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Efficient Synthesis of Macrocyclic Diamides

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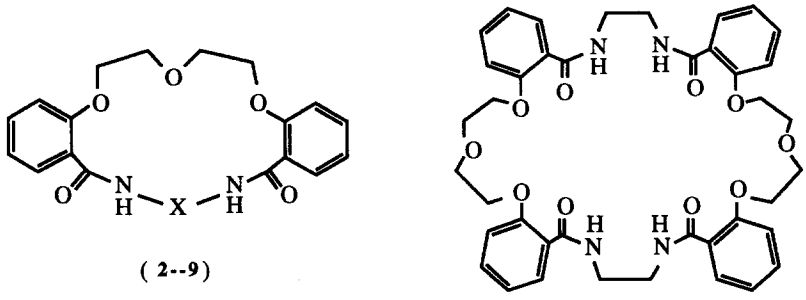
Abstract: Some new macrocyclic dibenzotrioxadiamides, tribenzotrioxadiamides and tetrabenzohexaoxatetraamide **(1-9)** have been prepared. Compounds **(2-9)** were obtained in the macrocyclization step by reacting the dicarboxylic acid dichloride **(13)** with appropriate diamine in CH_2Cl_2. The cyclization does not require high dilution techniques or template effect and provides the expected dilactams in high yields, ranging from 80% to 95%. However, the reaction of diamine **(14a)** with dicarboxylic acid dichloride **(13)** in high dilution conditions yielded the mixture of dilactam **(2)** and tetralactam **(1)** in moderate yields.

Introduction

The interaction of crown polyethers with non-transition-metal ions has been studied extensively since the inherent selectivity of this ligand type has implications for a number of areas, including: the mechanisms of biological transport across membranes, the solubilisation of inorganic salts in non-polar solvents for use in organic reactions, the development of cation selective electrodes as well as a number of potential other analytical and therapeutic applications[1-3]. Although their interaction with transition metals has also received some attention, these macrocycles show general low affinity for such ions[4]. Incorporation of nitrogen-donor atoms in the macrocycle to produce rings containing mixed oxygen-nitrogen donor sets has been demonstrated to increase the affinity for transition-metal ions[5-9].

Generally, macrocyclic polyethers (crown ethers) form stable complexes preferably with alkali metal ions[2,10]. Ligands with high potassium /sodium affinity have been found among these compounds. However, the selectivity of crown ethers for alkaline-earth metal ions is much lower.When the ether groups were successively replaced by lactone ones, the resulting ring systems showed reduced binding affinity. However a good selectivity towards alkaline-earth cations was observed with some polyoxalactones[11]. Of particular interest is the introduction of an amide linkage in the polyether ring. These groups modify the binding properties of the crown compounds in favour of alkaline-earth cations with respect to alkali metal ions[12-17]. In other study, a 14-membered ligand containing two amide and two sulfur donor groups was shown to be selective for Pd(II) and Pt(II) over Co(II), Ni(II) and Cu(II)[18].Lariat crown ether ligands containing amide groups in their side chains exhibit remarkable selectivity for calcium over sodium[19]. The metal complexing abilities of other cyclic species containing amide linkages have been widely investigated. For example, a number of synthetic cyclopeptides have been reported to be potassium or calcium ionophores[20] and they form complexes with transition metal ions[21].



(2--9)

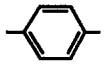
(1)

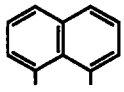
(2) X= $-(CH_2)_2-$

(3) X= $-CH_2CHCH_3$ (with CH$_3$ branch)

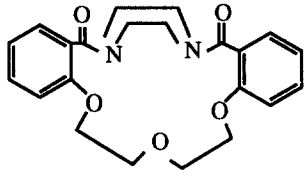
(4) X = $-(CH_2)_6-$

(5) X= 

(6) X= 

(7) X = 

(8) X = $-CH_2CH_2NHCH_2CH_2-$



(9)

