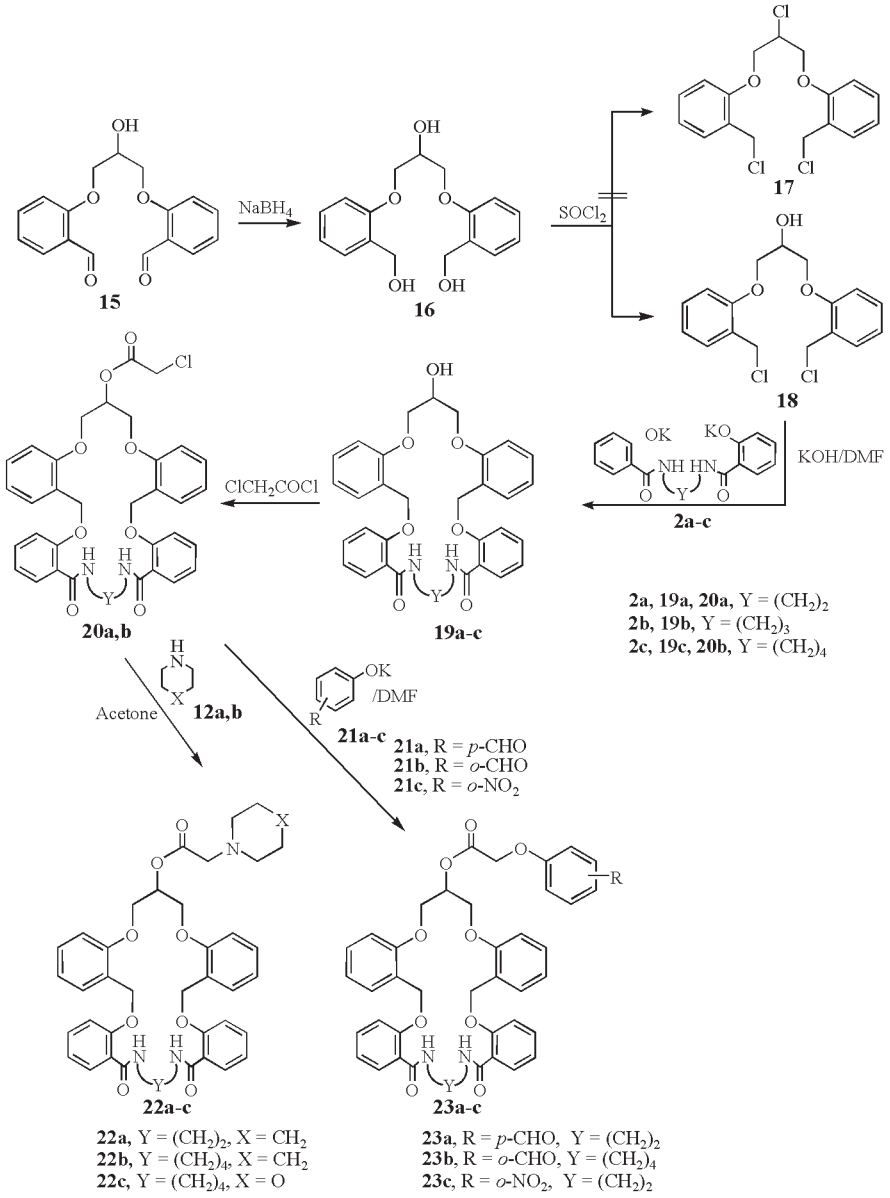
In an attempt to extend the spacing between the terminal bis functional group in compounds **3** and to increase the intervening ether functions we reported also the synthesis of the novel macrocyclic diamides **19** as outlined in Scheme 3. Thus, reduction of the bis aldehyde **15** [39] with $NaBH_4$ in refluxing methanol gave the corresponding bis(hydroxymethyl) ether **16** in 75% yield. Treatment of the latter compound with $SOCl_2$ in chloroform gave the corresponding bis(chloromethyl) ethers **18** in 65% yield. It is noteworthy to mention that the ^{1}H-NMR spectrum of the crude product indicate the absence of the trichloro derivative **17**. The macrocycles **19** could be obtained in 40-55% yields by heating **18** with the dipotassium salts **2** in refluxing DMF. Acylation of the hydroxy group of compounds **19a,c** with 2-chloroacetylchloride (**9**) in DMF afforded the corresponding chloroacetyloxy macrocycles **20a,b** in 60-62% yields.

The reactivities of **20a,b** towards different nucleophiles were investigated aiming at the preparation of their lariat analogues as well as their bis-macrocyclic derivatives. Thus, compounds **20** react exclusively with piperidine (**12a**) and morpholine (**12b**) to give the corresponding amino derivatives **22a-c** in 60-63% yields,

Scheme 2



Scheme 3



respectively. Moreover, compound **20a,b** reacted successfully with the potassium salts **21a-c** (obtained upon treatment of the corresponding phenol with methanolic KOH) in DMF to give the corresponding lariat derivatives **23a-c** in 50-55% yields, respectively. The now available chloroacetoxy macrocycles **20a,b** and its successful reaction with amines as well as phenols, to give the corresponding lariat macrocycles prompted us to study its reaction with diamines, dihydroxy arenas and bis phenols aiming at preparing a new series of novel bis-macrocyclic diamines. Thus, reaction of **20a,b** with piperarazine in boiling acetone gave the corresponding bis(macrocycles) **26a,b** in 62% and 60% yields, respectively, as outline in Scheme 4.

