Synthesis and X-ray Study of Novel Azofurazan-annulated macrocyclic Lactams

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Reaction of 1,4-di-(3-aminofurazan-4-oyl)piperazine **4** with dibromoisocyanurate (DBI) affords azofurazan-annulated macrocyclic lactam **7**; the X-ray structure of the macrocycle **7** is reported. The synthesis was started with 3-aminofurazan-4-carboxylic acid **1**. A one-pot method for preparation of the amino acid was elaborated from commercially available cyanoacetic ester. Amides of the acid have been prepared *via* the esterification and subsequent amination.

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Introduction.

There is considerable current interest in the design of drugs molecules which combined together natural moieties with unnatural synthetic blocks. These combinations generally provide properties ideal for optimal receptor interaction, selective mode of action and clearance from the site of action. It is well known that piperazine chemistry have received much attention since the saturated nitrogen heterocycle is an important building block in natural products and synthetic drugs exhibiting diverse properties.

Macrocycles incorporating the piperazine subunit have the ability to act as host to both neutral molecules and ionic species [1]. Photoresponsive azobenzene bridged piperazine incorporating macrocycles have been shown to change their cavities by the UV-induced *E-Z* isomerism of the N=N bond [2]. As a result, their binding ability would be corrected. A few photoresponsive piperazine macrocycles have been synthesized by condensation of 4,4'-bis(bromomethyl)-azobenzene with piperazine precursors [2].

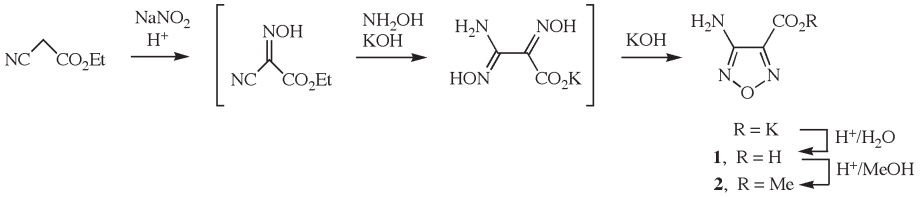
We have recently reported the synthesis and activity of several novel, highly preorganized azofurazan-annulated, piperazine containing chromophoric macrocycles, when the furazan ring was directly N-attached to the piperazine ring [3,4]. The macrocycles closure was a result of N=N bond formation at oxidative cyclization of the corresponding bis(3-aminofurazan-4-yl) piperazine, a procedure that has been currently developed by us [3-7] and others [8-12].

Furazan fused to seven-membered lactams have been synthesized by amide bond formation [13]. No azofurazan macrocycles containing amide moieties have been prepared. Macrocycles when azofurazan, piperazine, and amide units can be combined together to form multisite complexing agents, would be of biological interest.

Results and Discussion.

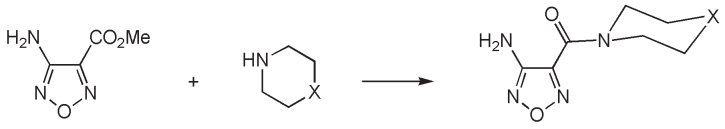
In a series of azofurazan-annulated macrocyclic lactam syntheses, based on the generation and oxidation reactions of bis(3-aminofurazan-4-yl) compounds, the 3-aminofurazan-4-carboxylic acid **1** served as a key synthetic precursor [7]. This acid **1** was previously synthesized by Longo [14] from malononitrile in six steps in a 9% yield. Because of the recurring use of compound **1** this paper details an alternative advantageous route to this versatile intermediate. The most attractive seemed the use of a strategy we recently developed [15-17], based on the reaction of diverse precursors related to α-dicarbonyl compounds with hydroxylamine being oximating, aminating, and redox reagent. We have successfully adapted this strategy to the synthesis of the amino acid **1**. As outlined in Scheme 1, commercially available cyanoacetic ester was converted to cyano oxime (nearly quantitative yield) by nitrosation with sodium nitrite in the presence of an acid by a modified literature procedure [18]. Subsequent treatment with an excess of hydroxylamine hydrochloride and a mixture of NaOH and KOH with heating and vigorous stirring followed by acidification gave the amino acid **1** in 78% yield. The stages are carried out in one-pot. Esterification of the acid **1** with HCl/MeOH at refluxing for 7 h was accomplished by formation of the 3-amino-4-carbmethoxyfurazan **2** in 85% yield. The synthesis of ester **2** was thus achieved in two steps in an overall yield of 69%, which is a significant improvement over the previous route.