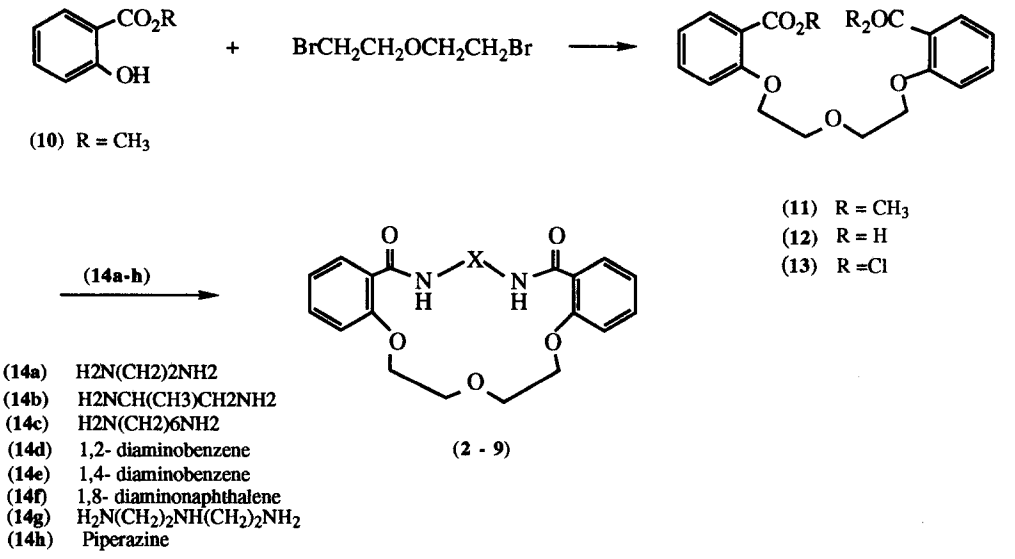
Figure 1: New polylactam compounds

In this paper we have studied synthetic routes towards new dilactam derivatives with **17-21** and **26** ring atoms. The target molecules were intended to include two, three and four benzo-condensed systems with the macrocycles to study their effect on their metal-ion complexing behaviour related to that discussed above (Figure 1). Also, these products are potential precursors which yield by reduction many useful known[22] as well as new aza crown ethers.

RESULT AND DISCUSSION

The preparation of macrocyclic polylactams from diamines and activated diacids requires direct condensation reactions to form ring products in favour of polymers. In an attempt to achieve this goal, many different cyclization procedures have been developed. Early high-dilution techniques[23-26] have been complemented by various double-activation methods[27-30] and by a series of consecutive "zipper-type" reactions[31]. In most of these methods the macrocyclic lactams and polylactams are obtained by cyclization of a polyfunctional, linear precursor to a ring product.The high dilution technique is, however, inconvenient as it requires a simultaneous addition of the diamine and diacid chloride to a large volume of solvent over an extended period of time. Recently, Morphy et al.[32] and Jurczak et al.[33] have reported that, consistent with the earlier findings of Tabushi et al. [34] ,no high

Scheme 1



dilution technique was required for the reaction of dimethyl malonates with α,ω-diamines to form the cyclic diamides. This fact promoted us to apply a similar approach to the synthesis of dilactame (**2-9**)(Scheme 1).

The reaction of methylsalicylate(**10**) with diethylenglycol dibromide in acetone using potassium carbonate as the base resulted in the formation of diester **11** in 96% yield. Treatment of diester **11** with ethylenediamine under ambient conditions (methanol as a solvent, 25°C, 7 days) gave a mixture of products that after column chromatography, diamide **2** was obtained in a 20% yield. In order to find the optimum condition to increase the yield of diamide **2**, this reaction was carried out at higher temperature (reflux) or longer times (3 mounths), but a satisfactory result was not obtained. The yield of diamide **2** was indeed substantially low and highly contaminated with oligomeric substances. This seems to be consistent with the assumed course of the reaction, according to which the diester and diamine form a linear amido compound which then undergoes the cyclization or oligomerization[24].

