

# Synthesis of Novel Macrocyclic Peptido-calix[4]arenes and Peptido-pyridines as Precursors for Potential Molecular Metallacages, Chemosensors and Biologically Active Candidates

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Novel macrocyclic dipicolinic acid acylated peptides based on upper rim bridged peptido-calix[4]arenes, peptido-pyridines or hybrid structures of both, were synthesized as potential molecular metallacages and chemosensors. While conventional azide or mixed anhydride (ethyl chloroformate) peptide couplings served well for assembling the L-tyrosine or L-ornithine peptide backbones, the acid chloride of pyridine-2,6-dicarboxylic acid (dipicolinic acid) acid served as the complementary acylating agent. The structure assignment of the new compounds was based on chemical and spectroscopic evidences. Some of these compounds exhibit antimicrobial activities.

**Key words:** Pyridine-2,6-bisamino Acid, Chiral Macrocycles, Peptido-calix[4]arenes, Antimicrobial Agents

## Introduction

The synthesis of chemosensors has become an interesting trend in different fields of analytical chemistry [1–3]. Calixarenes present a unique class of molecular structures having a three-dimensional cavity that can host other atoms or molecules. The structures possess a wide rim with hydrocarbon functionalities and a narrow rim with phenolic groups. Synthetic modifications at these rims can be carried out to introduce desired molecular properties, namely, extra ligands [4, 5]. Accordingly, for versatile applications, narrow rim metal-narrow rim, narrow rim metal-wide rim or wide rim metal-wide rim cages could be assembled for hosting organic molecules [6–8]. Analogously, for the analytical aspects of hazardous heavy metal contaminants, chemosensors based on calixarene metallacage architectures seemed particularly attractive [5]. In this context, we reported the synthesis of chemosensors as an interesting approach providing accurate analytical tools in different analytical fields. In particular, 2,6-peptido-pyridines exhibited a general ionophoric potency [9] and were used for inventing novel thiocyanate-selective membrane sensors [10]. Furthermore, macrocyclic peptido-calixarenes have been synthesized and investigated as analogues of vancomycin-type antibiotics [11–13].

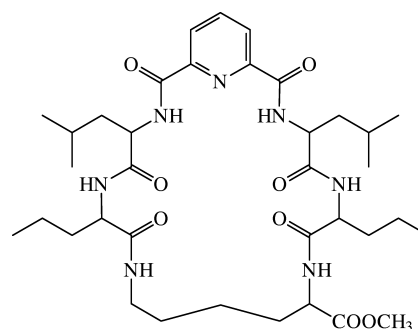


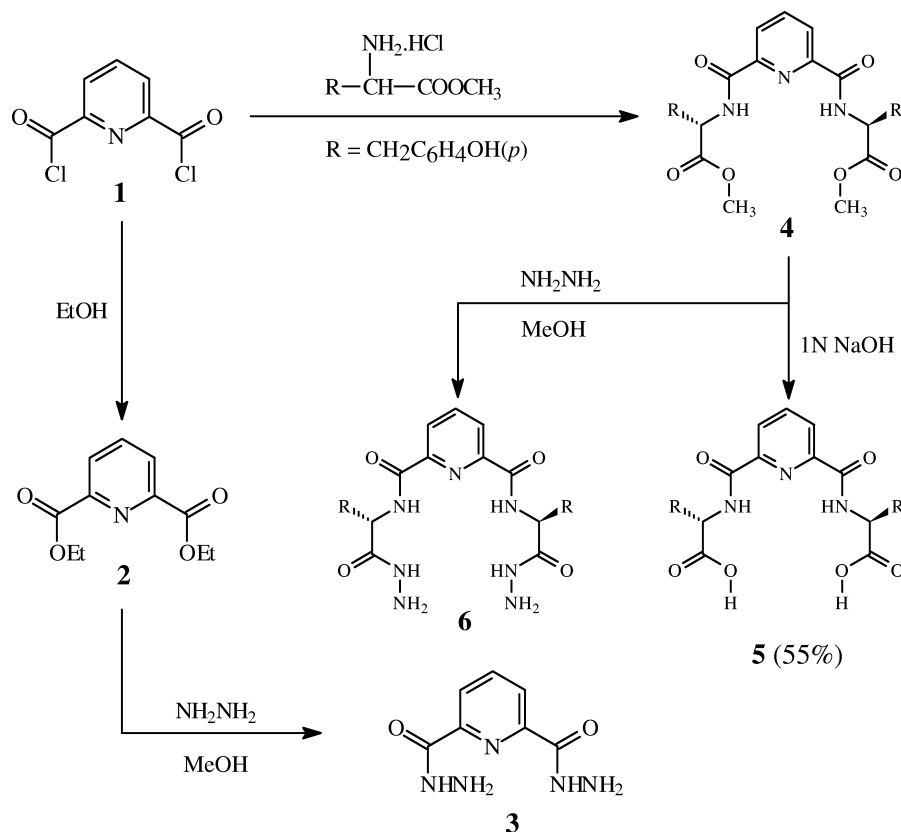
Fig. 1. Anticancer cyclic pentapeptide **X** [19].

Recently, we have demonstrated the significance of 2,6-di-substituted pyridine derivatives as biologically active congeners [14–18]. We have, accordingly, reported a potent anti-cancer activity for the cyclic peptido-pyridines **X** (Fig. 1) [19].

In view of these findings, we synthesized some novel macrocyclic 2,6-peptido-pyridines, as well as the corresponding peptido-calix[4]arenes, as precursors for molecular chemo-sensors and potentially biologically active compounds.

## Results and Discussion

In the present work we report the synthesis and a preliminary antimicrobial screening of several macro-



Scheme 1. Synthetic routes for compounds 3–6.