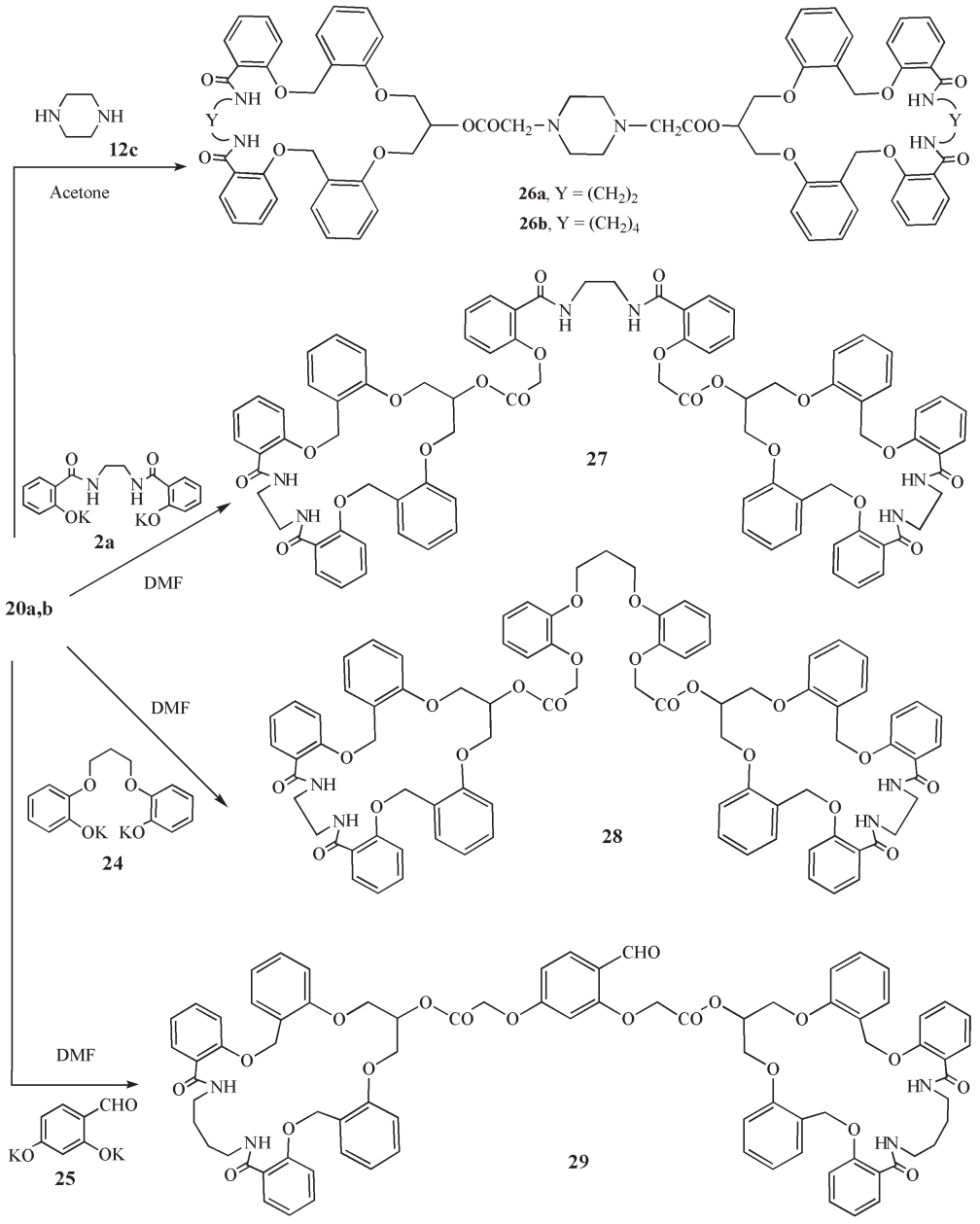
Moreover, the novel bis(macrocycles) **27-29** could be prepared in 45-52% yields by reacting **20a,b** with the dipotassium salts **2a**, **24** and **25**, respectively, in DMF as shown in Scheme 4. The salts **24** and **25** were obtained directly from the corresponding bis-phenols upon treatment with methanolic KOH. The successful synthesis of the new bis-macrocycles **27** and **28** from the reaction of **20a,b** with the appropriate bis-phenols should open new access to novel heteronuclear metal ion receptors.

The structures of all the new compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses data. A comparison of the ^{1}H NMR and ^{13}C NMR spectra of the macrocycles **4** (A = $(CH_2)_n$, n = 2-5, *o*-CH_2-C_6H_4-CH_2, *m*-CH_2-C_6H_4-CH_2, *etc*; Y = $(CH_2)_n$, n = 2-4) [32-34]

with the new macrocycles **8, 13, 14, 19, 22, 23, 26-29** reveals some interesting conclusions:- 1) The magentic equivalence of the OCH_2 and NCH_2 protons in compounds **4** indicate rapid conformational change in these macrocyles; 2) Contorary to compounds **4**, the hydroxyl substituted macrocyles **8**, **19**, the chloroacetoxy macrocycles **10**, **20**, the lariat macrocycles **13**, **22**, **23** and the bis-macrocycles **14**, **26-29** 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. 3) Evidence for the existence of the new macrocyles entirely as one stable non-convertible conformer comes from ^{13}C NMR data (*c.f.* Experimental).

In conclusion we prepared a new series of macrocyclic diamides having pendant hydroxyl group and utilized them successfully as a key intermediate for the synthesis of novel lariat macrocyclic dilactams containing strong donor atoms as a supporting ligand at the end of the side-arm. We expect this should improve the binding abilities of the new macrocycles compared to their corresponding precursors where the side arm can effectively participate in the coordination and lead to higher cation-binding. We also prepared a series of novel bis macrocycles in which two

Scheme 4



macrocyclic dilactam units are connected by a flexible bridge. We believe that these new series of compounds should exhibit useful analytical uses on account of their abilities to bind two or more metal ions. The new synthesized macrocycles offer an advantage due to their easy synthesis on a large scale in a simple procedure from inexpensive starting materials. Study of the cation binding properties of the new macrocycles is still underway.