These observations led us to design another synthetic process (Scheme 1). Dicarboxylic acid (**12**) was obtained by saponification of compound **11** followed by acid treatment in a quantitative yield. Treatment of **12** with thionyl chloride gave 94% yield of the dicarboxylic acid dichloride (**13**). The cyclization between compound **13** and ethylenediamine was performed by the following high dilution method[21]. A solution of **13** (2 mmol) in CH_2Cl_2(200 ml) and a solution of ethylenediamine (2 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (200 ml) were added dropwise using two mechanically driven syringes (commercial name: microfeeder) over 5 hr into CH_2Cl_2 (1.5 l) under nitrogen with stirring at 0°C and then the mixture was stirred at room temperature for a further 3 hr. The precipitates were filtered and the filtrate was evaporated. The residue was chromatographed on silica gel using CH_2Cl_2 to give **1**(125 mg, 17%), mp., 90°C and then was eluated with acetone to give **2**(200 mg, 27%). However, when a mixture of ethylenediamine (2 mmol) and triethylamine(4 mmol) in CH_2Cl_2(10 ml) was added dropwise to a solution of **13** (2 mmol) in CH_2Cl_2(10 ml) over 15 mins. with stirring

at room temperature, compound **2** was obtained in 85% yield. This result clearly indicates the cyclization of compound **13** with ethylenediamine dose not need high dilution method. In addition, the cyclization was carried out with fast addition of a mixture of ethylenediamine (2 mmol) and triethylamine (4 mmol) in CH_2Cl_2 (10 ml) into a solution of compound **13** (2 mmol) in CH_2Cl_2(10 ml) over 5 sec with vigorous stirring at 0°C and then the mixture was stirred at room temperature for 10 mins. to give compound **2** in 95% yield. A low reaction time was observed for this macrocyclization reaction (10 mins.) When this method was used at room termperature without triethylamine, the same result was obtained.

In a preliminary study, the effect of some solvents on the yield of the macrocyclization reaction was investigated with the formation of dilactam **2** as model reaction (Table 1). Table 1, clearly indicates, CH_2Cl_2 and CH_3CN are suitable solvents for this macrocyclization reaction. It should be noted that, when ethylenediamine

Table 1. Effect of solvents in macrocyclization yield(%) between compound **13** and ethylenediamine

Solvent	CH_2Cl_2	CH_3CN	$CHCl_3$	DMF	C_6H_6	$CHCl_2CHCl_2$
dilactam(**2**)	95	95	45	40	20	20
tetralactam(**1**)	-	-	15	-	-	-
other products	5	5	40	60	80	80

(2 mmol) and triethylamine (4 mmol) were injected to a solution of compound **13** (2 mmol) in different solvent (10 ml),dilactam (**2**) and tetralactam (**1**) were not obtained at all.

Compounds **3-9** were readily obtained by reacting the compound **13** with appropriate diamine derivatives in high yields (Table 2). The structures proposed for the macrocyclic compounds are consistent with data derived from infrared and proton nuclear magnetic resonance spectra in addition to satisfactory combustion analysis and molecular weights determined by mass spectrometric analyses.

The advantages of this method are as follow:

(i) synthetic versatility. This allows to provide even or odd membered dilactams; (ii) high yields of cyclization without additional external cyclization factors (as high dilution approach or template effect); (iii) ease of purification; (iv) low reaction time.

Table 2. Cyclization Yields and Physical Properties of Macrocyclic Dilactames **2-9**.

	Starting Materials		Time/ (min)	Yield%	melting point(°C) (recrystallization solvent)	^{1}H NMR spectra (90 and 500 MHz,$CDCl_3$,δ)[a]
2	**13**	**14a**	10	95	110(CH_2Cl_2)	3.68-3.73(m,4H,CH_2N),3.99-4.30(m,8H, CH_2O)6.96-8.17(m,8H,Ar),8.42(b,2H, CONH-)
3	**13**	**14b**	20	85	160-162 (CH_3OH)	1.80(d,J=7 Hz,3H,CH_3),3.50-4.30(complex, 11H,CH_2N+CHN+CH_2O),6.75-8.00(m,8H, Ar),8.05(b,2H,CONH)
4	**13**	**14c**	10	95	140-141 (CH_2Cl_2/ (C_6H_{12})	1.55(m,8H),3.20-3.60(m,4H,CH_2N),3.90-4.20(m,8H,CH_2O),6.85-8.00(m,8H,Ar), 8.05(b, 2H,CONH).
5	**13**	**14d**	15	96	267 (C_6H_{12}/ CH_3COCH_3)	3.37-3.81(m,8H,CH_2O),6.69-8.08(m,12H, Ar),9.75(s,2H,CONH)
6	**13**	**14e**	20	91	245-246 (CH_3OH)	3.40-3.90(m,8H,CH_2O),6.60-7.90 (m,12H, Ar),9.90(S,2H, CONH).
7	**13**	**14f**	10	80	240-242 (CH_3OH)	3.90-4.20(m,8H,CH_2O),6.20-7.85(m,14H, Ar), 8.00(b,2H, CONH)
8	**13**	**14g**	15	90	283-285	1.45(m,1H,NH),3.00-3.70(m,8H,CH_2N), 3.90-4.10(m,8H,CH_2O),6.80-8.00(m,8H, Ar), 8.50(b,2H,CONH)
9	**13**	**14h**	10	92	270 (CH_2Cl_2/C_6H_{12})	3.05-3.83(m,8H,CH_2N),3.90-4.22(m,8H, CH_2O),6.78-7.29(m,8H,Ar)