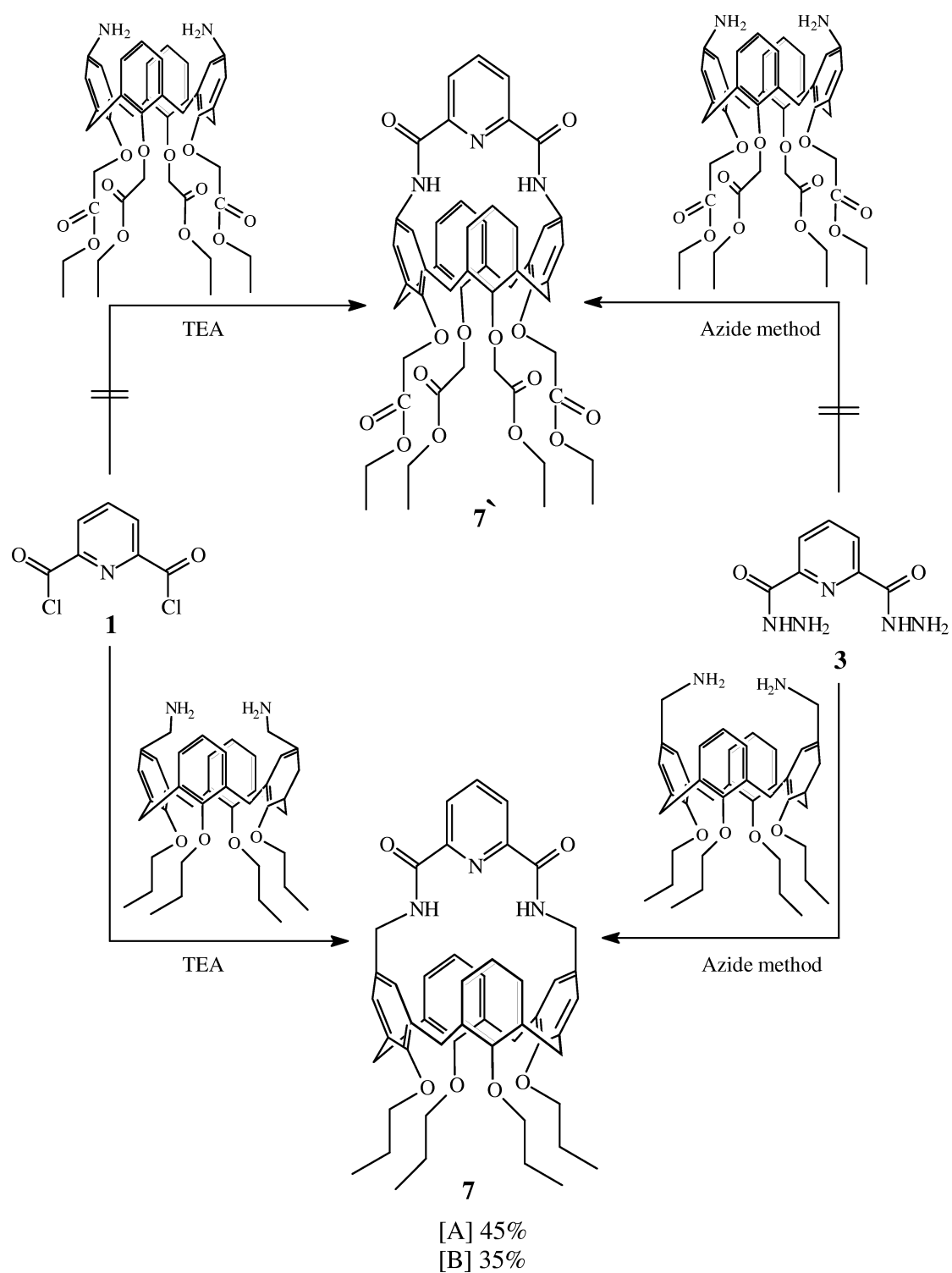
cyclic derivatives based on 2,6-pyridinedicarbonyl dichloride (**1**), 2,6-pyridine-dicarboxylic acid dihydrazide (**3**), *N,N*-bis-[1-carboxy-2-(*p*-hydroxybenzyl)]-2,6-(diaminocarbonyl)-pyridine (**5**) and the corresponding hydrazide (**6**) which was obtained from the corresponding ester (**4**), according to published procedures [20–24]. The synthesis of compounds **1–6** is presented in Scheme 1.

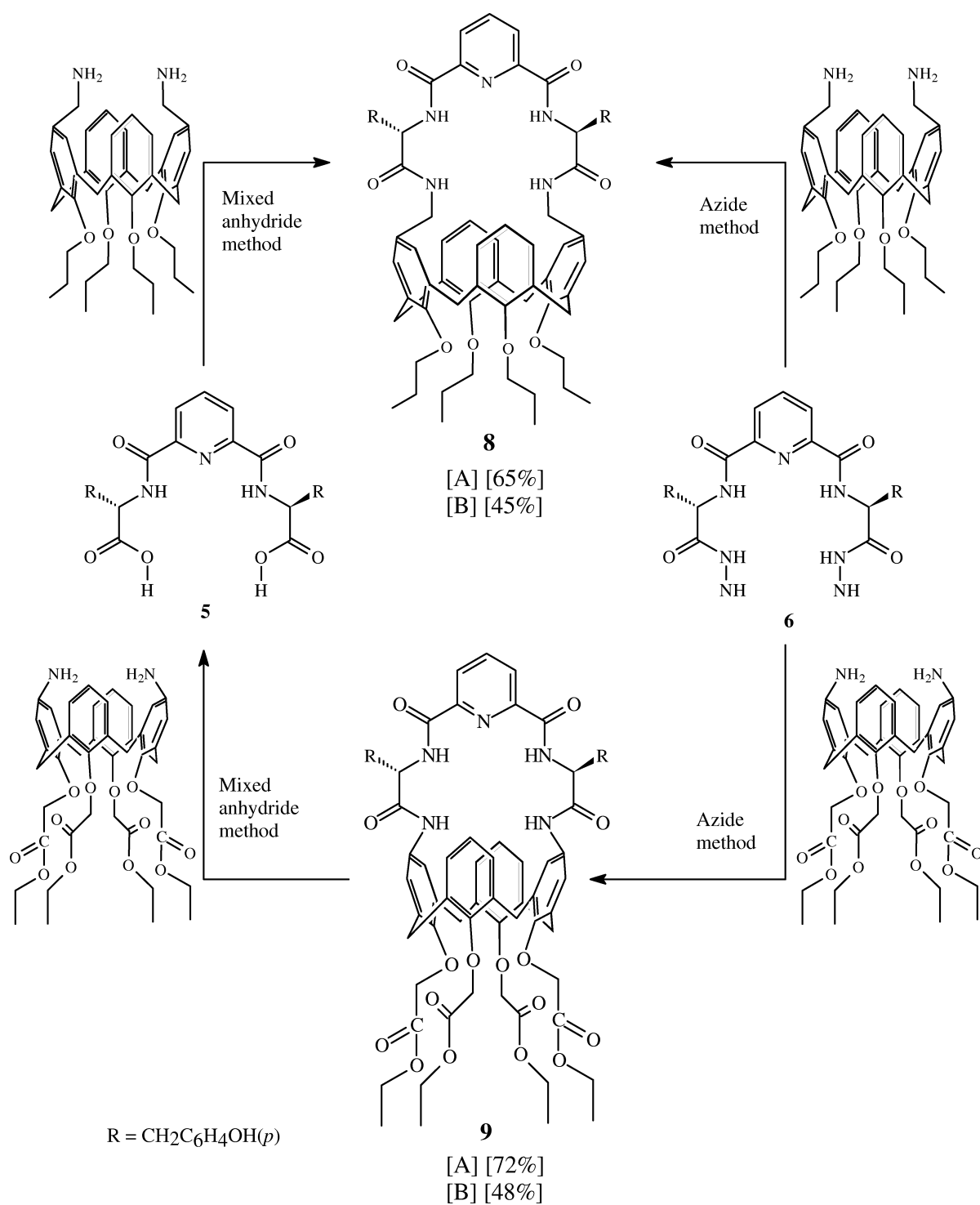
In addition, the synthesis of macrocyclic amide and peptido-calixarene derivatives was realized by the use of the potent azide and mixed anhydride coupling methods [21,25], which lead mostly to the formation of optically pure products. The diester derivative **4** was hydrolyzed to the corresponding diacid **5** by 1N sodium hydroxide. Coupling of 5,17-diaminomethyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene with 2,6-pyridinedicarbonyl dichloride (**1**) (Method A) in the presence of triethylamine afforded the macrocyclic pyridino-calix[4]arene derivative **7**. This compound was also obtained by reacting 2,6-pyridinedicarboxylic acid hydrazide (**3**) (as azide, Method B) with the same diamino-calix[4]arene. How-

ever, when 5,17-diamino-25,26,27,28-tetrakis[(ethoxycarbonyl)-methoxy]calix[4]arene was allowed to react with the same diacid dichloride or diazide, the chiral macrocyclic calix[4]arene **7'** was not formed, presumably due to steric hinderance (Scheme 2).