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 pulse sequence. Mass spectra were recorded on HP 5988A (EI, 15 eV). 1,2-Diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane and epichlorohydrin were used as purchased from Aldrich. The starting compound **15** were prepared as reported [39].

1,3-Bis(2-hydroxymethylphenoxy)propan-2-ol (**16**).

To a hot stirred solution (50 °C) of the bis(carbonyl) ethers **15** (10 mmol) in methanol (15 mmol) was added solid sodium borohydride (20 mmol) over a period of 10 minutes. The reaction mixture was heated under reflux for 1 h. The solvent was then removed *in vacuo* and the remaining material was washed with water. The solid obtained was collected and crystallized from toluene to give colorless crystals (75%), mp.125 °C; IR (cm^{-1}) 3425, 3279 (OH); ^{1}HNMR ($CDCl_3$) δ 3.43 (brs, 2H, CH_2OH), 4.10-4.21 (m, 4H, CH_2O), 4.33 (brs, 1H, CHOH), 4.62 (s, 4H, CH_2Ar), 4.97 (brs, 1H, OH), 6.85-7.28 (m, 8H, ArH's).

Anal. Calcd for $C_{17}H_{20}O_5$ (304.34): C, 67.09; H, 6.62. Found: C, 66.90; H, 6.80.

1,3-Bis(2-chloromethylphenoxy)propan-2-ol (**18**).

To a cold stirred solution (-2 °C) of **16** (10 mmol) in chloroform (100 ml) was added dropwise thionyl chloride (5 ml). Stirring was continued for 2 h at 0 °C. The solvent was then removed *in vacuo* and the remaining residue was collected and crystallized from benzene/petroleum ether (40-60) mixture as colorless crystals (65%), mp. 70-72 °C; IR (cm^{-1}) 3287 (OH); ^{1}H NMR ($CDCl_3$) δ 2.93 (d, 1H, *J* = 5.7 Hz, OH), 4.30 (d, 4H, *J* = 5.6 Hz, OCH_2), 4.48 (m, 1H, CHOH), 4.66 (s, 4H, CH_2Cl), 6.94-7.35 (m, 8H, ArH's).

Anal. Calcd for $C_{17}H_{18}O_3Cl_2$ (341.233): C, 59.84; H, 5.32. Found: C, 59.70; H, 5.60.

Preparation of the Potassium Salts **2a-c, 21a-c, 24** and **25**.

To a solution of KOH (1.14 g, 10 mmol) in methanol (10 ml) was added each of salicylaldehyde, *o*-nitrophenol and *p*-hydroxybenzaldehyde (10 mmol) or bis-phenols **1a-c**, **24** and **25** (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.

17-Hydroxy-5,6,7,8,9,10,17,18-octahydro-16*H*-dibenzo[*b*,*j*]-[1,12,5,8]dioxadiazacyclopentadecine-5,10-dione (**8**).

A solution of **1** [Y = $(CH_2)_2$] (10 mmol), NaOH (20 mmol) and water 200 ml are stirred at 90 °C until solution is achieved. After the solution is cooled to 50 °C, epichlorohydrin (**7**) (10 mmol) was added over a period of 3 h. Upon completion of the addition, the reaction mixture is stirred at 50 °C for an additional 3-5 h and then cooling to room temperature. The solid obtained was collected by filtration and crystallized from ethanol as colorless crystals, mp. 216-218 °C;^{1}H NMR ($CDCl_3$): δ 3.38–3.66 (m, 4H, $NHCH_2$), 4.20- 4.42 (m, 4H, OCH_2), 4.36 (m, 1H, CH-O), 5.78 (d, 1H, *J* = 3.9 Hz, OH), 7.05-7.84 (m, 8H, ArH's), 8.5 (brs, 2H, NH).

Anal. Calcd for $C_{19}H_{20}N_2O_5$ (356.37): C, 64.04; H, 5.66; N, 7.86. Found: C, 64.30; H, 5.70; N, 8.00.

Synthesis of macrocycles **19a-c**.

General Procedure.

A solution of the appropriate potassium salts of **2a-c** (10 mmol) and the dichloro compound **18** (10 mmol) in DMF (20 ml) was heated under reflux for 10 min. during which time KCl was precipitated. The solvent was then removed *in vacuo* and the remaining material was washed with water (50 ml) and purified to give compounds **19a-c**.

13-Hydroxy-6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo-[*b*,*f*,*n*,*r*][1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dione (**19a**).

With the use of the general procedure **2a** and **18** gave crude **19a** which was crystallized from dioxane as colorless crystals (55%), mp. 284-286 °C; IR (cm^{-1}) 3363 (broad, OH, NH), 1640 (C=O); MS: m/z 568 (M^+, 12%), 447 (13%), 404 (10%), 300 (100%), 250 (13%), 162 (50%), 150 (70%);^{1}H NMR (DMSO): δ 3.15 (brs, 4H, NCH_2), 3.92-4.1 (m, 5H, OCH_2, CHOH), 5.01-5.21 (m, 4H, OCH_2Ar), 5.42 (d, 1H, *J* = 4.4 Hz, OH), 6.66-7.90 (m, 18H, ArH's, NH).

Anal. Calcd for $C_{33}H_{32}N_2O_7$ (568.625): C, 69.71; H, 5.67; N, 4.93. Found: C, 69.80; H, 5.90; N, 5.10.

