# An Efficient Synthesis of Novel Benzo-Fused Macrocyclic Dilactams

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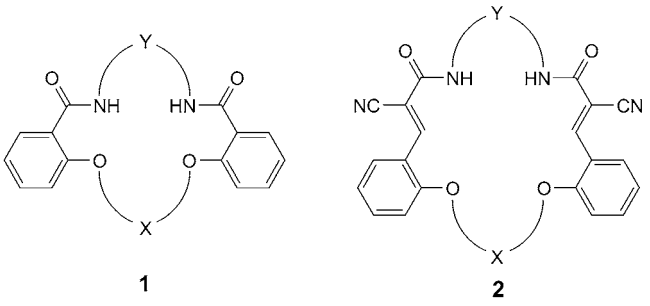
A facile synthetic approach was adopted towards the synthesis of benzo-fused macrocyclic lactams **2a**–**2g** *via* the base-catalyzed condensation reaction of 2,2′-[alkanediylbis(oxy)]bis[benzaldehydes] **3a**–**3c** with *N*,*N*′-substituted bis[2-cyanoacetamide] derivatives **7a**–**7c** (*Scheme 2*). The latter compounds were obtained by the reaction of the appropriate diamines **6a**–**6c** with ethyl 2-cyanoacetate (**4**). Attempts to prepare the oxaaza macrocycles **2** by alternative pathways were also investigated. The novel pyrazolo-fused macrocycles **13a** and **13b** were obtained in 48 and 52% yield, respectively, upon treatment of **2d** and **2g** with $NH_2NH_2 \cdot H_2O$ at 100° (*Scheme 4*).

**Introduction.** – Over the past few decades and since the pioneering work of *Pedersen* [1], *Lehn* [2], and *Cram* [3] on the syntheses and application of macrocyclic host systems, such compounds have attracted much attention. These macrocycles have been shown to exhibit important applications including selective ion separation and detection, molecular recognition, catalysis, biological applications, as well as many other interesting applications in diverse fields of supramolecular chemistry [4]. Of particular interest are crown ethers incorporating amide groups [5]. It was reported that such groups modify the binding properties of the crown compounds with respect to alkali metal ions [6]. Furthermore, macrocyclic lactams are precursors in the preparation of azacrown ethers and cryptands [7]. Some diamide-containing macrocycles have been utilized as new catalysts [8]. Moreover, the insertion of aromatic and/or heterocyclic ring systems into the macrocycles provide rigidity and the possibility, in some cases, to participate in complexation *via* their soft donor atoms [4f].

In connection with these findings and in continuation of our interest on the synthesis of oxaaza macrocyclic dilactams [9], we report herein on the synthesis of a novel class of macrocyclic dilactams **2** by a simple and facile synthetic approach.

**Results and Discussion.** – Previously we reported the synthesis of dibenzo-fused macrocyclic dilactams **1** by reacting the appropriate bis-phenol with the corresponding dihalo compounds in basic solution [9]. Compounds **1** could also be prepared *via* amidation of the appropriate diesters or dicarbonyl dichlorides with the corresponding diamine derivatives [10]. The synthesis of **1** by ring closure metathesis (RCM) of the appropriate bis[2-(allyloxy)benzamide] in the presence of *Grubbs* catalyst was also reported recently [11].