Scheme 1



In order to relieve the identification of macrocyclic furazanamide structures, a series of more ordinary model amides was synthesized. Thus, an methanolic solution of the ester **2** and morpholine, thiomorpholine or *N*-methylpiperazine under reflux for 5 h gave the morpolide **3a**, thiomorpolide **3b**, and the piperazide **3c** in 47%, 51%, and 36% yields respectively, together with great recovered starting material (Scheme 2). It is interesting that refluxing of the ester **2** and *N*-methylpiperazine in *n*-butanol 3-aminofurazan-4-carboxylic acid *n*-butyl ester was obtained in 76% yield. We have found that the amides **3a-c** can be synthesized by employing mild amination conditions, in which the ester **2** was heated with a slight excess of the appropriate secondary amine under argon in the absence of any solvent. The reaction was usually accomplished at 120-130 °C over 1 hour. Yields of the amides **3a-c** were *ca*. 80%.

Scheme 2



2

3a (X = O)
3b (X = S)
3c (X = NMe)

The IR spectra of compounds **3a-c** exhibit a band at *ca*. 1650 cm^{-1}, typical of the carbonyl group in amides and a pair of bands at *ca*. 3320 and 3420 cm^{-1}, typical for the amino group attached to the furazan ring. The ^1H NMR spectra show two methylene resonances and a singlet at *ca*. 6.3 ppm, which is characteristic of the amino group [19]. In the ^{13}C NMR spectrum, the low field signal at *ca*. 157 ppm was assigned to the amide carbon atom [20]. Two signals, at *ca*. 156 ppm from quanternary C-NH_2 and at *ca*. 141 ppm from second furazanic carbon, were also observed.

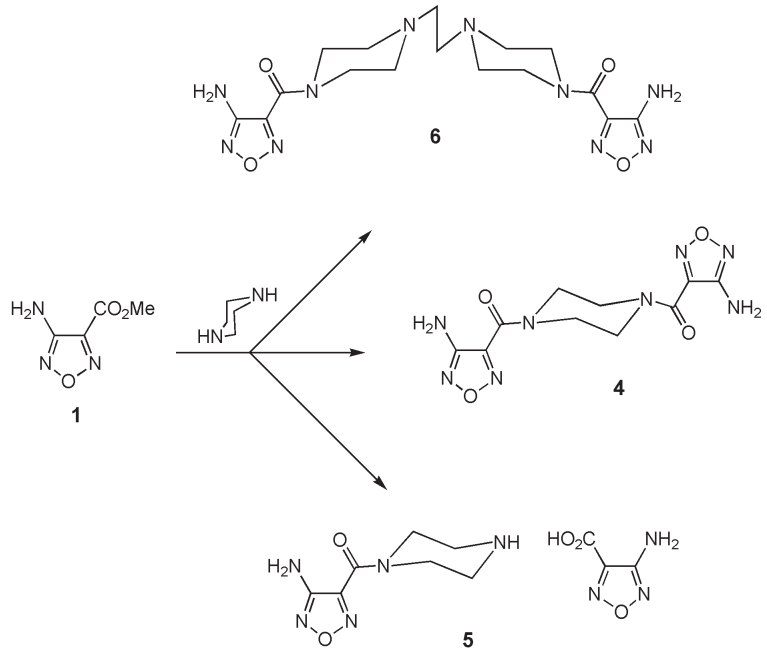
On the other hand, the reaction of ester **2** with piperazine was more complex and three compound were isolated (Scheme 3). Desired diamide **4** (35%) was obtained as a poorly soluble white solid whose spectral data supported structure **4**. A small amount (12%) of water soluble salt **5** was separated. It is interesting that the major product (45%) was tertiary amine **6**. Structure **6** was based on MS, NMR, IR, and microanalysis. Thus, the mass spectrum of **6** showed a strong molecular ion at m/z 420 (100%), which analyzed for $C_{16}H_{24}N_{10}O_4$. The fragment at m/z 390 indicated the loss of NO.