13-Hydroxy-6,12,13,20,28,29-hexahydro-14*H*,30*H*-tetrabenzo[*b*,*f*,*o*,*s*][1,5,17,21,9,13]tetraoxadiazatetracosin-26,32-(27*H*,31*H*)dione (**19b**).

With the use of the general procedure **2b** and **18** gave crude **19b** which was crystallized from ethanol as colorless crystals (35%), mp. 238-240 °C; IR (cm^{-1}) 3381 (broad, OH, NH), 1641 (C=O); MS: m/z 582 (M^+, 9%), 461 (23%), 404 (38%), 314 (64%), 269 (100%), 194 (12%), 132 (23%);^{1}H NMR ($CDCl_3$): δ 1.15 (quintet, 2H, *J* = 6.3 Hz, NCH_2CH_2), 2.46 (d, 1H, *J* = 6.2 Hz, OH), 2.61-2.71 (m, 4H, NCH_2CH_2), 4.03 (d, 4H, *J* = 4.8 Hz, OCH_2), 4.18 (brs, 1H, CHOH), 5.07 (d, 2H, *J* = 9.1 Hz, upfield of OCH_2Ar), 5.12 (d, 2H, *J* = 9.2 Hz, downfield of OCH_2Ar), 6.62-8.26 (m, 16H, ArH's), 7.65 (t, 2H, *J* = 5.4 Hz, NH).

Anal. Calcd for $C_{34}H_{34}N_2O_7$ (582.652): C, 70.09; H, 5.88; N, 4.81. Found: C, 70.20; H, 6.10; N, 4.60.

13-Hydroxy-6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo[*b*,*f*,*p*,*t*][1,5,18,22,9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dione (**19c**).

With the use of the general procedure **2c** and **18** gave crude **19c** which was crystallized from dioxane as colorless crystals (40%), mp. 254-256 °C; IR (cm^{-1}) 3380 (broad, OH, NH), 1641(C=O); MS: m/z 596 (M^+, 7%), 404 (23%), 328 (100%), 251 (4%), 208

(10%), 120 (37%);^{1}H NMR (DMSO): δ 0.79 (brs, 4H, NCH_2CH_2), 2.87 (brs, 4H, NCH_2), 3.82-3.99 (m, 5H, OCH_2, CHOH), 5.13 (d, 2H, *J* = 9.5 Hz, upfield of OCH_2Ar), 5.19-5.28 (m, 3H, downfield of OCH_2Ar, OH), 6.59-8.06 (m, 16H, ArH's), 7.69 (brs, 2H, NH).

Anal. Calcd for $C_{35}H_{36}N_2O_7$ (596.678): C, 70.45; H, 6.08; N, 4.69. Found: C, 70.60; H, 6.10; N, 4.90.

Reaction of Chloroacetyl Chloride with **8** and **19a,c**. (Synthesis of Compounds **10** and **20a,b**).

General Procedure.

To a solution of each of **8** and **19a,c** (5 mmol) in DMF (10 ml) was added chloroacetyl chloride (**9**) (12 mmol). The reaction mixture was stirred at room temperature for 2 h then poured on crushed ice. The solid obtained was collected by filtration and crystallized from the proper solvent for each derivative to afford compounds **10** and **20a,b**.

17-Chloroacetoxy-5,6,7,8,9,10,17,18–octahydro-16*H*-dibenzo-[*b,j*][1,12,5,8]dioxadiazacyclopentadecine-5,10-dione (**10**).

With the use of the general procedure, **8** gave crude **10** which was crystallized from ethanol as colorless crystals (70%), mp. 152 °C;^{1}H NMR ($CDCl_3$): δ 3.64-3.83 (m, 4H, $NHCH_2CH_2NH$), 4.42- 4.56 (m, 4H, OCH_2), 4.17 (s, 2H, $OCOCH_2Cl$), 5.56 (quintet, 1H, *J* = 6.0 Hz, CH-O), 7.02-8.09 (m, 10H, ArH's, NH).

Anal. Calcd for $C_{21}H_{21}N_2O_6Cl$ (432.86): C, 58.27; H, 4.89; N, 6.47. Found: C, 58.40; H, 4.70; N, 6.70.

13-Chloroacetoxy-6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo-[*b,f,n,r*][1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)-dione (**20a**).

With the use of the general procedure **19a** gave crude **20a** which was crystallized from benzene as colorless crystals (60%), mp. 90-92 °C; IR (cm^{-1}) 3374 (NH), 1760 (OCO), 1650 (CO, amide); MS: m/z 645 (M^+, 2.5%), 523 (6%), 374 (8%), 300 (33%), 251 (9.5%), 147 (100%), 121 (64%);^{1}H NMR ($CDCl_3$): δ 3.13 (s, 4H, NCH_2), 3.92-3.98 (m, 4H, OCH_2), 4.02 (s, 2H, CH_2Cl), 5.0-5.07 (m, 4H, OCH_2Ar), 5.27 (quintet, 1H, *J* = 4.2 Hz, CHOCO), 6.25-8.23 (m,16H, ArH's), 7.59 (brs, 2H, NH).

Anal. Calcd for $C_{35}H_{33}N_2O_8Cl$ (645.107): C, 65.17; H, 5.16; N, 4.34. Found: C, 65.20; H, 5.30; N, 4.50.

13-Chloroacetoxy-6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo[*b,f,p,t*][1,5,18,22,9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dione (**20b**).