a) 90 MHz for **3,4,6-8** ; 500 MHz for **2,5,9.**

Acknowledgment. We are thankful to Shiraz University Research Council for their financial support.

EXPERIMENTAL

Solvents, reagents, and chemical materials were obtained from Merck chemical company (West Germany) and Fluka(Switzerland). Melting points were determined in open capillary tubes in a Buchi 510 circulating oil melting point apparatus and uncorrected. IR spectra were recorded on a Perkin Elmer 781 spectrophotometers. ^{1}H NMR spectra were obtained on a VXR-500 and Jeol-EX 90Q for solutions in $CDCl_3$ with tetramethylsilane as internal standard. Mass spectra (MS) were performed with a GC-MS Trio 1000 spectrometer and GCMS-QP 1000 EX at 70 ev.UV spectra were recorded on a UV/vis spectrometer PU 8750.Thin-layer chromatography were carried out on silica gel 60F 254 analytical sheets obtained from Merck chemical company. Column chromatography was carried out on the short column of silica gel 60 Merck (230-400 mesh) in glass columns (ϕ 2-3 cm) using 15-30 g of silica gel per one gram of crude mixture.

Satisfactory microananlyses were obtained for compounds **1,2,5-7**: C ±0.29, H ± 0.29, N ± 0.18; compounds **3, 4**: C ± 0.25, H ± 0.15, N± 0.22; compounds **8,9**: C± 0.3, H ± 0.25, N± 0.17.

1,7-Bis(2'-methylbenzoate)-1,4,7-trioxaheptane(11).

A mixture of bis-(2-bromoethyl)ether (23.5 g, 0.1 mol) and methyl salicylate (30.5 g, 0.2 mol) in acetone(500 ml) containing potassium carbonate (20 g) was refluxed for seven days. The mixture was cooled and the solid was filtered and solvent evaporated. Chloroform (400 ml) was added and the organic layer was washed with cold 10% aqueous sodium hydroxide solution, then with water and dried with magnesium sulphate. The solvent was evaporated to give yellow viscous oil of **11**; yield: 36 g (96%); rf=0.78 (CH_2Cl_2-CH_3OH/96-4); IR(neat): 1720 cm^{-1}(CO); ^{1}H NMR($CDCl_3$, 90 MHz) δ 3.8(s, 6H), 3.95(t, 4H, J=4.5 Hz), 4.15(t, 4H, J=4.5 Hz), 6.8-7.1(m, 4H), 7.35(dt, 2H, J_1=7.5 Hz, J_2=2 Hz), 7.7(dd, 2H, J_1=8 Hz, J_2=2 Hz); UV(dioxane) λ 232 (ε_{max}=19400), 292 nm (ε=10800).

1,7-Bis(2'-benzoic acid)-1,4,7-trioxaheptane(12).

A solution of 1,7-bis(2'-methyl benzoate)-1,4,7-trioxaheptane (**11**; 37.5 g, 0.1 mol) in 10% aqueous NaOH (500 ml) was refluxed for 24 hrs. The mixture was cooled and washed with chloroform (2 X 100 ml) and acidified with 6N HCl and extracted with CH_2Cl_2 (5 X 150 ml). The solvent was evaported and the white solid was recrystallized from CH_2Cl_2 to give white crystal of **12**; yield: 34.5 g (100%); m.p. 105 °C; IR(KBr): 1700 cm-1(CO); ^{1}H NMR ($CDCl_3$), δ 3.85(t, 4H, J=4.5 Hz), 4.20(t, 4H, J=4.5 Hz), 6.8-7.1(m,4H), 7.35(dt,2H, J_1=8 Hz, J_2=2 Hz), 7.9(dd, 2H, J_1=8 Hz, J_2=2 Hz), 8.3(b, 2H); UV(CH3OH) λ 235(ε_{max}=24460), 293nm (ε=15070)

1,7-Bis(2'-benzoyl chloride)-1,4,7-trioxaheptane(13).