Four groups of protons are observed in the ^1H NMR spectrum of **6**, namely one singlet of the amino group at 6.34 ppm, another singlet of bridge CH_2-groups at 2.7 ppm, and two broadened triplets of the piperazine rings at 3.5 and 3.6 ppm, indicative of a symmetrical structure. Comparison of the ^{13}C NMR spectral data for compound **6** with its analog **3c** showed that they are similar, in agreement with the presence of the tertiary amine fragment.

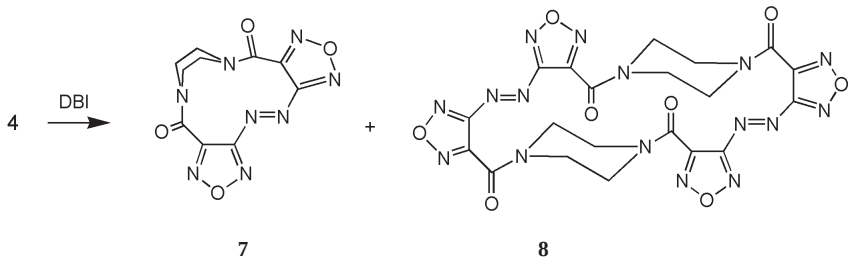
Treatment of diamine **4** with dibromoisocyanurate (DBI) in CH_2Cl_2 at room temperature, according to our recently reported method [6] led to a brown-red slurry (Scheme 4). After 5 h the presence of **4** was no longer detectable and a solution of macrocycles **7** and **8** was easily colleted by filtration from cyanuric acid, which is the product of the transformation of DBI. The solvent was removed under reduced pressure and the crude residue separated by flash column chromatography (SiO_2, typically 5:1 $CHCl_3$-CH_3CN) to give the 12-membered lactam **7** as the major product (55%), together with a small amount of the 24-membered lactam **8** (0,5%).

Treatment of diamine **6** with DBI, carried out in CH_2Cl_2, according to above method, led to a brown-red slurry, which was hard to separate.

Scheme 3



Scheme 4



Lactams **7** and **8** are red orange crystals with high melting points, soluble in warm polar organic solvents and insoluble in water. The electron impact mass spectra of **7** and **8** showed the expected molecular ions at m/z 304 and m/z 608, respectively, and significant peaks due to loss of one (M^+ - 30) and two NO (M^+ - 60) from the molecular ions. The IR spectra of **7** and **8** were similar and exhibited C=O stretches at *ca*. 1650 cm^{-1}. It is important to note, we were unable to measure the ^1H and ^{13}C NMR spectra of **7** due to broad lines possibly caused by dynamic processes.

The structural assignment was unequivocally confirmed by the X-ray crystallographic study of 12-membered lactam **7**. In the Figure 1 molecule **7** is presented in two orientations to show clearly conformation of the azofurazan and the piperazine moieties and their mutual arrangement. The dihedral angle between plane of the furazan ring and plane of neighboring amide fragment equal to 74.32(7)° for C(9)-N(10)-O(11)-N(12)-C(13) and C(8)-O(7)-N(4)-C(3)-C(5), and to 52.07(6)° for C(16)-N(17)-O(18)-N(19)-C(20) and C(21)-O(22)-N(1)-C(2)-C(6). Due to these large values of dihedral angles there is no conjugation between furazan rings and the amide fragments, and the C(8)-C(9) and C(20)-C(21) bonds demonstrate standard bond length for single C-C bond (1.506(2) Å).