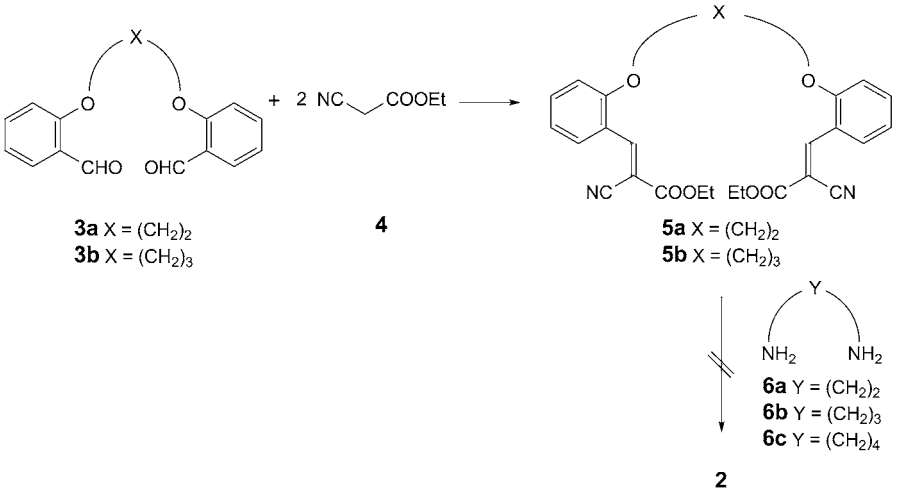
In this study, we intended to synthesize macrocyclic diamides of type **2** as a new class of macrocycles with structure variations within the ligand **1** aiming at improving their selective binding of charged or neutral species. Two strategies were investigated for the




X, Y = aliphatic or aromatic moiety

synthesis of the target compound **2**. In the first strategy (*Scheme 1*), we elaborated the synthesis of bis[2-benzylidene-2-cyanoacetates] **5** [12] by condensation of the corresponding bis-aldehydes **3** [13] with ethyl 2-cyanoacetate (**4**). Compounds **5** should then undergo cyclocondensation with the appropriate diamines **6** to give macrocycles **2**. Unfortunately, cyclocondensation of **5** with diamines **6** did not yield the corresponding macrocyclic diamides **2**. The reaction gave instead a mixture of products that were difficult to separate and have not been characterized yet.

*Scheme 1*




**3a** X = $(CH_2)_2$
**3b** X = $(CH_2)_3$

**4**

**5a** X = $(CH_2)_2$
**5b** X = $(CH_2)_3$

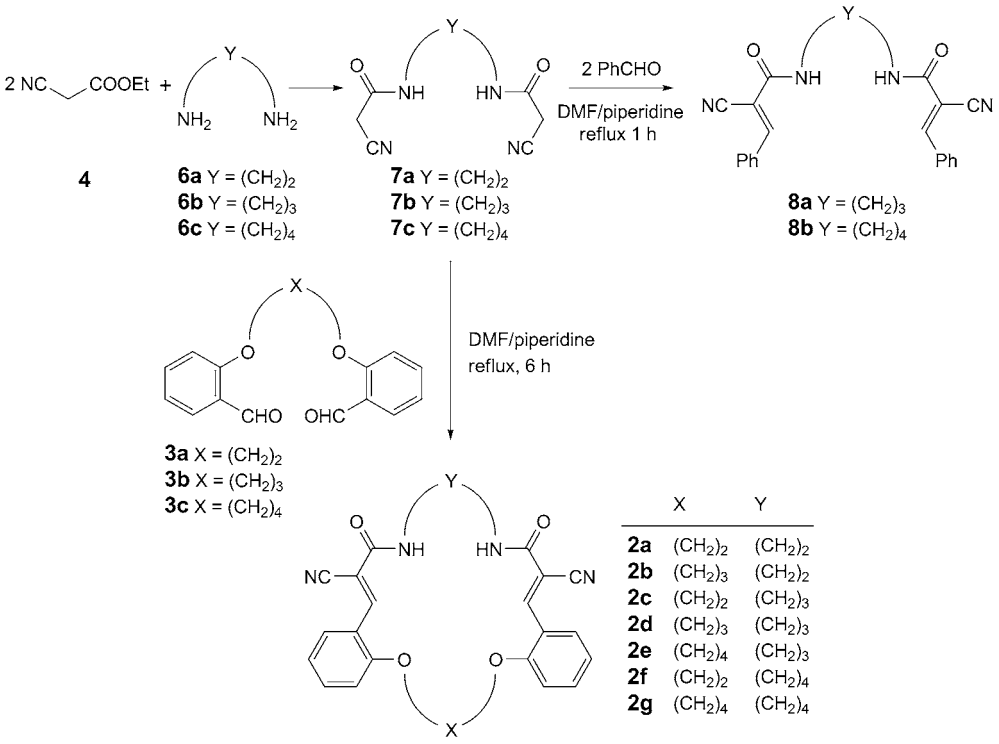
**6a** Y = $(CH_2)_2$
**6b** Y = $(CH_2)_3$
**6c** Y = $(CH_2)_4$