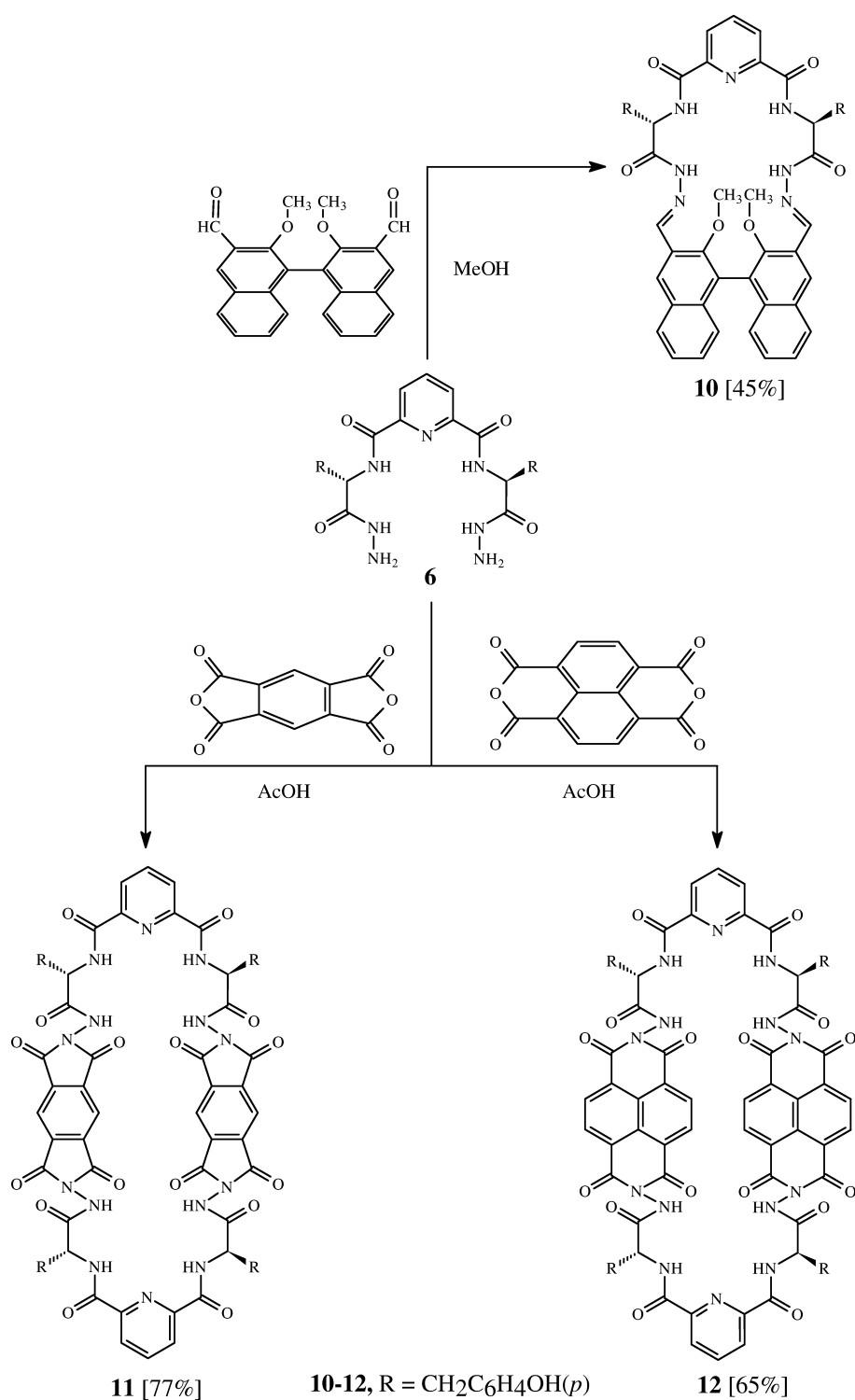
Reaction of 5,17-diaminomethyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene with the diacid derivative **5** in the presence of ethyl chloroformate (Method A) or with the diazide of **6** afforded the corresponding chiral macrocyclic calix[4]arene **8**. When 5,17-diamino-25,26,27,28-tetrakis-[(ethoxycarbonyl)methoxy]calix[4]arene was allowed to react with the same mixed anhydride or the diazide, chiral macrocyclic calix[4]arene **9** was isolated (Scheme 3).

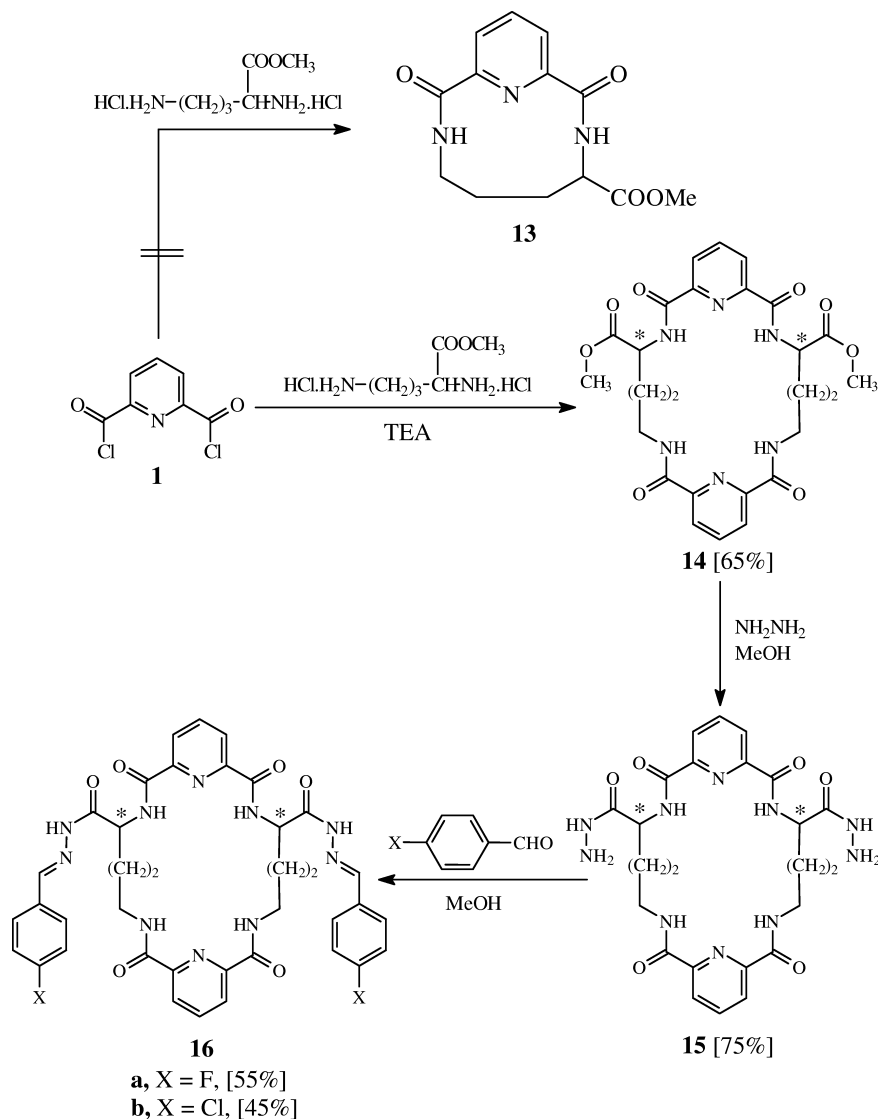
Additionally, in the present work, it was found interesting to extend this course of investigation to the synthesis of some new macrocyclic compounds with a chiral cavity formed by bridging 2,6-bis-(aminocarbonyl)pyridine with 3,3'-binaphthylaldehyde. Thus, condensation of acid hydrazide **6** with 3,3'-binaphthylaldehyde was undertaken in refluxing methanol to afford the corresponding macrocyclic hy-

Scheme 2. Synthetic routes for macrocyclic calix[4]arene **7**.