1,7-Bis(2'-benzoic acid)-1,4,7-trioxaheptane (**12**; 8.65 g, 0.025 mol) was refluxed in thionyl chloride (50 ml) for 12 hrs. The thionyl chloride was evaporated in vacuum at room temperature to give a brown solid of **13**; yield: 9 g (94%); mp: 60°C; IR(KBr): 1780 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$), δ 3.95(t, 4H, J=4.5 Hz), 4.1(t,4H, J=4.5 Hz), 6.8-7.1(m, 4H), 7.45(dt, 2H, J_1=7.5 Hz, J_2=2 Hz), 7.95(dd, 2H, J_1=8 Hz, J_2=2 Hz); UV(dioxane) λ 222 (ε_{max}=13800), 252(ε=11800), 314 nm(ε=5450).

Preparation of Macrocyclic Diamides 2-9

General Procedure: A solution of diamine (0.002 mol) and triethylamine (0.004 mol) in CH_2Cl_2 (50 ml) was

added fastly (5 sec.) to a vigorously stirring solution of diacid chloride (**13**, 0.002 mol) in CH_2Cl_2(50 ml) at 0°C. The reaction mixture was stirred at room temperature for 10-30 mins. The precipitate was filtered off and the filtrate washed with water (2 X 50 ml) and 10% aqueous NaOH solution (50 ml) and then with water (100 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give a solid product.

1,15-Diaza-3,4;12,13-dibenzo-5,8,11-trioxacycloheptadecane-2,14-dione(2). **2** was obtained from **13** and **14a** following the general procedure in 95% yield ; white solids; m.p.=110°C; rf=0.18`(CH_2Cl_2-CH_3OH/96-4); IR(KBr); 3360(NH), 1640 cm^{-1}(CO); ^1H NMR($CDCl_3$, 500 MHz), δ 3.68(dt, 2H, J_1=5.96 Hz, J_2=0.88 Hz),3.73(dt, 2H, J_1=5.97 Hz, J_2=0.88 Hz), 3.99(t, 4H, J=4.64 Hz), 4.30(t,4H, J=4.64 Hz), 6.96(dd, 2H, J_1=8.4 Hz, J_2=0.66 Hz), 7.08(dt, 2H, J_1=7.29 Hz, J_2=0.66 Hz), 7.42(dt, 2H, J_1=7.29 Hz, J_2=1.77 Hz), 8.17(dd, 2H, J_1=7.74 Hz, J_2=1.77 Hz), 8.42(b, 2H); MS: m/z = 372($M+2H)^+$, 371,342, 328, 314, 234, 208,190,165, 147,136,120,121(base peak), 119, 105; UV(CH_3OH) λ 230 (ε_{max} = 17500), 287 nm (ε=5400).

1,15-diaza-3,4;12,13-dibenzo-17-methyl-5,8,11-trioxacycloheptadecane-2,14-dione(3). **3** was obtained from **13** and **14b** following the general procedure in 85% yield; white solids; m.p. = 160-2°C ; rf = 0.45(CH_2Cl_2-CH_3OH/96-4); IR(KBr): 3420(NH), 3360(NH), 1650(CO), 1630 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 90 MHz), δ 1.80(d, 3H, J=7 Hz), 3.50-4.30(complex, 11H), 6.75(d, 2H, J=8 Hz), 6.95(t, 2H, J=7 Hz), 7.20(dt, 2H, J_1=8 Hz, J_2=2 Hz), 8.00(dd, 2H, J_1=8 Hz,J_2=2 Hz), 8.05(b, 2H); MS:m/z = 386, 385, 384(M^+), 369, 367, 340, 328, 284, 266, 191, 164, 147, 121(base peak) , 76, 69, 56, 44; UV(CH_3OH) λ 233 (ε_{max} = 21 600), 289 nm (ε=7100).