**2**

In search of an expedient pathway to prepare the target macrocyclic dilactams **2**, our attention focused on *N*,*N*′-substituted bis[2-cyanoacetamide] derivatives **7** as precursors, which should undergo cyclocondensation with the appropriate bis-aldehydes **3** to give **2** (*Scheme 2*). *N*,*N*′-Substituted bis[2-cyanoacetamide] derivatives **7a**–**7c** could be prepared *via* the reaction of **4** with the appropriate diamines **6a**–**6c** [14]. First the reactivity of compounds **7a**–**7c** towards aromatic aldehydes was investigated. Thus, condensation of **7b** or **7c** with benzaldehyde in DMF in the presence

of piperidine as a basic catalyst gave the corresponding arylidene derivatives **8a** and **8b** [16] in 87 and 72% yield, respectively (*Scheme 2*). Meanwhile, reaction of **7a** with the bis-aldehyde **3a** in DMF in the presence of a catalytic amount of piperidine under high-dilution conditions gave the corresponding macrocyclic dilactam **2a** in 53% yield. Similarly, macrocycles **2b**–**2g** were prepared in 54–78% by cyclocondensation of the appropriate *N*,*N*′-substituted bis[2-cyanoacetamide] derivatives **7a**–**7c** with the corresponding bis-aldehydes **3a**–**3c** (*Scheme 2*). The structures of **2a**–**2g** as well as of **8a** and **8b** were established by IR, $^1$H-NMR, and mass spectra, and elemental analysis. Thus, their $^1$H-NMR spectra revealed the absence of the activated $CH_2$ group and exhibited the presence of the ylidene olefinic H-atoms at $\delta$(H) 7.94–8.51. The olefinic H-atom signals at these chemical shift values indicated that the methine protons were located in a *trans* position to the CN group [15].