With the use of the general procedure **19c** gave crude **20b** which was crystallized from benzene as colorless crystals (65%), mp. 212-214 °C; MS: m/z 673 (M^+, 2.3%), 551 (6%), 480 (8%), 404 (8%), 328 (37%), 251 (49%), 147 (100%); ^{1}H NMR ($CDCl_3$): δ 0.74 (s, 4H, NCH_2CH_2), 2.98 (m, 4H, NCH_2), 3.88 (s, 2H, CH_2Cl), 3.98-4.11 (m, 4H, OCH_2), 5.11 (s, 4H, OCH_2Ar), 5.19 (quintet, 1H, *J* = 3 Hz, CHOCO), 6.59-8.38 (m, 16H, ArH's), 7.74 (brs, 2H, NH).

Anal. Calcd for $C_{37}H_{37}N_2O_8Cl$ (673.161): C, 66.02; H, 5.54; N, 4.16. Found: C, 65.90; H, 5.60; N, 4.30.

Reaction of Compounds **10** and **20a,b** with Secondary Amines (Synthesis of Compounds **13a-c, 14, 22a-c** and **26a,b)**.

General Procedure.

A mixture of each of **10**, and **20a,b** (5 mmol) and excess of the appropriate secondary amines (*N*,*N*-diethylamine (**11**), piperidine (**12a**), morpholine (**12b**) or [(6 mmol) of compounds **10, 20a,b** and (3 mmol) of piperazine (**12c**) and few drops of triethylamine for synthesis of compounds **14**, **26a,b**] in acetone (50 ml) was heated under reflux for 10 min, then stirring at rt over night. [In case of synthesis of compound **14** and **26a,b**, the reaction mixture was heated under reflux for 24 h]. The solvent was then removed *in vacuo*. The solid obtained was washed with cold water and purified using the proper method to give compounds **13a-c, 14, 22a-c** and **26a,b.**

17-(*N*,*N*-diethylaminoacetoxy-5,6,7,8,9,10,17,18-octahydro-16*H*-dibenzo[*b,j*][1,12,5,8]-dioxadiazacyclopentadecine-5,10-dione (**13a**).

With the use of the general procedure **10** and **11** gave crude material which was purified by column chromatography using ethyl acetate/petroleum ether (40-60) to give **13a** as oily product (60%); ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 6H, *J* = 7.2 Hz, NCH_2CH_3), 2.56 (q, 4H, *J* = 7.2 Hz, NCH_2CH_3), 3.34 (s, 2H, NCH_2CO), 3.51-3.72 (m , 4H, NCH_2CH_2N), 4.28-4.44 (m, 4H, OCH_2), 5.45 (brs, 1H, CH-O) , 6.93-7.97 (m, 10H, ArH's, NH).

Anal. Calcd for $C_{25}H_{31}N_3O_6$ (469.536): C, 63.95; H, 6.65; N, 8.95. Found: C, 64.10; H, 6.30; N, 8.70.

17-(*N*-Piperidinoacetoxy-5,6,7,8,9,10,17,18–octahydro-16*H*-dibenzo[*b,j*][1,12,5,8]-dioxadiazacyclopentadecine-5,10-dione (**13b**).

With the use of the general procedure, **10** and **12a** gave crude material which was purified by column chromatography using ethyl acetate/petroleum ether (40-60) to give **13b** as oily product (61%); ^{1}H NMR ($CDCl_3$): δ 1.2 (brs, 2H, $NCH_2CH_2CH_2$), 1.33 (brs, 4H, $NCH_2CH_2CH_2$), 3.07 (s, 4H, NCH_2), 3.34-3.63 (m, 4H, $NHCH_2$), 4.14-4.34 (m, 4H, OCH_2), 5.35 (brs, 1H, CH-O), 6.8-7.80 (m, 8H, ArH's), 8.00 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 23.78, 25.72, 39.35, 54.47, 60.40, 69.09 (Alipahtic CH_2's), 69.09 (Alipahtic CH), 114.55, 122.56, 131.62, 132.78 (Aromatic CH's), 123.44, 156.29 (Aromatic C's), 165.68, 16968 (C=O).

Anal. Calcd for $C_{26}H_{31}N_3O_6$ (481.547): C, 64.85; H, 6.49; N, 8.73. Found: C, 64.70; H, 6.60; N, 8.90.

17-(*N*-Morpholinoacetoxy-5,6,7,8,9,10,17,18–octahydro-16*H*-dibenzo[*b,j*][1,12,5,8]dioxadiazacyclopentadecine-5,10-dione (**13c**).

With the use of the general procedure **10** and **12b** gave crude material which was purified by column chromatography using ethyl acetate/petroleum ether (40-60) to give **13c** as oily product (65%); ^{1}H NMR ($CDCl_3$): δ 2.55 (t, 4H, *J* = 6.4 Hz, NCH_2CH_2O), 3.29 (s, 2H, NCH_2CO), 3.67 (t, 4H, *J* = 6.4Hz, OCH_2CH_2N), 3.59-3.84 (m, 4H, CH_2N), 4.34-4.51 (m, 4H, OCH_2), 5.52 (m, 1H, CH-O), 6.92-8.07 (m, 10H, ArH's , NH).

Anal. Calcd for $C_{25}H_{29}N_3O_7$ (483.52): C, 62.10; H, 6.05; N, 8.69. Found: C, 62.40; H, 6.20; N, 8.90.

13-(*N*-Piperidinoacetoxy)-6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo[*b,f,n,r*][1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dione (**22a**).