Scheme 3. Amidolysis of diaminocalix[4]arenes with diacid **5** or dihydrazide **6**. Formation of peptido-calix[4]arenes **8** and **9**.

Scheme 4. Synthetic routes for macrocyclic compounds **10**–**12**.



Scheme 5. Synthetic routes for macrocyclic bicyclodipyridyl derivatives **14**–**16**.

drazone **10** (Scheme 4). Condensation of the same hydrazide **6** with selected tetraacid dianhydrides, namely, 1,2,4,5-benzenetetracarboxylic dianhydride or 1,4,5,8-naphthalene-tetracarboxylic dianhydride in refluxing acetic acid afforded the corresponding macrocyclic tetraamide pyridine derivatives **11** and **12**, respectively (Scheme 4).

Treatment of 2,6-pyridinedicarbonyl dichloride (**1**) with L-ornithine methyl ester dihydrochloride in the presence of triethylamine to afford the expected 4-carbomethoxy-2,9-dioxo-3,8,14-triazabicyclo[8,3,1]dodeca-1(13),12,10-triene (**13**) was, however, unsuccessful. Instead, 8,17-dicarbomethoxy-

3,8,16,21,27,28-hexaaza-2,9,15,22-tetraoxotricyclo-[3,21,1,1<sup>10,14</sup>]octacos-1(26),10,11,13,23,25-hexene (**14**) was isolated in a pure form. The latter compound **14** was reacted with excess hydrazine hydrate in boiling methanol to give the corresponding hydrazide **15**, which was then treated with aromatic aldehydes, namely, *p*-fluorobenzaldehyde or *p*-chlorobenzaldehyde in refluxing methanol to afford the corresponding hydrazones **16a**, **b**, respectively (Scheme 5).

#### Antimicrobial activity

The newly synthesized compounds were tested for their preliminary antimicrobial activity against differ-

| Compound No.     | Inhibition zones (cm) |                  |                      |                | Yeast | Fungi |
|------------------|-----------------------|------------------|----------------------|----------------|-------|-------|
|                  | Gram + ve bacteria    |                  | Gram -ve bacteria    |                |       |       |
|                  | <i>B. subtilis</i>    | <i>B. aureus</i> | <i>Staph. aureus</i> | <i>E. coli</i> |       |       |
| <b>5</b>         | 1.43                  | 1.32             | 1.55                 | 0.65           | –     | 1.75  |
| <b>7</b>         | 1.75                  | 1.00             | 1.65                 | 0.60           | –     | 1.65  |
| <b>8</b>         | 1.88                  | 1.95             | 2.00                 | 0.75           | 0.98  | 1.50  |
| <b>9</b>         | 1.78                  | 1.66             | 1.85                 | 0.88           | 1.05  | 1.98  |
| <b>10</b>        | 1.54                  | 1.85             | 1.66                 | 0.68           | 1.20  | 1.42  |
| <b>11</b>        | 1.48                  | 1.86             | 1.55                 | 0.65           | –     | 2.00  |
| <b>12</b>        | 1.77                  | 1.55             | 1.95                 | 0.55           | –     | 1.85  |
| <b>13</b>        | 1.98                  | 1.45             | 1.56                 | 0.88           | 1.00  | 2.35  |
| <b>15</b>        | 2.05                  | 2.00             | 1.98                 | 0.98           | 1.25  | 2.05  |
| <b>16a</b>       | 1.89                  | 2.05             | 2.00                 | 0.90           | 0.95  | 2.15  |
| <b>16b</b>       | 1.46                  | 1.72             | 1.56                 | 0.64           | –     | 1.50  |
| Chloramphenicol® | 2.00                  | 2.10             | 2.00                 | 0.95           | –     | 2.10  |

Table 1. Antimicrobial activities of newly synthesized compounds **5**, **7**–**16**.

ent microorganisms representing Gram-positive bacteria (*Bacillus subtilis*, *Bacillus aureus* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*), yeast (*Candida albicans*) and fungi (*Aspergillus niger*). The most active compounds were: **14**, **15**, **16** (all organisms), **8** (*B. aureus*), **8**, **12** (*Staph. aureus*), **9** (*E. coli*), **8**–**10** (*C. albicans*) and **9**, **11** (*A. niger*). The results are summarized in Table 1.

## Experimental Section

Melting points were determined in open glass capillaries using in Electrothermal IA 9000 Series digital melting point apparatus (Electrothermal, Essex, U.K.) and are uncorrected. Elemental analyses were performed with all final compounds with an Elementar, Vario EL, Microanalytical Unit, National Research Centre, Cairo Egypt and were in good agreement ( $\pm 0.2\%$ ) with the calculated values. The IR spectra (KBr) were recorded on an FT IR-8201 PC spectrophotometer (Schimadzu, Japan). The  $^1\text{H}$  NMR spectra were measured with a Jeol 270 MHz spectrometer (FTGNM-EX 270, Japan) in DMSO- $d_6$  or  $\text{CDCl}_3$ . The chemical shifts were recorded relative to TMS. The Mass spectra (EI) were run at 70 eV with a Finnegan SSQ 7000 spectrometer (Thermo-instrument System Incorporated, USA),  $m/z$  values are indicated in Dalton. TLC (Silica gel, aluminum sheets 60 F<sub>254</sub>, Merck, Darmstadt, Germany) was used for tracing the reactions. The starting materials **1**, **3** and **6** were prepared according to reported procedures [20–24].

### Synthesis of *N,N*-bis[1-carboxy-2-(*p*-hydroxybenzyl)]-2,6-(diaminocarbonyl)pyridine (**5**)

1 N Sodium hydroxide (25 mL) was added dropwise to a stirred solution of the dimethyl ester derivative **4** (1 mmol) in methanol (20 mL) at  $-5^\circ\text{C}$ . Stirring was continued for 2 h at  $-5^\circ\text{C}$ , then for 12 h at r. t. Methanol was distilled off

under reduced pressure and the residue cooled and acidified with 1 N hydrochloric acid to pH ca. 3. The resulting solid was filtered off, washed with water and crystallized from EtOH/H<sub>2</sub>O to give **5**.