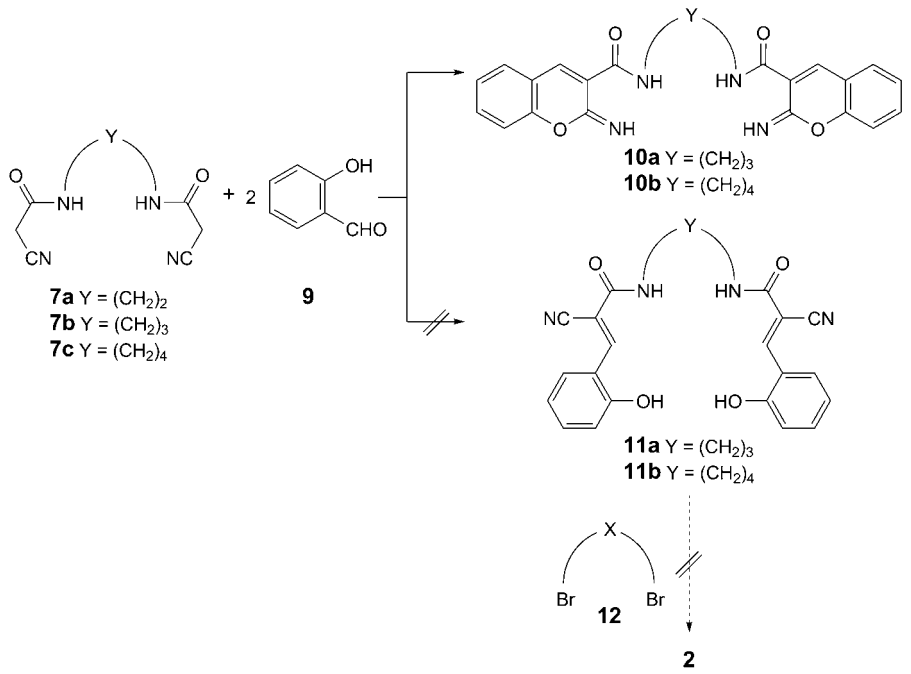
*Scheme 2*




We also attempted to prepare the oxaaza macrocycles **2** by an alternative pathway, *i.e.*, by the reaction of **7** with salicylaldehyde (=2-hydroxybenzaldyhyde; **9**) to give bis-phenols **11**, and by subsequent bis-alkylation with the corresponding dihaloalkanes **12** in basic solution. Unfortunately, we were not able to isolate pure samples of **11** upon treatment of **7b** or **7c** with **9** in DMF in the presence of a catalytic amount of piperidine at 100°. Instead, the corresponding bis[2-imino-2*H*-1-benzopyran] derivatives **10a** and **10b** [17] were obtained (*Scheme 3*). The reaction probably took place by condensation

of the aldehyde function with the methylene group to give **11a** and **11b**, followed by nucleophilic attack of the OH group at the neighboring CN group resulting in **10a** and **10b**. The absence of the CN group in the IR spectra of **10a** and **10b** confirmed its involvement in the cyclization process. Moreover, the isolation of **10a** and **10b** from the reaction confirmed the existence of the intermediate **11** as (*E*) isomer, in which CN is in a *trans* position to the olefinic H-atom as only this isomer can easily undergo cyclization to the corresponding benzopyran.

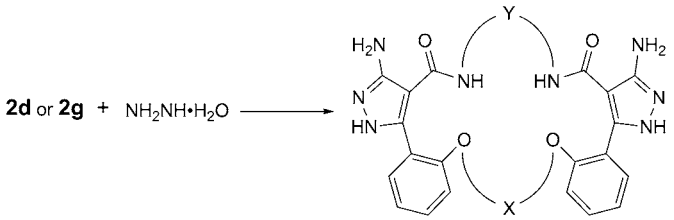
*Scheme 3*




The acrylonitrile moiety in compounds **2d** and **2g** prompted us to study their synthetic utility as building blocks for novel pyrazolo-fused macrocycles **13a** and **13b**. The latter compounds were obtained in 48 and 52% yields, respectively, upon treatment of **2d** and **2g** with $NH_2NH_2 \cdot H_2O$ at 100° (*Scheme 4*). Again, the absence of the CN absorption in the IR spectra of **13a** and **13b** confirmed its involvement in the cyclization process. The IR spectra of **13a** and **13b** revealed, in addition to the disappearance of the stretching vibration at 2200 $cm^{-1}$ due to the cyano function, the appearance of the stretching vibration at 3300–3100 $cm^{-1}$, the characteristic band for the $NH_2$ group. Also, the $^1$H-NMR spectra showed the signals of NH moieties at $\delta$(H) *ca.* 8.50–8.90 and of $NH_2$ groups at $\delta$(H) *ca.* 6.40–6.50.

**Conclusions.** – We prepared a new series of macrocyclic diamides by structure variations within some previously prepared derivatives. These variations involve an

*Scheme 4*




**13a** X = Y = $(CH_2)_3$
**13b** X = Y = $(CH_2)_4$

alteration of the arrangement of the donor atoms in the macrocyle as well as the insertion of heterocyclic moieties into the macrocycles. The novel compounds were prepared by a simple base-catalyzed condensation reaction of the appropriate bis-aldehydes with the corresponding *N*,*N*′-substituted bis[2-cyanoacetamide] derivatives and subsequent reaction with $NH_2NH_2 \cdot H_2O$. We expect an improvement of the binding abilities of the new macrocycles compared to their corresponding precursors. The new macrocycles offer the advantage of their easy synthesis in a simple procedure from inexpensive starting materials. A study of their complexing properties will be described in detail when the work is completed.