1,15-Diaza-3,14;12,13-dibenzo- 5,8,11-trioxacyclouneicosane-2,14-dione (4). **4** was obtained from **13** and **14c** following the general procedure in 95% yield; white needls; m.p. = 140-1°C; rf=0.50(CH_2Cl_2-CH_3OH/96-4); IR(KBr): 3400(NH), 1650 cm^{-1}(CO); ^1H NMR ($CDCl_3$, 90 MHz), δ 1.55(m, 8H), 3.40(m, 4H), 3.90(t,4H,J=4 Hz), 4.20(t, 4H, J=4 Hz), 6.85(d, 2H, J=8 Hz), 7.00(t, 2H, J=8 Hz), 7.25(dt, 2H, J_1=8 Hz, J_2=2 Hz), 8.00(s, 2H), 8.05(dd, 2H, J_1=8 Hz, J_2=2 Hz); MS: m/z = 428, 427, 426(M^+), 409, 328, 190, 147, 135, 121(base peak), 120, 84, 56, 43; UV(CH_3OH) λ 230 (ε_{max} = 21800), 287 nm (ε = 7300).

1,15-Diaza-3,4; 12,13; 16,17-tribenzo-5,8,11-trioxacycloheptadecane-2,14-dione(5). **5** was obtained from **13** and **14d** following the general procedure in 96% yield; white solids; m.p. = 267°C ; rf = 0.55(CH_2Cl_2-CH_3OH/96-4)IR(KBr): 3300(NH), 1660 cm^{-1} (CO); ^1H NMR($CDCl_3$, 500 MHz), δ 3.37(t, 4H, J=4.5 Hz), 3.81(t, 4H, J=4.4 Hz), 6.69(d, 2H, J=8.17 Hz), 7.05(dt, 2H, J_1=7.4 Hz, J_2=0.7 Hz), 7.23(d, 1H, J=3.54 Hz), 7.24(d, 1H, J=3.1 Hz), 7.30(dt, 2H, J_1=7.8 Hz, J_2=1.78 Hz), 7.81(dd, 2H, J_1=5.97 Hz, J_2=3.7 Hz), 8.08(dd, 2H, J_1=7.75 Hz, J_2=1.75 Hz), 9.75(s, 2H); MS: m/z = 419, 418(M^+), 237, 211, 210(base peak), 208, 193, 179, 163, 137, 105, 86 ; UV(CH_3OH) λ 208 (ε_{max} = 11400), 280 nm (ε= 2000).

1,15-Diaza-3,4; 12,13; 16,19-tribenzo-5,8,11-trioxacyclononadecane-2,14-dione(6). **6** was obtained from **13** and **14e** following the general procedure in 91% yield; white solids; m.p.=245-6 °C; rf=0.41 (CH_2Cl_2-CH_3OH/96-4);IR(KBr): 3360(NH), 1660 cm^{-1}(CO); ^1H NMR($CDCl_3$, 90 MHz), δ 3.40(t, 4H, J=4.5 Hz), 3.90(t, 4H, J=4.5 Hz), 7.40(s, 4H), 6.60-7.60 (complex, 6H), 7.90(dd, 2H, J_1=8 Hz, J_2=2 Hz), 9.90(s,

2H); MS: m/z = 419, 418(M^+); 299, 283, 313, 255, 237, 211, 210, 208, 205, 193, 179, 163,137, 105, 86(base peak); UV(CH_3OH) λ 233 (ε_{max}= 19100), 300 (ε = 18000), 310 nm (ε = 19100).

1,15-Diaza-3,4;12,13-dibenzo-16,18-naphtalino-5,8,11-trioxacyclooctadecane-2,14-dione(7). **7** was obtained from **13** and **14f** following the general procedure in 80% yield; white solids; m.p.=240-2°C; rf=0.50(CH_2Cl_2-CH_3OH/96-4); IR(KBr): 3380(NH), 1660 cm^{-1}(CO); ^1H NMR($CDCl_3$, 90 MHz), δ 3.90(t, 4H, J=4.5 Hz), 4.20(t, 4H, J=4.5 Hz), 6.20-6.80(complex, 6H), 6.90(t, 2H, J=7 Hz), 7.30(dt, 2H, J_1=8.0 Hz, J_2=2 Hz), 7.50(t, 2H, J=7 Hz), 7.85(dd, 2H, J_1=8 Hz, J_2=2 Hz), 8.00(b, 2H); MS: m/z = 470, 469, 468(M^+), 435, 348, 331, 287, 260(base peak), 258, 147, 120; UV(CH_3OH) λ 229 (ε_{max} = 26500), 301 nm(ε = 7800).