M. p.  $142-5^\circ\text{C}$ . –  $[\alpha]_D^{25} = +10$  (MeOH). – IR (film):  $\tilde{\nu} = 3600-2617$  (broad band, OH and NH), 1732 (C=O, acid), 1657, 1533, 1350 (amide I, II and III)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR (270 MHz, DMSO- $d_6$ ):  $\delta = 3.35$  (d, 4H,  $2 \times \text{CH}_2\text{Ph}$ ), 4.40–4.50 (m, 2H,  $2 \times \text{CH-N}$ ), 7.20–7.35 (m, 8H, 2Ph-*H*), 8.15–8.30 (m, 3H, pyr-*H*), 8.58 (br. s, 2H,  $2 \times \text{NH}$ , exchangeable with D<sub>2</sub>O), 9.86 (br. s, 2H,  $2 \times \text{OH}$ , exchangeable with D<sub>2</sub>O) and 10.40 (br. s, 2H,  $2 \times \text{OH}$ , exchangeable with D<sub>2</sub>O). –  $^{13}\text{C}$  { $^1\text{H}$ } NMR (270 MHz, DMSO- $d_6$ ):  $\delta = 45.66$  ( $\text{CH}_2\text{Ph}$ ), 51.90 ( $\text{CHNH}$ ), 115.31, 124.86, 128.01, 130.23, 138.43, 139.62, 148.53, 156.02 (Ar-C), 123.68, 138.22, 148.15 (pyr-C), 163.24, 172.90 (CO). – MS (EI, 70 eV):  $m/z$  (%) = 493 [ $\text{M}^+$ , 15], 459 [ $\text{M}^+ - 2\text{OH}$ , 100], 311 [ $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4$ , 80]. –  $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_8$  (493.47): calcd. C 60.84, H 4.69, N 8.51; found C 60.78, H 4.61, N 8.48.

### Synthesis of the macrocyclic calix[4]arene derivative **7**

#### Method A: [Acid chloride method]

To a solution of 5,17-diaminomethyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene (0.33 g, 0.5 mmol) in dry dichloromethane (50 mL), triethylamine (0.101 g, 1 mmol) was added with stirring at  $-10^\circ\text{C}$  over 1/2 h, then pyridine-2,6-dicarbonyl dichloride (**1**) [22, 23] (0.102 g, 0.5 mmol) in dry dichloromethane (10 mL) was slowly added. The reaction mixture was stirred for 3 h at  $-10^\circ\text{C}$  and left overnight at r. t., washed with water, 1 N hydrochloric acid, 1 N aqueous sodium bicarbonate and water, and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure, the product was purified by preparative chromatography (silica gel,  $\text{CHCl}_3:\text{MeOH}$ , 9:1, v/v) to give the macrocyclic calixarene derivative **7**.

## Method B: [Azide method]

A cold mixture ( $-5^{\circ}\text{C}$ ) of 2,6-pyridinedicarboxylic acid dihydrazide (**3**) [24] (0.01 g, 0.5 mmol) in 5 N hydrochloric acid (0.6 mL), glacial acetic acid (1.2 mL) and water (5 mL) was stirred for 10 min, then aqueous sodium nitrite (0.069 g, 1 mmol in 3 mL of water) was added in one portion and the mixture stirred for 30 min. The obtained azide was extracted with dichloromethane (60 mL), washed with cold water, 3% aqueous sodium bicarbonate, followed by cold water and dried over anhydrous sodium sulphate. The obtained azide solution was added in one portion to a cold solution ( $-5^{\circ}\text{C}$ ) of 5,17-diaminomethyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene (0.33 g, 0.5 mmol) in dry dichloromethane (15 mL). The reaction mixture was stirred at the same temperature for 3 h, then for 15 h at r.t., washed with 0.5 N hydrochloric acid, water, 3% aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure to dryness, the residue was purified by preparative chromatography using silica gel ( $\text{CHCl}_3:\text{MeOH}$ , 9:1, v/v) to give the macrocyclic calixarene derivative **7** as a white powder.

M. p.  $80-2^{\circ}\text{C}$ . – IR (film):  $\tilde{\nu} = 3344$  (NH, amide), 1660, 1529, 1260 (amide I, II and III)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR (270 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 0.90-1.00$  (t, 12H,  $4 \times \text{CH}_3$ ), 1.95–2.10 (m, 8H,  $4 \times \text{CH}_2$ ), 3.62 (t, 8H,  $4 \times \text{CH}_2\text{O}$ ), 4.18 (d, 4H,  $2 \times \text{CH}_2\text{N}$ ), 3.20, 4.42 (2d, 8H,  $4 \times \text{Ar}-\text{CH}_2-\text{Ar}$ ) [26], 6.62 (s, 4H, calix-*H*), 7.08–7.20 (m, 6H, calix-*H*), 8.10–8.22 (m, 3H, pyr-*H*) and 8.45 (t, 2H, 2NH, exchangeable with  $\text{D}_2\text{O}$ ). –  $^{13}\text{C}$  {H} NMR (270 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 14.12$ , 14.35 (*Me*), 31.18, 31.22 ( $\text{OCH}_2\text{CH}_2$ ), 40.54 ( $\text{CH}_2\text{NH}$ ), 61.00 ( $\text{OCH}_2$ ), 71.94 ( $\text{Ar}-\text{CH}_2-\text{Ar}$ ), 123.72, 138.18, 148.10 (pyr-*C*), 124.82, 128.62, 129.84, 130.50, 133.05, 151.62, 153.22, 158.32, 169.32 (all calix-*C*), 163.92 (*CONH*). – MS (EI, 70 eV):  $m/z$  (%) = 782 [ $\text{M}^+$ , 100], 753 [ $\text{M}^+ - \text{C}_2\text{H}_5$ , 50], 710 (70), 627 (24), 452 (18), 121 (60), 105 (45) and 78 (45). –  $\text{C}_{49}\text{H}_{55}\text{N}_3\text{O}_6$  (781.99): calcd. C 75.25, H 7.08, N 5.37; found: C 75.18, H 6.98, N 5.32.

Synthesis of the peptidocalixarines **8** and **9**

## Method A: [Mixed anhydride method]

A cold mixture ( $-30^{\circ}\text{C}$ ) of the diacid derivative **5** (0.493 g, 1 mmol) in dry dichloromethane (50 mL) with ethyl chloroformate (0.216 g, 2 mmol) and triethylamine (0.202 g, 2 mmol) was stirred for 10 min, then, the diaminocalixarene derivatives, namely, 5,17-diamino-methyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene or 5,17-di-amino-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]-arene (1 mmol) in dry dichloromethane (25 mL) were added dropwise. The reaction mixture was stirred at the same temperature for 3 h and for 12 h at r.t., washed with water, 1 N hydrochloric acid, 1 N aqueous sodium bicarbonate, and water, and dried

over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure, and the crude product was purified by preparative chromatography (silica gel,  $\text{CHCl}_3:\text{MeOH}$ , 8.5:1.5, v/v) to give the corresponding macrocyclic derivatives **8** and **9**, respectively.

## Method B: [Azide method]

A cold mixture ( $-5^{\circ}\text{C}$ ) of the dihydrazide **6** [21] (0.521 g, 1 mmol) in 5 N hydrochloric acid (1.2 mL) with glacial acetic acid (2.4 mL) and water (10 mL) was stirred for 10 min, then aqueous sodium nitrite (0.138 g, 2 mmol in 6 mL of water) was added in one portion and the mixture stirred for 30 min. The obtained azide was extracted with dichloromethane (120 mL), washed with cold water, 3% aqueous sodium bicarbonate followed by cold water, and dried over anhydrous sodium sulphate. The obtained azide solution was added in one portion to a cold solution ( $-5^{\circ}\text{C}$ ) of the diaminocalixarene derivatives, namely, 5,17-diaminomethyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene or 5,17-diamino-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (1 mmol) in dry dichloromethane (25 mL). The reaction mixture was stirred at the same temperature for 3 h, then overnight at r.t., washed with 0.5 N hydrochloric acid, 3% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure, and the crude product was purified by preparative chromatography (silica gel,  $\text{CHCl}_3:\text{MeOH}$ , 8.5:1.5, v/v) to give the corresponding macrocyclic derivatives **8** and **9**, respectively. The products were identified by their m.p. and  $R_f$ -values in comparison with authentic samples previously obtained by Method A.