The geometry of azofurazan moiety in molecule **7** is similar to the geometry of this fragment in macrocycle **9**, studied by us earlier [6]. The bond lengths of this fragment in molecule **7** are presented in caption to Figure 1. It is worth mentioning that the lengthening of internal N-O bonds (N(12)-O(11) and N(17)-O(18)) in comparison with external N-O bonds (N(10)-O(11) and N(19)-O(18)) is about 0.03 Å. In contrast to the macrocycle **9** [6], in molecule **7** the azofurazan moiety is more planar; the tor-

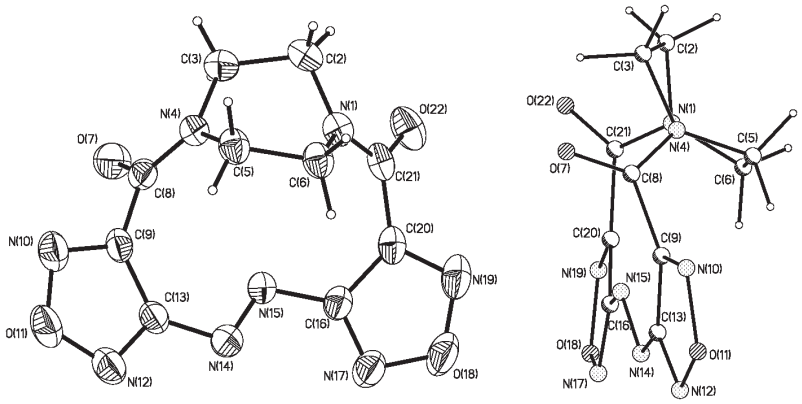
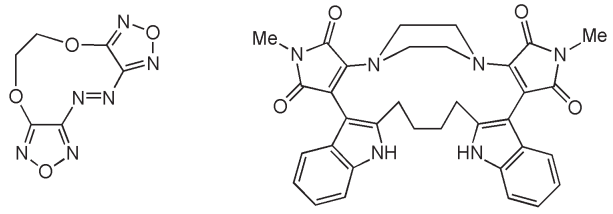


Figure 1. The general view of molecule **7**. Two projections of the molecule, demonstrating conformations of azofurazan and piperazine fragments and their mutual arrangement are shown. Displacement ellipsoids for view **a** are drawn at the 50% probability level. The view **b** is represented as a "ball and stick" model for clarity. The bond lengths for azofurazan fragment (Å): C(9)-N(10) 1.301(2), C(9)-C(13) 1.423(2), N(10-O(11) 1.391(2), O(11)-N(12) 1.358(2), N(12)-C(13) 1.308(2), C(13)-N(14) 1.407(2), N(14)-N(15) 1.244(2), N(15)-C(16) 1.409(2), C(16)-N(17) 1.299(2), C(16)-C(20) 1.425(2), N(17)-O(18) 1.367(2), O(18)-N(19) 1,395(2), N(19)-C(20) 1.296(2).

sion angles N(12)-C(13)-N(14)-N(15) and N(14)-N(15)-C(16)-N(17) are -179.8(2) and 18.9(2)° respectively, while in molecule **9** they are equal to 167 and 32°. The angle between two planes of the furazan rings is 16.51(8) in **7** and 20.9° in **9**. This difference in planarity is evidently a result of smaller size of macrocycle **9** in comparison with **7** (10 versus 12).



9 **10**

Figure 2. Macrocycles **7** and **10**.

Due to incorporation into the macrocycle, the piperazine ring adopts an unusual twist conformation. The atoms C(2) and C(3) deviate from the least square plane of the other four atoms (mean deviation 0.08 Å) by 1.202(2) and 0.847(3) Å respectively. The Cremer & Pople puckering parameters, calculated by RICON program [22] are Q = 0.74, θ = 85°, φ = 26°. Our analysis of the 157 piperazine fragments found in the Cambridge Crystallographic Database [23] revealed only one analogues fragment (CSD refcode QUJDOO), which conformation is not described as a chair [24]. In this structure **10** the piperazine ring is incorporated in the 15-membered macrocycle like in our case (Figure 2). The Cremer & Pople puckering parameters for compound **10** are Q = 0.75, θ = 89°, φ = 2°, hence, the conformation is a boat. Because the nitrogen atoms of the piperazine ring in macrocycle **7** are also included in amide groups, they have planar geometry. The internal piperazine bond angles at N(1) and N(4) are increased to 112.0(1) and 115.8(1)° respectively.

Despite of somewhat higher density of crystals **7**, no shortened intermolecular contacts or peculiarities of crystal packing were found.