## Experimental Part

*General.* M.p.: *Gallenkamp* apparatus; in open glass capillaries; not corrected. IR Spectra: *Pye-Unicam-SP-3-300* and *Shimadzu-FTIR-8101-PC* spectrophotometers; in KBr; $\tilde{\nu}$ in $cm^{-1}$. $^1$H- and $^{13}$C-NMR Spectra: *Varian-Mercur-VX-300* spectrometer; $SiMe_4$ as internal standard and $(D_6)$DMSO as solvent; $\delta$ in ppm and *J* in Hz. MS: *GCMS-QP1000 EX* spectrometer; at 70 eV; in *m*/*z* (rel. %).

*Macrocycles* **2a**–**2g**; *General Procedure.* To a soln. of the appropriate bis-aldehyde **3a**–**3c** [13] (10 mmol) in DMF (50 ml) was added a soln. of the appropriate bis[2-cyanoacetamide] **7a**–**7c** [14] (10 mmol) in DMF (50 ml), in the presence of a cat. amount of piperidine. The mixture was then heated under reflux for 6 h. The solvent was evaporated and the remaining solid recrystallized from DMF/EtOH: **2a**–**2g** as yellowish brown crystals.

*(5*E*,13*E*)-7,8,9,10,11,12,20,21-Octahydro-7,12-dioxodibenzo[*e,q*][1,4,10,13]dioxadiazacyclooctadecine-6,13-dicarbonitrile* (**2a**): Yield 53%. M.p. 264–266°. IR (KBr): 3389 (NH), 2211 (CN), 1644 (CO). $^1$H-NMR ($(D_6)$DMSO): 3.44 (*s*, 2 $CH_2$N); 4.47 (*s*, 2 $CH_2$O); 7.11 (*t*, *J* = 7.5, 2 arom. H); 7.28 (*d*, *J* = 8.4, 2 arom. H); 7.54 (*t*, *J* = 7.5, 2 arom. H); 8.01 (*d*, *J* = 7.8, 2 arom. H); 8.27 (*s*, 2 NH, $D_2$O-exchangeable); 8.46 (*s*, 2 =CH). MS: 428 (39.9, $M^+$). Anal. calc. for $C_{24}H_{20}N_4O_4$ (428.44): C 67.28, H 4.71, N 13.08; found: C 67.25, H 4.73, N 13.06.

*(5*E*,13*E*)-7,8,9,10,11,12,21,22-Octahydro-7,12-dioxo-20*H*-dibenzo[*f,r*][1,5,11,14]dioxadiazacyclononadecine-6,13-dicarbonitrile* (**2b**): Yield 54%. M.p. 268–270°. IR (KBr): 3396 (NH), 2211 (CN), 1660 (CO). $^1$H-NMR ($(D_6)$DMSO): 2.24 (*t*, *J* = 6.0, $OCH_2CH_2CH_2O$); 3.46 (*s*, $NCH_2CH_2N$); 4.26 (*t*, *J* = 5.7, $OCH_2CH_2CH_2O$); 7.13 (*t*, *J* = 7.2, 2 arom. H); 7.24 (*d*, *J* = 8.4, 2 arom. H); 7.55 (*t*, *J* = 7.8, 2 arom. H); 7.99 (*d*, *J* = 7.8, 2 arom. H); 8.34 (*s*, 2 =CH); 8.74 (*s*, 2 NH, $D_2$O-exchangeable). $^{13}$C-NMR ($(D_6)$DMSO): 28.1; 38.9; 66.1; 107.7; 114.5; 116.3; 121.2; 121.8; 128.4; 133.8; 144.5; 157.3; 162.0. MS: 442 (75.1, $M^+$). Anal. calc. for $C_{25}H_{22}N_4O_4$ (442.46): C 67.86, H 5.01, N 12.66; found C 67.83, H 5.03, N 12.64.