Peptidocalixarene **8**

M. p.  $123-5^{\circ}\text{C}$ . –  $[\alpha]_D^{25} = +25$  (MeOH). – IR (film):  $\tilde{\nu} = 3595-3340$  (broad band, OH and NH), 1667, 1525, 1304 (amide I, II and III)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR (270 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 0.90-1.00$  (t, 12H,  $4 \times \text{CH}_3$ ), 1.90–2.08 (m, 8H,  $4 \times \text{CH}_2$ ), 3.45 (d, 4H,  $2 \times \text{CH}_2\text{Ph}$ ), 3.55 (t, 8H,  $4 \times \text{CH}_2\text{O}$ ), 4.16 (d, 4H,  $2 \times \text{CH}_2\text{N}$ ), 3.25, 4.35 (2d, 8H,  $4 \times \text{Ar}-\text{CH}_2-\text{Ar}$ ), 4.52–4.56 (m, 2H,  $2 \times \text{CH}-\text{N}$ ), 6.58 (s, 4H, calix-*H*), 7.05–7.15 (m, 6H, calix-*H*), 7.20–7.42 (m, 8H,  $2 \times \text{Ph}-\text{H}$ ), 8.05–8.15 (m, 3H, pyr-*H*), 8.55 (t, 2H,  $2 \times \text{NH}$ , exchangeable with  $\text{D}_2\text{O}$ ), 9.24 (d, 2H,  $2 \times \text{NH}$ , exchangeable with  $\text{D}_2\text{O}$ ) and 10.50 (br. s, 2H,  $2 \times \text{OH}$ , exchangeable with  $\text{D}_2\text{O}$ ). –  $^{13}\text{C}$  {H} NMR (270 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 14.15$ , 14.42 (*Me*), 31.10, 31.25 ( $\text{OCH}_2\text{CH}_2$ ), 40.64 ( $\text{CH}_2\text{NH}$ ), 42.44 ( $\text{CH}_2\text{Ph}$ ), 52.15 (*CHNH*), 59.98 ( $\text{OCH}_2$ ), 72.00 ( $\text{Ar}-\text{CH}_2-\text{Ar}$ ), 123.75, 137.97, 148.15 (pyr-*C*), 124.68, 127.18, 128.00, 128.38, 128.64, 129.82, 130.54, 133.10, 134.65, 151.58, 153.26, 158.38, 169.36 (all Ar-*C*), 163.92, 172.10 (*CONH*). – MS (EI, 70 eV):  $m/z$  (%) = 1108 [ $\text{M}^+$ , 35], 936 [ $\text{M}^+ - 4\text{C}_3\text{H}_9$ , 65], 459 [ $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_6$ , 100], 297



[C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>, 85], 163 [C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>, 78]. – C<sub>67</sub>H<sub>73</sub>N<sub>5</sub>O<sub>10</sub> (1108.36): calcd. C 72.60, H 6.64, N 6.32; found C 72.57, H 6.61, N 6.30.

#### Peptidocalixarene **9**

M. p. 123–5 °C. –  $[\alpha]_D^{25} = +32$  (MeOH). – IR (film):  $\tilde{\nu} = 3598$ –3350 (broad band, OH and NH), 1758 (C=O, ester), 1667, 1525, 1304 (amide I, II and III) cm<sup>-1</sup>. – <sup>1</sup>H NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 1.25$  (t, 12H, 4 × CH<sub>3</sub>), 3.56 (d, 4H, 2 × CH<sub>2</sub>Ph), 4.25–4.30 (m, 8H, 4 × CH<sub>2</sub>O), 3.32, 4.60 (2d, 8H, 4 × Ar-CH<sub>2</sub>-Ar), 4.56–4.60 (m, 2H, 2 × CH-N), 4.75 (s, 8H, 4 × OCH<sub>2</sub>CO), 6.68 (s, 4H, calix-H), 7.10–7.18 (m, 6H, calix-H), 7.24–7.35 (m, 8H, 2 × Ph-H), 8.12–8.24 (m, 3H, pyr-H), 8.75 (d, 2H, 2 × NH, exchangeable with D<sub>2</sub>O), 9.86 (s, 2H, 2 × NH, exchangeable with D<sub>2</sub>O) and 10.48 (br. s, 2H, 2 × OH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 17.15$ , 18.42 (Me), 31.65, 31.68 (COOCH<sub>2</sub>), 42.44 (CH<sub>2</sub>Ph), 52.28 (CHNH), 61.65 (OCH<sub>2</sub>CO), 72.16 (Ar-CH<sub>2</sub>-Ar), 123.86, 138.16, 148.12 (pyr-C), 124.70, 127.21, 127.98, 128.42, 128.66, 129.85, 130.56, 133.05, 134.75, 151.60, 153.26, 158.25, 168.96 (all Ar-C), 164.10, 172.25 (CONH), 172.94 (CO-ester). – MS (EI, 70 eV):  $m/z$  (%) = 1256 [M<sup>+</sup>, 24], 907 [M<sup>+</sup>–4CH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub>, 54], 459 [C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub>, 100], 297 [C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>, 82], 163 [C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>, 66]. – C<sub>69</sub>H<sub>69</sub>N<sub>5</sub>O<sub>18</sub> (1256.34): calcd. C 65.96, H 5.54, N 5.57; found C 65.90, H 5.51, N 5.53.

#### Synthesis of the macrocyclic binaphthyl hydrazone **10**

A mixture of the hydrazide derivative **6** (0.521 g, 1 mmol) and binaphthyl-3,3'-dialdehyde derivative (0.370 g, 1 mmol) in absolute methanol (100 mL) was heated under reflux for 6 h. The solvent was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration, washed with ether and crystallized from ethanol to give the corresponding bicyclo-macrocyclic hydrazone derivative **10** as orange crystals.

M. p. > 280 °C. –  $[\alpha]_D^{25} = +15$  (DMF). – IR (film):  $\tilde{\nu} = 3650$ –3450 (broad band, OH and NH), 1668 (C=N, hydrazone), 1645, 1528, 1265 (amide I, II and III) cm<sup>-1</sup>. – <sup>1</sup>H NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 3.20$  (s, 6H, 2 × OCH<sub>3</sub>), 3.46 (d, 4H, 2 × CH<sub>2</sub>Ph), 4.50–4.55 (m, 2H, 2 × CH-N), 5.25 (s, 2H, 2 × CH=N), 7.10–7.40 (m, 16H, Ph-H+naphthyl-H), 8.00–8.18 (m, 3H, pyr-H), 8.24 (s, 2H, naphthyl-H), 8.60 (t, 2H, 2 × NH, exchangeable with D<sub>2</sub>O), 9.18 (s, 2H, 2 × NH, exchangeable with D<sub>2</sub>O) and 10.35 (br. s, 2H, 2 × OH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 34.75$  (OMe), 41.95 (CH<sub>2</sub>Ph), 52.45 (CHNH), 123.76, 138.05, 148.10 (pyr-C), 147.84 (CH=N), 124.66, 127.18, 127.52, 128.05, 128.44, 128.62, 130.05, 130.54, 131.75, 134.26, 134.58, 151.35, 152.45, 153.10 (all Ar-C), 163.96, 172.60 (CONH). – MS

(EI, 70 eV):  $m/z$  (%) = 855 [M<sup>+</sup>, 12], 793 [M<sup>+</sup>–2OCH<sub>3</sub>, 84], 459 [C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub>, 100], 297 [C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>, 18], 163 [C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>, 14]. – C<sub>49</sub>H<sub>41</sub>N<sub>7</sub>O<sub>8</sub> (855.90): calcd. C 68.75, H 4.83, N 11.45; found C 68.69, H 4.78, N 11.40.