EXPERIMENTAL

Melting points were determined on Gallenkamp melting point apparatus and they are not corrected. Infrared spectra were determined in KBr pellets on a Perkin-Elmer Model 577 spectrometer. Mass-spectra were recorded on a Varian MAT-311A instrument. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz on a Bruker AM-300 instrument. Chemical shifts for both ^{1}H NMR and ^{13}C NMR are referred to chemical shifts for solvent (for DMSO-d_6 it is 2.50 ppm and 39.51 ppm for proton and carbon NMR, respectively). All separations were carried out under flash chromatography condition on silica gel. Analytical thin layer chromatography (TLC) was conducted on precoated silica gel plates (Silufol F_{254}).

Crystallographic Data for Macrocycle (**7**).

Crystallographic data was acquired at 298 K, crystals of compound **7** are triclinic, space group P-1, a = 6.517(3) Å, b = 9.323(4) Å, c = 10.203(5) Å, α = 92.06(4)°, β = 105.57(4), γ = 93.48(4), V = 595.2(5) Å^3, Z = 2, M = 304.24, d_{calc} = 1.697 g•cm^{-3}, μ(Mo-K_α) = 0.137 mm^{-1}, F(000) = 312. Intensities of 3774 reflections were

measured with a Siemens P3/PC diffractometer at 293K [λ(Mo-K_α) = 0.71071 Å, θ/2θ scanning, 2θ < 60°], and 3484 independent reflections (R_{int} = 0.0426) were used in further refinement. The structure was solved by direct methods and refined by full-matrix least squares against F^2 in the anisotropic approximation for the non-hydrogen atoms. All hydrogen atoms were located from the difference electron density synthesis and were refined isotropically. The refinement converged to wR_2 = 0.1423 and GOF = 1.037 for all independent reflections [R_1 = 0.0472 was calculated against F for 2390 observed reflections with I > 2σ(I)]. All calculations were performed using SHELXTL program package [25]. Atomic coordinates, atomic anisotropic displacement parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Center as supplementary publication numbers 258586.

3-Aminofurazan-4-carboxylic acid (**1**).

To a stirred emulsion of ethyl cyanoacetate (56.6 g, 0.5 mol) and sodium nitrite (34.5 g, 0.5 mol) in a mixture of EtOH (35 ml) and water (400 ml) was added dropwise 85% H_3PO_4 (20 ml) at 25-30 °C. After 1 h, the mixture was cool to 10 °C, stirred for a further 12 h and treated with sodium hydroxide (4×20 g, 2 mol) and potassium hydroxide (2×28 g, 1 mol). To the resulting solution $NH_2OH•HCl$ (139 g, 2 mol) was slowly added at room temperature. The mixture was heated to 95-100 °C, stirred for 2 h, cooled to ambient temperature and quenched with conc. HCl to pH 1. Precipitation occurred on cooling to 0-5 °C for 6 h and the precipitate was collected by filtration and dried. The filtrate was extracted with diethyl ether (3×60 ml). The combined organic extracts were evaporated under reduced pressure. The residue was combined with the precipitate and recrystallized from hot water to give the title compound **1** (101 g, 78%) as white solid, mp 214-215 °C (lit. mp 213-214°C [21], 216-217°C [14]); ^{1}H nmr (DMSO-d_6): 6.31 (s, 2H, NH_2), 9.1 (b, 1H). ^{13}C nmr (DMSO-d_6): 140.4 (*C*-CO_2H), 156.8 (*C*-NH_2), 160.5 (*C*=O).

3-Amino-4-carbmethoxyfurazan (**2**).

HCl gas was bubbled through a solution of acid **1** (129 g, 1 mol) in methanol (300 ml) at refluxing for 7 h. The solvent was removed and the residue diluted with CH_2Cl_2 (500 ml) and washed with water (100 ml), NaOH (0.1 *M*, 2×50 ml) and finally with water (2×70 ml). Removal of the dried solvent gave colorless solid which was recrystallized from $CHCl_3$ to give ester **2** (122 g, 85%), mp 154-155 °C; ^{1}H nmr (acetone-d_6): 3.97 (s, 3H, OMe), 6.00 (s, 2H, NH_2). ^{13}C nmr (acetone-d_6): 53.5 (OCH_3), 140.2 (*C*-CO_2H), 157.5 (*C*-NH_2), 160.6 (*C*=O). ms: (*m/z*) 143 (M^+), 113 (M^+ - NO).