With the use of the general procedure **20a** and **12a** gave crude **22a** which was crystallized from benzene as colorless crystals (60%), mp. 180-182 °C; MS: m/z 693 (M^+, 0.16%), 568 (2%),

404 (17.5%), 300 (34%), 269 (100%), 203 (60%), 147 (99%), 121 (35%); ^{1}H NMR ($CDCl_3$): δ 1.42 (quintet, 2H, *J* = 5.1 Hz, $NCH_2CH_2CH_2$), 1.59 (quintet, 4H, *J* = 5.1 Hz, $NCH_2CH_2CH_2$), 2.46 (t, 4H, *J* = 5.1 Hz, $NCH_2CH_2CH_2$), 3.14 (s, 4H, NCH_2), 3.17 (s, 2H, $COCH_2N$), 3.90-3.99 (m, 4H, OCH_2), 4.99-5.06 (m, 4H, OCH_2Ar), 5.25 (m, 1H, CHOCO), 6.25-8.23 (m,16H, ArH's), 7.56 (brs, 2H, NH).

Anal. Calcd for $C_{40}H_{43}N_3O_8$ (693.795): C, 69.25; H, 6.25; N, 6.06. Found: C, 69.40; H, 6.30; N, 5.90.

13-(*N*-Piperidinoacetoxy)-6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo[*b,f,p,t*][1,5,18,22,9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dione(**22b**).

With the use of the general procedure **20b** and **12a** gave crude **22b** which was crystallized from ethanol as colorless crystals (63%), mp 181-183 °C; ^{1}H NMR ($CDCl_3$): δ 0.73 (brs, 4H, $HNCH_2CH_2$), 1.41 (quintet, 2H, *J* = 5.1 Hz, $NCH_2CH_2CH_2$), 1.58 (quintet, 4H, *J* = 5.1 Hz, $NCH_2CH_2CH_2$), 2.43 (t, 4H, *J* = 5.1 Hz, $NCH_2CH_2CH_2$), 2.97 (m, 4H, $HNCH_2$), 3.04 (s, 2H, $COCH_2N$), 3.95-4.05 (m, 4H, OCH_2), 5.10 (m, 4H, OCH_2Ar), 5.17 (m, 1H, CHOCO), 6.59- 8.38 (m, 16H, ArH's), 7.72 (brs, 2H, NH).

Anal. Calcd for $C_{42}H_{47}N_3O_8$ (721.85): C, 69.88; H, 6.56; N, 5.82. Found: C, 70.10; H, 6.70; N, 5.60.

13-(*N*-Morpholinoacetoxy)-6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo[*b,f,p,t*][1,5,18,22, 9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dione (**22c**).

With the use of the general procedure **20b** and **12b** gave crude **22c** which was crystallized from ethanol as colorless crystals (60%), mp. 188-190 °C; IR (cm^{-1}) 3380 (NH), 1753 (OCO), 1650 (CO, amide); MS: m/z 723 (M^+, 1.4%), 680 (5.5%), 475 (5%), 359 (20%), 328 (18%), 246 (37%), 205 (59%), 100 (100%); ^{1}H NMR ($CDCl_3$): δ 0.73 (s, 4H, NCH_2CH_2), 2.51 (t, 4H, *J* = 4.5 Hz, NCH_2CH_2O), 2.98 (m, 4H, NCH_2), 3.06 (s, 2H, $COCH_2N$), 3.71 (t, 4H, *J* = 4.5 Hz, NCH_2CH_2O), 3.90-4.08 (m, 4H, OCH_2), 5.13 (m, 4H, OCH_2Ar), 5.18 (quintet, 1H, *J* = 3 Hz,CHOCO), 6.59-8.38 (m, 16H, ArH's), 7.72 (brs, 2H, NH); ^{13}C NMR($CDCl_3$) δ 25.85, 39.89, 53.00, 59.00, 63.92, 66.70, 67.29 (Aliphatic CH_2's), 70.31 (Aliphatic CH), 111.91, 111.97, 121.37, 131.37, 131.45, 131.81, 132.31, 132.71 (Aromatic CH's), 121.32, 123.00, 156.65, 157.30 (Aromatic C's), 164.58, 169.04 (CO).

Anal. Calcd for $C_{41}H_{45}N_3O_9$ (723.82): C, 68.03; H, 6.27; N, 5.81. Found: C, 68.20; H, 6.40; N, 5.90.

1,4-Bis{5,6,7,8,9,10,17,18–octahydro-16*H*-dibenzo[*b,j*]-[1,12,5,8]dioxadiazacyclopentadecine-5,10-dion-17-yloxycarbonylmethyl}piperazine (**14**).

With the use of the general procedure **10** and **12c** gave crude **14** which was crystallized from ethanol as colorless crystals (60%), mp. 110-112 °C; ^{1}H NMR ($CDCl_3$): δ 2.5 (s, 8H, NCH_2CH_2N), 3.25 (s, 4H, CH_2COO), 3.45-3.77 (m, 8H, $NHCH_2$), 4.31-4.48 (m, 8H, OCH_2), 5.49 (q, 2H, *J* = 4.0 Hz, CHOCO), 6.95-8.01 (m, 20H, ArH's, NH); ^{13}C NMR ($CDCl_3$) δ 39.29, 52.44, 59.06, 68.73 (Aliphatic CH_2's), 69.47 (Aliphatic CH), 114.29, 122.63, 131.71, 132.58 (Aromatic CH's), 132.21, 155.85 (Aromatic C's), 165.22, 68.89 (C=O).

Anal. Calcd for $C_{46}H_{50}N_6O_{12}$ (878.934): C, 62.86; H, 5.73; N, 9.56. Found: C, 62.90; H, 5.40; N, 9.40.

1,4-Bis{6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo[*b,f,n,r*]-[1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dion-13-yloxycarbonylmethyl}piperazine (**26a**).