1,15,18-Triaza-3,4;12,13-dibenzo-5,8,11-trioxacycloeicosane-2,14-dione (8). **8** was obtained from **13** and **14g** following the general procedure in 90% yield; white solids; m.p. = 283-5°C; rf=0.15(CH_2Cl_2-CH_3OH/96-4); IR(KBr): 3600(NH) 3380(NHCO), 1650 cm^{-1} (CO); ^1H NMR($CDCl_3$, 90 MHz), δ 1.45(t, 1H),3.00(dt, 4H, J_1=4.5, J_2=2 Hz), 3.70(t, 4H, J=4.5 Hz), 3.90(dt, 4H, J_1=4.5 Hz, J_2=2 Hz), 4.10(t, 4H, J=4.5 Hz),6.80(d,2H, J=8 Hz), 7.00(t, 2H, J=7 Hz), 7.20(dt, 2H, J_1=8 Hz, J_2=2 Hz), 8.00(dd, 2H, J_1=8 Hz, J_2=2 Hz), 8.50(b, 2H); MS:m/z = 413(M^+), 412, 341, 328, 310, 275, 207, 163, 190, 156, 138, 121, 72(base peak); UV(CH_3OH)λ 233 (ε_{max} = 22200), 283 nm (ε= 7650).

1,15-Diaza-3,4; 12,13-dibenzo-5,8,11-trioxa-bicyclo [13,2,2] heptadecane-2,14-dione (9). **9** was obtained from **13** and **14h** following the general procedure in 92% yield; white solids; m.p. = 270°C; rf=0.45(CH_2Cl_2-CH_3OH/96-4); IR(KBr): 1630(CO); ^1H NMR ($CDCl_3$, 500 MHz), δ 3.05(m, 2H), 3.70(t, 4H, J=4.5 Hz), 3.83(m, 2H), 3.90(t, 4H, J=4.5 Hz). 3.99(td, 2H, J_1=8.83 Hz, J_2=1.1 Hz), 4.22(t, 2H, J_1=10.16 Hz, J_2=1.1 Hz), 6.78(dd, 2H, J_1=8.85 Hz, J_2=0.89 Hz), 6.96(dt, 2H, J_1=7.5 Hz, J_2=0.89 Hz), 7.29(dt, 4H, J_1=7.5 Hz, J_2=1.76 Hz); MS: m/z = 398, 397, 396(M^+), 381, 368, 312, 285, 276, 248, 232, 204, 191, 188, 148, 121(base peak), 111, 84, 43; UV(CH_3OH) λ 210 (ε_{max} = 13000), 280 nm (ε = 2200).

Compound 1: White solids ; m.p. = 90°C ; rf=0.6(CH_2Cl_2-CH_3OH/96-4); IR(KBr): 3360(NH), 1640 cm^{-1} (CO); ^1H NMR($CDCl_3$, 500 MHz), δ 3.68 (dt, 2H, J_1=5.96 Hz, J_2=0.88 Hz), 3.73(dt, 2H, J_1=5.97 Hz, J_2=0.88 Hz), 3.99(t, 4H, J=4.64 Hz), 4.30(t, 4H, J=4.64 Hz), 6.96(dd, 2H , J_1=8.40 Hz, J_2=0.66 Hz), 7.08(dt, 2H, J_1=7.29 Hz, J_2=0.66 Hz), 7.42(dt, 2H, J_1=7.29 Hz, J_2=1.77 Hz), 8.17(dd, 2H, J_1=7.74 Hz, J_2= 1.77 Hz), 8.42(b, 2H); MS : m/z = 740(M^+), 614, 503, 502(base peak), 464, 416, 415, 414, 314, 264, 231, 226, 220, 219, 169, 120, 83;UV(CH_3OH) λ 229.5 (ε_{max} = 21000), 286 nm (ε = 6300).

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