Anal. Calcd. for $C_4H_5N_3O_3$ (143.10): C, 33.57; H, 3.52; N, 29.36. Found: C, 33.62; H, 3.54; N, 29.33.

4-(3-Aminofurazan-4-oil)morpholine (**3a**).

Method 1.

To a stirred solution of ester **2** (1.4 g, 10 mmol) in methanol (15 ml) morpholine (0.96 g, 11 mmol) was added in one portion under nitrogen. The mixture was refluxed for 6 h. The solvent was removed and the residue separated by chromatography (silica gel, 5% $CH_3CN/CHCl_3$) to give amide **3a** as a white powder: mp 136-138 °C (MeOH); ^{1}H nmr (DMSO-d_6): 3.64 (bs, 4H), 3.68 (bs, 4H), 6.36 (s, 2H, NH_2). ^{13}C nmr (DMSO-d_6): 42.3, 46.9 (OCH_2), 65.7, 66.1 (NCH_2), 141.3 (*C*-CO_2H), 156.1 (*C*-NH_2), 157.1 (*C*=O). ms: (*m/z*) 198 (M^+), 168 (M^+ - NO).

Anal. Calcd. for $C_7H_{10}N_4O_3$ (198.18): C, 42.42; H, 5.09; N, 28.27. Found: C, 42.47; H, 5.13; N, 28.25.

Method 2.

A mixture of ester **2** (1.4 g, 10 mmol) and morpholine (0.87 g, 10 mmol) was stirred at 120-130 °C for 1 h under nitrogen. On cooling to room temperature a white solid was obtained. The solid was washed with $CHCl_3$ and recrystallized from propanol-2 to yield the product **3a** in 93% yield.

The following amides were prepared by the same methods as for **3a**.

4-(3-Aminofurazan-4-oil)thiomorpholine (**3b**).

This compound has the following properties: mp 112-113 C; ir: 3408, 3320, 2928, 1640, 1560, 1512, 1448, 1288, 1164, 992, 956, 848 cm^{-1}; ^{1}H nmr (DMSO-d_6): 3.64 (bs, 4H), 3.68 (bs, 4H), 6.36 (s, 2H, NH_2). ^{13}C nmr (DMSO-d_6): 42.3, 46.9 (OCH_2), 65.7, 66.1 (NCH_2), 141.3 (*C*-CO_2H), 156.1 (*C*-NH_2), 157.1 (*C*=O). ms: (*m/z*) 198 (M^+).

Anal. Calcd. for $C_7H_{10}N_4O_3$ (198.18): C, 42.42; H, 5.09; N, 28.27. Found: C, 42.47; H, 5.13; N, 28.25.

1-Methyl-4-(3-aminofurazan-4-oil)piperazine (**3c**),

This compound has the following properties: mp 100-101 °C; ^{1}H nmr (DMSO-d_6): 2.24 (s, 3H), 2.52 (t, J=4.6 Hz, 4H), 3.68 (t, J=4.6 Hz, 4H), 6.37 (s, 2H, NH_2). ^{13}C nmr (DMSO-d_6): 41.9, 46.5 (CON*C*H_2), 45.5 (Me), 54.0, 54.7 (MeN*C*H_2), 141.5 (*C*-CO_2H), 156.2 (*C*-NH_2), 157.1 (*C*=O). ms: (*m/z*) 211 (M^+).

Anal. Calcd. for $C_8H_{13}N_5O_2$ (211.22): C, 45.49; H, 6.20; N, 33.16. Found: C, 45.58; H, 6.16; N, 33.09.

Quaternary Salt, 1-Benzyl-1-methyl-4-(3-aminofurazan-4-oil)piperazinium Chloride.