#### Synthesis of macrocyclic octaamide tetraimide pyridine derivatives **11** and **12**

A suspension of the hydrazide derivative **6** (0.521 g, 1 mmol) and 1,2,4,5-benzenetetracarboxylic dianhydride or 1,4,5,8-naphthalinetetracarboxylic dianhydride (1 mmol) in acetic acid (50 mL) was refluxed for 7 h. The solid was collected by filtration, washed with acetic acid and crystallized from dimethylformamide to give the corresponding macrocyclic octaamide dipyridyl derivatives **11** and **12**, respectively.

#### Macrocyclic **11**

M. p. 240–2 °C. –  $[\alpha]_D^{25} = +42$  (DMF). – IR (film):  $\tilde{\nu} = 3550$ –3290 (broad band, OH and NH), 1734 (C=O, anhydride), 1654, 1532, 1290 (amide I, II and III) cm<sup>-1</sup>. – <sup>1</sup>H NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 3.55$  (d, 8H, 4 × CH<sub>2</sub>Ph), 4.35–4.38 (m, 4H, 4 × CH-N), 7.25–7.45 (m, 16H, 4 × Ph-H), 8.10–8.22 (m, 6H, 2 × pyr-H), 8.64 (t, 4H, 4 × NH, exchangeable with D<sub>2</sub>O), 9.10 (s, 4H, Ar-H), 9.70 (s, 4H, 4 × NH, exchangeable with D<sub>2</sub>O) and 10.26 (br. s, 4H, 4 × OH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 42.12$  (CH<sub>2</sub>Ph), 51.96 (CHNH), 124.32, 138.36, 148.45 (pyr-C), 126.62, 128.48, 129.38, 134.58, 138.18, 152.45 (all Ar-C), 164.12, 171.98 (CONH), 174.20 (CON). – MS (EI, 70 eV):  $m/z$  (%) = 1407 [M<sup>+</sup>, 12], 978 [M<sup>+</sup>–4 CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH, 62], 459 [C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub>, 100], 297 [C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>, 8], 163 [C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>, 4]. – C<sub>70</sub>H<sub>50</sub>N<sub>14</sub>O<sub>20</sub> (1407.24): calcd. C 59.74, H 3.58, N 13.93; found C 59.68, H 3.53, N 13.88.

#### Macrocyclic **12**

M. p. 265–7 °C. –  $[\alpha]_D^{25} = +34$  (DMF). – IR (film):  $\tilde{\nu} = 3565$ –3300 (broad band, OH and NH), 1732 (C=O, anhydride), 1656, 1530, 1288 (amide I, II and III) cm<sup>-1</sup>. – <sup>1</sup>H NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 3.50$  (d, 8H, 4 × CH<sub>2</sub>Ph), 4.36–4.42 (m, 4H, 4 × CH-N), 7.10–7.55 (m, 16H, 4 × Ph-H), 8.10–8.20 (m, 6H, 2 × pyr-H), 8.58 (t, 4H, 4 × NH, exchangeable with D<sub>2</sub>O), 8.85 (d, 8H, naphthyl-H), 9.36 (s, 4H, 4 × NH, exchangeable with D<sub>2</sub>O) and 10.12 (br. s, 4H, 4 × OH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 41.12$  (CH<sub>2</sub>Ph), 51.96 (CHNH), 124.32, 138.36, 148.45 (pyr-C), 125.78, 128.88, 132.49, 135.40, 138.00, 149.45, 153.00 (all Ar-C), 163.98, 169.75 (CONH), 173.88 (CON). – MS (EI, 70 eV):  $m/z$  (%) = 1507 [M<sup>+</sup>, 32], 1078 [M<sup>+</sup>–4 CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH, 46], 459 [C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub>, 100], 297 [C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>, 15], 163

[C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub>, 44]. – C<sub>78</sub>H<sub>54</sub>N<sub>14</sub>O<sub>20</sub> (1507.36): calcd. C 62.15, H 3.61, N 13.01; found C 61.99, H 3.55, N 12.99.

*Synthesis of 7,17-dicarbomethoxy-3,8,16,21,27,28-hexaaza-2,9,15,22-tetraoxotricyclo-[3,21,1,1<sup>10,14</sup>]octacosa-1(26),10,12,14,23,24-hexene (14)*

To a solution of L-ornithine methyl ester (0.146 g, 1 mmol), [obtained from L-ornithine methyl ester dihydrochloride (0.219 g, 1 mmol) and triethylamine (0.202 g, 2 mmol) in dry tetrahydrofuran], 2,6-pyridinedicarbonyl dichloride (**1**) (0.204 g, 1 mmol) in dry tetrahydrofuran (10 mL) was added slowly with stirring. Triethylamine was added to the reaction mixture to adjust pH ≈ 8. The reaction mixture was stirred for 3 h at –15 °C and for 12 h at r. t. The triethylamine hydrochloride was filtered off and excess solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), washed with water, 1 N hydrochloric acid, 1 N aqueous sodium bicarbonate, and water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to dryness and the product was purified by preparative TLC chromatography on (silica gel, benzene: MeOH, 7.5 : 2.5, v/v) to give the tricyclodimethyl ester derivative **14** as a white powder.

M. p. 124–6 °C. –  $[\alpha]_D^{25} = +40$  (EtOH). – IR (film):  $\tilde{\nu} = 3355$  (NH, amide), 1745 (C=O, ester), 1669, 1530, 1310 (amide I, II and III) cm<sup>–1</sup>. – <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 1.26$ – $1.30$  (m, 4H, 2 × CH<sub>2</sub>), 1.55–1.62 (m, 4H, 2 × CH<sub>2</sub>), 3.15–3.30 (m, 4H, 2 × CH<sub>2</sub>), 3.65 (s, 6H, 2 × OCH<sub>3</sub>), 4.35–4.52 (m, 2H, 2 × CH–N), 8.05–8.15 (m, 6H, 2 × pyr–H), 8.65 (t, 2H, 2 × NH, exchangeable with D<sub>2</sub>O) and 9.50 (d, 2H, 2 × NH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 28.24$ , 30.34, 38.10 (CH<sub>2</sub>), 52.11 (CHNH), 55.18 (OCH<sub>3</sub>), 125.15, 125.45, 138.68, 138.76, 148.95, 149.05 (pyr–C), 164.15, 169.85 (CONH), 172.75 (CO–ester). – MS (EI, 70 eV):  $m/z$  (%) = 554 [M<sup>+</sup>, 45], 492 [M<sup>+</sup> – 2 OCH<sub>3</sub>, 76], 247 [C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O, 35], 245 [C<sub>11</sub>H<sub>7</sub>N<sub>3</sub>O<sub>4</sub>, 100]. – C<sub>26</sub>H<sub>30</sub>N<sub>6</sub>O<sub>8</sub> (554.55): calcd. C 56.31, H 5.45, N 15.16; found: C 56.25, H 5.42, N 15.12.