With the use of the general procedure **20a** and **12c** gave crude **26a** which was crystallized from dioxane as colorless crystals (62%), mp.144-146 °C; IR (cm^{-1}) 3385 (NH), 1750 (OCO), 1653 (CO amide); ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 8H, NCH_2), 3.14 (brs, 8H, $NHCH_2$), 3.20 (s, 4H, $COCH_2N$), 3.91-3.99 (m, 8H, OCH_2), 4.99-5.05 (m, 8H, OCH_2Ar), 5.25 (m, 2H, CHOCO) 6.24-8.23 (m, 32H, ArH's), 7.55 (brs, 4H, NH).

Anal. Calcd for $C_{74}H_{74}N_6O_{16}$ (1303.429): C, 68.19; H, 5.72; N, 6.45. Found: C, 68.40; H, 5.90; N, 6.70.

1,4-Bis{6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo-[*b,f,p,t*][1,5,18,22,9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dion-13-yloxycarbonylmethyl}piperazine(**26b**).

With the use of the general procedure **20b** and **12c** gave crude **26b** which was crystallized from ethanol as colorless crystals (60%), mp.122-124 °C; IR (cm^{-1}) 3387 (NH), 1750 (OCO), 1652 (CO, amide); ^{1}H NMR ($CDCl_3$): δ 0.72 (brs, 8H, $HNCH_2CH_2$), 2.53 (s, 8H, NCH_2), 2.97 (m, 8H, $HNCH_2$), 3.04 (s, 4H, $COCH_2N$), 3.94-4.05 (m, 8H, OCH_2), 5.05-5.15 (m, 8H, OCH_2Ar), 5.17 (quintet, 2H, *J* = 2.7 Hz, CHOCO), 6.57-8.36 (m, 32H, ArH's), 7.71 (t, 4H, *J* = 3.9 Hz, NH); ^{13}C NMR($CDCl_3$): δ 25.78, 39.79, 52.42, 58.53, 63.83, 67.2 (Aliphatic CH_2's), 69.92 (Aliphatic CH), 111.84, 111.92, 121.29, 131.37, 131.71, 132.19, 132.64 (Aromatic CH's), 121.21, 122.94, 156.57, 157.21 (Aromatic C's), 164.49, 169.02 (CO).

Anal. Calcd for $C_{78}H_{82}N_6O_{16}$ (1359.536): C, 68.91; H, 6.08; N, 6.18. Found: C, 69.10; H, 6.10; N, 6.30.

Reaction of Compounds **20a,b** with **21a-c, 2b, 24** and **25.** (Synthesis of Compounds **23a-c,** and **27-29**).

General Procedure.

A solution of the appropriate potassium **21a-c, 2a, 24** and **25** (10 mmol) and the chloroacetoxy compounds **20a,b** (10 mmol for synthesis of compounds **2a-c** or 20 mmol for synthesis of compounds **27-29**) in DMF (20 ml) was heated at 80-90 °C for 5 h. during which time KCl was precipitated. The solvent was then removed *in vacuo* and the remaining material was washed with water (50 ml) and purified to give compounds **23a-c,** and **27-29**.

13-(4-Formylphenoxy)acetoxy-6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo[*b,f,n,r*][1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dione (**23a**).

With the use of the general procedure **20a** and **21a** gave crude product which was purified by preparative thin layer chromatography using CH_2Cl_2:MeOH (25:1) as an eluent to give **23a** as colorless crystals (50%), mp. 98-100 °C; IR (cm^{-1}) 3384 (NH), 2878 (C*H*O), 1763 (OCO), 1691 (CO, aldehyde), 1652 (CO, amide); MS: m/z 730 (M^+, 39%), 592 (27%), 489 (33%), 414 (33%), 310 (72%), 166 (100%), 81 (52%); ^{1}H NMR ($CDCl_3$): δ 3.13 (brs, 4H, NCH_2), 3.19-4.03 (m, 4H, OCH_2), 4.71 (s, 2H, $COCH_2$), 4.9-5.0 (m, 4H, OCH_2Ar), 5.32 (m, 1H, CHOCO), 6.32-8.24 (m, 22H, ArH's, NH), 9.81 (s, 1H, CHO).

Anal. Calcd for $C_{42}H_{38}N_2O_{10}$ (730.769): C, 69.03; H, 5.24; N, 3.83. Found: C, 68.90; H, 5.40; N, 4.10.

13-(2-Formylphenoxy)acetoxy-6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo[*b,f,p,t*][1,5,18,22,9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dione (**23b**).

With the use of the general procedure **20b** and **21b** gave crude **23b** which was crystallized from ethanol as colorless crystals (55%), mp.188-190 °C; IR (cm^{-1}) 3392 (NH), 2873 (C*H*O), 1749

(OCO), 1686 (CO, aldehyde), 1652(CO, amide); ^{1}H NMR ($CDCl_3$): δ 0.72 (brs, 4H, $NHCH_2CH_2$), 2.97 (brs, 4H, $NHCH_2$), 3.95-4.11 (m, 4H, OCH_2), 4.62 (s, 2H, $COCH_2$), 4.99 (d, 2H, *J* = 9 Hz, upfield of OCH_2Ar), 5.02 (d, 2H, *J* = 9 Hz, downfield of OCH_2Ar), 5.26 (m, 1H, CHOCO), 6.56-8.37 (m, 20H, ArH's), 7.68 (brs, 2H, NH), 10.52 (s, 1H, CHO).

Anal. Calcd for $C_{44}H_{42}N_2O_{10}$ (758.82): C, 69.65; H, 5.58; N, 3.69. Found: C, 69.80; H, 5.70; N, 3.90.

13-(2-Nitrophenoxy)acetoxy-6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo[*b,f,n,r*][1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dione (**23c**).