This compound has the following properties: mp 238-240 °C; ^{1}H nmr (DMSO-d_6): 3.11 (s, 3H, Me), 4.00, 4.35 (bs, 8H, NCH_2), 4.82 (2H, CH_2Ph), 6.46 (2H, NH_2), 7.55 (m, 5H, Ph). ^{13}C nmr (DMSO-d_6): 36.0, 40.5 (CON*C*H_2), 45.4 (Me), 58.0, 58.3 (N^+CH_2), 67.2 (CH_2Ph), 127.3 (*i*-Ph), 129.1 (*m*-Ph), 130.6 (*p*-Ph), 133.4 (*o*-Ph), 141.1 (*C*-CO_2H), 156.2 (*C*-NH_2), 157.6 (*C*=O).

Anal. Calcd. for $C_{15}H_{19}N_5O_2Cl$ (336.80): C, 53.49; H, 5.69; N, 20.79. Found: C, 53.50; H, 5.71; N, 20.77.

3-Aminofurazan-4-carboxylic Acid *n*-Butyl ester.

To a stirred solution of ester **2** (1.4 g, 10 mmol) in n-butanol (25 ml) N-methyl piperazine (1.1 g, 11 mmol) was added in one portion under nitrogen. The mixture was refluxed for 6 h. The solvent was removed and the residue washed with water (325 ml) and crystallized from water to give the product (76%) as a white solid: mp 73-74 °C; ^{1}H nmr ($CDCl_3$): 0.95 (t, J=6.4 Hz, 3H), 1.46 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 4.41 (t, J=6.1 Hz, 2H, CH_2) 5.13 (s, 2H, NH_2). ^{13}C nmr ($CDCl_3$): 13.5 (Me), 18.9 (CH_2Me), 30.3, 66.6 (O*C*H_2) 138.6 (*C*-CO_2H), 155.9 (*C*-NH_2), 159.7 (*C*=O). ms: (*m/z*) 185 (M^+).

Anal. Calcd. for $C_7H_{11}N_3O_3$ (185.18): C, 45.40; H, 5.99; N, 22.69. Found: C, 45.43; H, 6.10; N, 22.65.

1,4-Di-(3-aminofurazan-4-oyl)piperazine (**4**).

Method 1.

To a stirred solution of ester **2** (1.4 g, 10 mmol) in methanol (40 ml) anhydrous piperazine (0.43 g, 5 mmol) was added in one

portion under nitrogen. The mixture was refluxed for 24 h until starting product spot could not be detected by TLC. On cooling, a white solid gradually precipitated from the reaction mixture. The solid was collected by filtration and washed with CH_2Cl_2 (2×30 ml) and water (2×25 ml) to afford the crude product (mp 292-294 °C) which was recrystallized from ethanol. The title compound **4** (0.17 g, 11%) was obtained as a white powder: mp 312-314 °C; ir: 3420, 3320, 1728, 1616, 1548, 1508, 1460, 1444, 1416, 1364, 1288, 1180, 996, 888, 860, 780 cm^{-1}; ^1H nmr (DMSO-d_6): 3.82 (s, 8H, CH_2), 6.24 (bs, 4H, NH_2). ^{13}C nmr (DMSO-d_6): 52.6 (CH_2), 141.0 (*C*-CO), 155.9 (*C*-NH_2), 157.2 (*C*=O). ms: (*m/z*) 308 (M^+), 292, 261, 251, 224, 196, 166, 112, 84.

Anal. Calcd. for $C_{10}H_{12}N_8O_4$ (308.26): C, 38.96; H, 3.92; N, 36.35. Found: C, 39.02; H, 3.95; N, 36.34.