*(5*E*,14*E*)-8,9,10,11,12,13,21,22-Octahydro-7,13-dioxo-7*H*-dibenzo[*e,r*][1,4,10,14]dioxadiazacyclononadecine-6,14-dicarbonitrile* (**2c**): Yield 60%. M.p. 286–288°. IR (KBr): 3351 (NH), 2212 (CN), 1672 (CO). $^1$H-NMR ($(D_6)$DMSO): 1.87 (br. *s*, $NCH_2CH_2CH_2N$); 3.38 (br. *s*, $NCH_2CH_2CH_2N$); 4.48 (*s*, 2

$CH_2O$); 7.15 (*t*, *J* = 7.8, 2 arom. H); 7.29 (*d*, *J* = 8.4, 2 arom. H); 7.58 (*t*, *J* = 7.8, 2 arom. H); 7.97 (*s*, 2 NH, $D_2O$-exchangeable); 8.12 (*d*, *J* = 7.8, 2 arom. H) , 8.51 (*s*, 2 =CH). $^{13}$C-NMR ((D$_6$)DMSO): 26.9; 35.1; 66.4; 105.8; 113.3; 116.8; 121.1; 121.2; 128.1; 134.0; 145.3; 157.3; 160.5. MS: 442 (23.5, $M^+$). Anal. calc. for $C_{25}H_{22}N_4O_4$ (442.46): C 67.86, H 5.01, N 12.66; found: C 67.85, H 4.98, N 12.68.

*(5*E*,14*E*)-8,9,10,11,12,13,22,23-Octahydro-7,13-dioxo-7*H*,21*H*-dibenzo[*f,s*][1,5,11,15]dioxadiazacycloeicosine-6,14-dicarbonitrile* (**2d**): Yield 78%. M.p. 235–237°. IR (KBr): 3285 (NH), 2207 (CN), 1648 (CO). $^1$H-NMR ((D$_6$)DMSO): 1.78 (br. *s*, $NCH_2CH_2CH_2N$); 2.27 (*t*, *J* = 5.4, $OCH_2CH_2CH_2O$); 3.29 (br. *s*, $NCH_2CH_2CH_2N$); 4.30 (*t*, *J* = 5.4, $OCH_2CH_2CH_2O$); 7.10 (*t*, *J* = 7.5, 2 arom. H); 7.20 (*d*, *J* = 8.4, 2 arom. H); 7.53 (*t*, *J* = 7.5, 2 arom. H); 8.01 (*d*, *J* = 7.8, 2 arom. H); 8.33 (*s*, 2 NH, $D_2O$-exchangeable); 8.47 (*s*, 2 =CH). MS: 456 (18.4, $M^+$). Anal. calc. for $C_{26}H_{24}N_4O_4$ (456.49): C 68.41, H 5.30, N 12.27; found: C 68.38, H 5.26, N 12.26.

*(5*E*,14*E*)-8,9,10,11,12,13,21,22,23,24-Decahydro-7,13-dioxo-7*H*-dibenzo[*g,t*][1,6,12,16]dioxadiazacycloheneicosine-6,14-dicarbonitrile* (**2e**): Yield 62%. M.p. 260–262°. IR (KBr): 3358 (NH), 2213 (CN), 1660 (CO). $^1$H-NMR ((D$_6$)DMSO): 1.71 (br. *s*, $NCH_2CH_2CH_2N$); 1.90 (br. *s*, $OCH_2CH_2CH_2CH_2O$); 3.26 (br. *s*, $NCH_2CH_2CH_2N$); 4.15 (br. *s*, $OCH_2CH_2CH_2CH_2O$); 7.09 (*t*, *J* = 7.5, 2 arom. H); 7.23 (*d*, *J* = 8.4, 2 arom. H); 7.56 (*t*, *J* = 7.5, 2 arom. H); 7.97 (*d*, *J* = 7.8, 2 arom. H); 8.32 (*s*, 2 =CH); 8.56 (*s*, 2 NH, $D_2O$-exchangeable). MS: 470 (74.5, $M^+$). Anal. calc. for $C_{27}H_{26}N_4O_4$ (470.52): C 68.92, H 5.57, N 11.91; found: C 68.94, H 5.54, N 11.88.