With the use of the general procedure **20a** and **21c** gave crude product which was purified by preparative thin layer chromatography using CH_2Cl_2:MeOH (20:1) as an eluent to give **23c** as pale yellow crystals (50%), mp.118-120 °C; MS: m/z 747 (M^+, 6%), 732 (9%), 611 (7.5%), 551 (10%), 431 (13%), 388 (17.5%), 149 (100%), 121 (45%); ^{1}H NMR ($CDCl_3$): δ 3.12 (m, 4H, NCH_2), 3.8-4.02 (m, 4H, OCH_2), 4.76 (s, 2H, $COCH_2$), 4.97 (s, 4H, OCH_2Ar), 5.32 (m, 1H, CHOCO), 6.18-8.23 (m, 22H, ArH's, NH).

Anal. Calcd for $C_{41}H_{37}N_3O_{11}$ (747.756): C, 65.86; H, 4.99; N, 5.62. Found: C, 65.90; H, 5.20; N, 5.90.

1,2-Bis{2-[6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo[*b,f,n,r*]-[1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dion-13-yloxycarbonylmethyloxyphenyl]carbonylamino}ethane (**27**).

With the use of the general procedure **20a** and **2a** gave crude product which was purified by preparative thin layer chromatography using ethyl acetate/petroleum ether (40-60) (10:1) to give **27** as colorless crystals (45%), mp.158-160 °C; ^{1}H NMR ($CDCl_3$): δ 3.12 (brs, 8H, $NHCH_2$), 3.67-3.68 (m, 4H, $NHCH_2$), 3.87-3.94 (m, 8H, OCH_2), 4.72 (s, 4H, OCH_2CO), 4.85-5.0 (m, 8H, OCH_2Ar), 5.28 (m, 2H, CHOCO), 6.18-8.56 (m, 46H, ArH's, NH); ^{13}C NMR($CDCl_3$): δ 39.69, 39.98, 64.14, 65.39, 66.59 (Aliphatic CH_2's), 71.16 (Aliphatic CH), 111.27, 112.12, 121.26, 121.55, 122.2, 130.49, 131.196, 132.37, 132.55, 132.74 (Aromatic CH's), 122.19, 123.01, 123.01, 155.54, 156.05, 157.07 (Aromatic C's), 165.08, 165.22, 167.65 (CO).

Anal. Calcd for $C_{86}H_{80}N_6O_{20}$ (1517.606): C, 68.06; H, 5.31; N, 5.54. Found: C, 68.30; H, 5.40; N, 5.70.

1,3-Bis{2-[6,12,13,20,28,29-hexahydro-14*H*-tetrabenzo[*b,f,n,r*]-[1,5,16,20,9,12]tetraoxadiazatricosin-26,31-(27*H*,30*H*)dion-13-yloxycarbonylmethyloxy]phenyl}propane (**28**).

With the use of the general procedure **20a** and **24** gave crude product which was purified by preparative thin layer chromatography using ethyl acetate/petroleum ether (40-60) (20:1) as an eluent to give **28** as colorless crystals (45%), mp. 108-110 °C; ^{1}H NMR ($CDCl_3$): δ 2.28 (quintet, 2H, *J* = 6 Hz, $OCH_2CH_2CH_2O$), 3.12 (brs, 8H, NCH_2), 3.87-3.97 (m, 8H, OCH_2), 4.21 (t, 4H, *J* = 6 Hz, $OCH_2CH_2CH_2O$), 4.62 (s, 4H, OCH_2CO), 4.94 (s, 8H, OCH_2Ar), 5.27 (quintet, 2H, *J* = 3.6 Hz, CHOCO), 6.20-8.22 (m, 40H, ArH's), 7.54 (brs, 4H, NH); ^{13}C NMR($CDCl_3$): δ 29.36, 29.99, 39.66, 64.16, 65.83, 66.59 (Aliphatic CH_2's), 70.58 (Aliphatic CH), 111.32, 112.04, 114.4, 115.27, 121.19, 121.47, 122.91, 130.42, 131.20, 132.34, 132.69 (Aromatic CH's), 121.52, 123.03, 147.59, 148.97, 156.16, 157.06 (Aromatic C's), 165.09, 168.36 (CO).

Anal. Calcd for $C_{85}H_{80}N_8O_{20}$ (1533.61): C, 66.57; H, 5.26; N, 7.31. Found: C, 66.70; H, 5.30; N, 7.10.

2,4-Bis{6,12,13,20,28,29,30,31-octahydro-14*H*-tetrabenzo[*b,f,p,t*]-[1,5,18,22,9,14]tetraoxadiazapentacosin-26,33-(27*H*,32*H*)dion-13-yloxycarbonylmethyloxy}benzaldehyde (**29**).

With the use of the general procedure **20b** and **25** gave oily product which was purified by column chromatography using ethyl acetate/petroleum ether (40-60) to give **29** as colorless crystal (52%), mp.188-190 °C; IR (cm^{-1}) 3390 (NH), 2874 (CHO), 1759 (OCO), 1685 (CO, aldehyde), 1652 (CO, amide); ^{1}H NMR ($CDCl_3$): δ 0.72 (m, 8H, $NHCH_2CH_2$), 2.98 (brs, 8H, NCH_2), 3.95-4.1(m, 8H, OCH_2), 4.34 (s, 2H, $COCH_2O$), 4.54 (s, 2H, $COCH_2O$), 4.95-5.08 (m, 8H, OCH_2Ar), 5.19-5.3 (m, 2H, CHOCO), 6.28-8.38 (m, 39H, ArH's, NH), 10.35 (s, 1H, CHO).

Anal. Calcd for $C_{81}H_{78}N_4O_{19}$ (1411.522): C, 68.92; H, 5.57; N, 3.97. Found: C, 69.20; H, 5.60; N, 4.20.

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