The filtrate was extracted with CH_2Cl_2 (2×30 ml). The organic layer was washed with H_2O, dried over $MgSO_4$, concentrated *in vacuo* and purified by crystallization from 2-propanol to give compound **6** (0.44 g, 21%) as a white powder: mp 125-127 °C; ir: 3395 (NH), 3300 (NH), 3205, 3105, 2970, 2740 (CH), 2680, 1690 (C=O), 1560 (C=N), 1510 (C=N), 1450, 1360, 1310, 1210, 1190 (CO), 1145, 1060, 1020, 940 (C=N), 860 cm^{-1}; ^1H nmr (DMSO-d_6): 2.73 (m, CH_2), 3.57 (m, CH_2), 6.37 (s, NH_2); ^{13}C nmr (DMSO-d_6): 43.1, 44.2, 45.1, 45.9, 47.9 (CH_2), 141.6 (*C*-CO), 155.9 (*C*-NH_2), 156.8 (*C*=O). ms: (*m/z*) 419 [M^+- H], 361 [M^+ - 2NO + H], 308 [M^+ - H_2N-*F*-CO], 224 [H_2N-*F*-CON(CH_2CH_2)$NCH_2CH_2^+$], 210 [H_2N-*F*-CON(CH_2CH_2)NCH_2^+], 197 [HN(CH_2CH_2)$_2$-$NCH_2CH_2N(CH_2CH_2)N^+$], 181, 152, 112 [H_2N-*F*-CO^+], 84 [H_2N-F^+] (where *F* is furazan ring).

Anal. Calcd. for $C_{16}H_{24}N_{10}O_4$ (420.43): C, 45.71; H, 5.75; N, 33.32. Found: C, 45.79; H, 5.83; N, 33.29.

The water layer was concentrated *in vacuo* and purified by crystallization from aqueous propanol-2 to gave the salt **5** (0.57 g, 35%) as a white powder: mp 186-187 °C; ir: 3420-3410, 3320-3310, 3150-2970, 2650-2610, 2470-2430, 1640, 1560, 1350, 1220, 980, 800 cm^{-1}; ^1H nmr (DMSO-d_6): 3.25 (bs, 4H, CH_2) 3.93 (bs, 4H, CH_2), 5.16 (NH_2), 6.13 (NH_2), 6.29 (NH + OH). ^{13}C nmr (DMSO-d_6): 42.3 (CH_2), 42.8 (CH_2), 141.0 (*C*-CO), 144.5 (*C*-CO), 156.1 (*C*-NH_2), 156.4 (*C*-NH_2), 157 (b, C=O).

Anal. Calcd. for $C_{10}H_{14}N_8O_5$ (326.27): C, 36.81; H, 4.32; N, 34.34. Found: C, 36.82; H, 4.48; N, 34.25.

Method 2.

A mixture of ester **2** (1.4 g, 10 mmol) and anhydrous piperazine (0.43 g, 5 mmol) was stirred at 120-130 °C for 30 min under argon. On cooling to room temperature a white solid was obtained. The solid was washed with CH_2Cl_2 and then dissolved in DMSO followed by the addition of water which precipitated the crude product. After the recrystallization from propanol-2 the product **4** was obtained in 35% yield, mp 312-314 °C. The CH_2Cl_2 layer was concentrated *in vacuo* and a residue was purified by crystallization from propanol-2 to give compound **6** (45%) as a white powder: mp 125-127 °C.

Macrocycle (**7**).

A suspension of the diamine **4** (1.54 g, 5 mmol) and DBI (5.74 g, 20 mmol) in CH_2Cl_2 (80 mL) was stirred vigorously for 5 h. The reaction mixture was filtered to remove cyanuric acid. The filtrate was concentrated *in vacuo* to give a crude orange mixture of compounds **7** and **8**. The products were separated by silica gel flash column chromatography using $CHCl_3$-CH_3CN (5:1) as eluent.

The first fraction, compound **7** (0.84 g, 55%) was obtained as orange crystals: mp 243-245 °C ($CHCl_3$); ms: (*m/z*) 304 (M^+), 274 (M^+ - NO), 245 (M^+ - 2NO), 219, 191, 165, 136, 124, 97, 84; ir: 1656 (C=O), 1548 (C=N), 1492, 1456, 1428, 1280, 1160, 1092, 1028, 1000 (C=N), 894 cm^{-1}.

Anal. Calcd. for $C_{10}H_8N_8O_4$ (304.22): C, 39.48; H, 2.65; N, 36.83. Found: C, 39.50; H, 2.69; N, 36.81.

The second fraction, 24-membered lactam **8** (0.0076 g, 0.5%) was obtained as yellow-orange powder: mp 335-339 °C; ms: (*m/z*) 608 (M^+), 578 (M^+ - NO). Calcd for $C_{20}H_{16}N_{16}O_8$ is 608.45.

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