*(5*E*,15*E*)-7,8,9,10,11,12,13,14,22,23-Decahydro-7,14-dioxodibenzo[*e,s*][1,4,10,15]dioxadiazacycloeicosine-6,15-dicarbonitrile* (**2f**): Yield 57%. M.p. 274–276°. IR (KBr): 3332 (NH), 2212 (CN), 1668 (CO). $^1$H-NMR ((D$_6$)DMSO): 1.48 (br. *s*, $NCH_2CH_2CH_2CH_2N$); 3.20 (br. *s*, $NCH_2CH_2CH_2CH_2N$); 4.49 (*s*, 2 $CH_2O$); 7.12 (*t*, *J* = 7.5, 2 arom. H); 7.28 (*d*, *J* = 8.4, 2 arom. H); 7.57 (*t*, *J* = 7.5, 2 arom. H); 7.98 (*d*, *J* = 7.8, 2 arom. H); 8.23 (*s*, 2 NH, $D_2O$-exchangeable); 8.50 (*s*, 2 =CH). MS: 456 (13.5, $M^+$). Anal. calc. for $C_{26}H_{24}N_4O_4$ (456.49): C 68.41, H 5.30, N 12.27; found: C 68.45, H 5.29, N 12.24.

*(5*E*,15*E*)-7,8,9,10,11,12,13,14,22,23,24,25-Dodecahydro-7,14-dioxodibenzo[*g,u*][1,6,12,17]dioxadiazacyclodocosine-6,15-dicarbonitrile* (**2g**): Yield 66%. M.p. 278–280°. IR (KBr): 3292 (NH), 2211 (CN), 1644 (CO). $^1$H-NMR ((D$_6$)DMSO): 1.50 (br. *s*, $NCH_2CH_2CH_2CH_2N$); 1.92 (br. *s*, $OCH_2CH_2CH_2CH_2O$); 3.21 (br. *s*, $NCH_2CH_2CH_2CH_2N$); 4.16 (br. *s*, $OCH_2CH_2CH_2CH_2O$); 7.09 (*t*, *J* = 7.8, 2 arom. H); 7.21 (*d*, *J* = 8.4, 2 arom. H); 7.54 (*t*, *J* = 7.8, 2 arom. H); 7.95 (*d*, *J* = 7.8, 2 arom. H); 8.30 (*s*, 2 =CH); 8.52 (*s*, 2 NH, $D_2O$-exchangeable). $^{13}$C-NMR ((D$_6$)DMSO): 25.0; 26.3; 39.3; 67.9; 107.1; 112.7; 116.3; 120.6; 120.7; 128.3; 133.9; 144.9; 157.3; 161.3. MS: 484 (59.1, $M^+$). Anal. calc. for $C_{28}H_{28}N_4O_4$ (484.54): C 69.41, H 5.82, N 11.56; found: C 69.37, H 5.80, N 11.53.

*Reaction of Bis[2-cyanoacetamide]* **7b** *and* **7c** *with Aromatic Aldehydes.* To a soln. of **7b** or **7c** (20 mmol) in DMF (15 ml) containing a few drops of piperidine, the corresponding aromatic aldehyde was added. The mixture was heated under reflux for 1 h. Then the solvent was evaporated and the remaining solid crystallized from the proper solvent: yellow crystals of **8a** and **8b** and **10a** and **10b**.

*(2*E*,2′*E*)-*N,N′*-Propane-1,3-diylbis[2-cyano-3-phenylprop-2-enamide]* (**8a**): Yield 87%. M.p. 140–141° (DMF/EtOH) ([16]: M.p. 138–140°).

*(2*E*,2′*E*)-*N,N′*-Butane-1,4-diylbis[2-cyano-3-phenylprop-2-enamide]* (**8b**): Yield 72%. M.p. 190° (DMF/EtOH) ([16]: M.p. 188–190°).

N,N′*-Propane-1,3-diylbis[2-imino-2*H*-1-benzopyran-3-carboxamide]* (**10a**): Yield 66%. M.p. 253–255° (EtOH) ([17]: M.p. 253–255°).

N,N′*-Butane-1,4-diylbis[2-imino-2*H*-1-benzopyran-3-carboxamide]* (**10b**): Yield 64%. M.p. 255° (EtOH) ([17]: M.p. 252–253°).

*Reaction of $NH_2NH_2 \cdot H_2O$ with* **2d** *and* **2g**: *General Procedure.* To a soln. of **2d** or **2g** (1 mmol) in EtOH (5 ml), $NH_2NH_2 \cdot H_2O$ 80% (5 ml) was added. The mixture was heated under reflux for 6 h and then poured on crashed ice. The solid product was collected by filtration and recrystallized from AcOH: **13a** and **13b**, resp.

*3,11-Diamino-6,7,8,9,20,21-hexahydro-1*H*,19*H*-dibenzo[*f,s*]dipyrazolo[3,4-*h*:4′,3′-*q*][1,5,11,15]dioxadiazacycloeicosine-4,10(5*H*,13*H*)-dione* (**13a**): Yield 48%. M.p. 168–170°. IR (KBr): 3368, 3232, 3180 (NH, $NH_2$), 1642 (CO). $^1$H-NMR ((D$_6$)DMSO): 1.88 (br. *s*, $NCH_2CH_2CH_2N$); 2.04 (*t*, *J* = 5.4, $OCH_2CH_2CH_2O$); 4.26 (br. *s*, $NCH_2CH_2CH_2N$); 4.36 (br. *s*, $OCH_2CH_2CH_2O$); 6.52 (*s*, 2 $NH_2$, $D_2O$-exchangeable); 7.00 (*t*, *J* = 7.5, 2 arom. H); 7.16 (*d*, *J* = 8.4, 2 arom. H); 7.45 (*t*, *J* = 7.5, 2 arom. H); 7.95

(*d*, *J* = 7.8, 2 arom. H); 8.49 (*s*, 2 NH, $D_2O$-exchangeable); 8.91 (*s*, 2 NH, $D_2O$-exchangeable). MS: 516 (21.3, $M^+$). Anal. calc. for $C_{26}H_{28}N_8O_4$ (516.55): C 60.45, H 5.46, N 21.69; found: C 60.48, H 5.42, N 21.66.

*3,12-Diamino-5,6,7,8,9,10,20,21,22,23-decahydrodibenzo[*g,u*]dipyrazolo[3,4-*i*:4′,3′-*s*][1,6,12,17]dioxadiazacyclodocosine-4,11(1*H*,14*H*)-dione* (**13b**): Yield 52%. M.p. 180–182°. IR (KBr): 3296, 3169 (NH, $NH_2$), 1605 (CO). $^1$H-NMR ($(D_6)$DMSO): 1.76 (br. *s*, $NCH_2CH_2CH_2CH_2N$); 1.93 (br. *s*, $OCH_2CH_2CH_2CH_2O$); 4.05 (br. *s*, $NCH_2CH_2CH_2CH_2N$, $OCH_2CH_2CH_2CH_2O$); 6.42 (br. *s*, 2 $NH_2$, $D_2O$-exchangeable); 6.88 (*t*, *J* = 7.8, 2 arom. H); 6.96 (*d*, *J* = 8.4, 2 arom. H); 7.16 (*t*, *J* = 7.8, 2 arom. H); 7.65 (*d*, *J* = 8.4, 2 arom. H); 8.04 (*s*, 2 NH, $D_2O$-exchangeable); 8.52 (*s*, 2 NH, $D_2O$-exchangeable). $^{13}$C-NMR ($(D_6)$DMSO): 22.3; 25.6; 39.4; 67.5; 106.8; 112.3; 116.3; 120.4; 124.3; 124.6; 128.5; 133.9; 155.3; 173.5. MS: 544 (19.3, $M^+$). Anal. calc. for $C_{28}H_{32}N_8O_4$ (544.60): C 61.75, H 5.92, N 20.58; found: C 61.77, H 5.89, N 20.62.

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*Received September 14, 2012*