*Synthesis of 7,17-di(oxohydrazinomethyl)-3,8,16,21,27,28-hexaaza-2,9,15,22-tetra-oxo-tricyclo[3,21,1,1<sup>10,14</sup>]octacosa-1(26),10,12,14,22,25-hexene (15)*

A mixture of the dimethyl ester **14** (0.554 g, 1 mmol) and hydrazine hydrate (0.4 mL, ~ 8 mmol) in absolute methanol (50 mL) was refluxed for 6 h. Excess solvent was evaporated under reduced pressure to dryness and the obtained solid was crystallized from ethanol to give the corresponding hydrazide derivative **15** as a white powder.

M. p. 185–6 °C. –  $[\alpha]_D^{25} = +38$  (DMF). – IR (film):  $\tilde{\nu} = 3650$ – $3100$  (broad band, NH, NH<sub>2</sub>), 1665, 1532, 1315 (amide I, II and III) cm<sup>–1</sup>. – <sup>1</sup>H NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 1.25$ – $1.32$  (m, 4H, 2 × CH<sub>2</sub>), 1.52–1.58 (m, 4H, 2 × CH<sub>2</sub>), 3.18–3.26 (m, 4H, 2 × CH<sub>2</sub>), 4.30–4.40 (br. s, 4H,

2 × NH<sub>2</sub>, exchangeable with D<sub>2</sub>O), 4.50–4.55 (m, 2H, 2 × CH–N), 8.10–8.25 (m, 6H, 2 × pyr–H), 8.58 (m, 2H, 2 × NH, exchangeable with D<sub>2</sub>O), 8.72 (m, 2H, 2 × NH, exchangeable with D<sub>2</sub>O) and 9.30 (m, 2H, 2 × NH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 28.22$ , 30.48, 38.32 (CH<sub>2</sub>), 51.96 (CHNH), 125.10, 125.34, 137.45, 137.70, 148.66, 148.86 (pyr–C), 163.65, 169.65 (CONH), 170.05 (CO–hydrazide). – MS (EI, 70 eV):  $m/z$  (%) = 554 [M<sup>+</sup>, 15], 492 [M<sup>+</sup> – 2 NHNH<sub>2</sub>, 16], 247 [C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O, 62], 245 [C<sub>11</sub>H<sub>7</sub>N<sub>3</sub>O<sub>4</sub>, 100]. – C<sub>24</sub>H<sub>30</sub>N<sub>10</sub>O<sub>6</sub> (554.56): calcd. C 51.97, H 5.45, N 25.26; found C 51.94, H 5.39, N 25.22.

*Synthesis of 7,17-di[oxo(p-substituted phenyl)carbohydrazonmethyl]-3,8,16,21,27,28-hexaaza-2,9,15,22-tetraoxotricyclo[3,21,1,1<sup>10,14</sup>]octacosa-1(26),10,12,14,23,25-hexene (16a, b)*

A mixture of the hydrazide derivative **6** (0.554 g, 1 mmol) and the appropriate aldehyde (1 mmol), namely, *p*-fluorobenzaldehyde or *p*-chlorobenzaldehyde in absolute ethanol (50 mL) was heated under reflux for 6 h. The solvent was evaporated under reduced pressure and the residue was solidified with ether. The solid was collected by filtration, washed with ether and crystallized from a proper solvent to afford the corresponding hydrazone derivatives **16a, b**, respectively.

*7,17-Di-[oxo(p-fluorophenyl)carbohydrazonmethyl]-3,8,16,21,27,28-hexaaza-2,9,15,22-tetra-oxotricyclo-[3,21,1,1<sup>10,14</sup>]octacosa-1(26),10,12,14,23,25-hexene (16a)*

M. p. 254–5 °C (EtOH). –  $[\alpha]_D^{25} = +44$  (DMF). – IR (film):  $\tilde{\nu} = 3340$  (NH, amide), 1645 (C=N), 1668, 1535, 1312 (amide I, II and III) cm<sup>–1</sup>. – <sup>1</sup>H NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 1.15$ – $1.28$  (m, 4H, 2 × CH<sub>2</sub>), 1.54–1.60 (m, 4H, 2 × CH<sub>2</sub>), 3.24–3.30 (m, 4H, 2 × CH<sub>2</sub>), 4.46–4.58 (m, 2H, CH–N), 5.45 (s, 2H, 2 × CH=N), 7.26–7.42 (m, 8H, 2 × Ph–H), 8.15–8.34 (m, 6H, 2 × pyr–H), 8.55 (m, 2H, 2 × NH, exchangeable with D<sub>2</sub>O), 8.68 (m, 2H, 2 × NH, exchangeable with D<sub>2</sub>O) and 9.42 (m, 2H, 2 × NH, exchangeable with D<sub>2</sub>O). – <sup>13</sup>C {H} NMR (270 MHz, DMSO-d<sub>6</sub>):  $\delta = 28.42$ , 30.56, 38.46 (CH<sub>2</sub>), 52.00 (CHNH), 147.56 (CH=N), 125.05, 125.30, 137.14, 137.28, 148.56, 148.64 (pyr–C), 124.30, 128.37, 129.24, 139.52 (Ar–C), 163.96, 169.85 (CONH), 172.14 (CO–hydrazone). – MS (EI, 70 eV):  $m/z$  (%) = 766 [M<sup>+</sup>, 5], 524 [M<sup>+</sup> – 2 F–C<sub>6</sub>H<sub>4</sub>CN, 100], 436 [524 – 2 H<sub>2</sub>N–CO, 16], 245 [C<sub>11</sub>H<sub>7</sub>N<sub>3</sub>O<sub>4</sub>, 10]. – C<sub>38</sub>H<sub>36</sub>F<sub>2</sub>N<sub>10</sub>O<sub>6</sub> (766.76): calcd. C 59.52, H 4.73, N 18.27; found C 59.48, H 4.68, N 18.22.

*7,17-Di[oxo(p-chlorophenyl)carbohydrazonmethyl]-3,8,16,21,27,28-hexaaza-2,9,15,22-tetraoxo-tricyclo-[3,21,1,1<sup>10,14</sup>]octacosa-1(26),10,12,14,23,25-hexene (16b)*

M. p. 262–4 °C (AcOH). –  $[\alpha]_D^{25} = +46$  (DMF). – IR (film):  $\tilde{\nu} = 3335$  (NH, amide), 1642 (C=N), 1665, 1540, 1315 (amide I, II and III) cm<sup>–1</sup>. – <sup>1</sup>H NMR (270 MHz,

DMSO- $d_6$ ):  $\delta$  = 1.18–1.30 (m, 4H,  $2 \times CH_2$ ), 1.50–1.60 (m, 4H,  $2 \times CH_2$ ), 3.26–3.33 (m, 4H,  $2 \times CH_2$ ), 4.42–4.55 (m, 2H,  $2 \times CH-N$ ), 5.48 (s, 2H,  $2 \times CH=N$ ), 7.25–7.38 (m, 8H, 2Ph-*H*), 8.10–8.28 (m, 6H,  $2 \times$  pyr-*H*), 8.58 (m, 2H,  $2 \times NH$ , exchangeable with  $D_2O$ ), 8.74 (m, 2H,  $2 \times NH$ , exchangeable with  $D_2O$ ) and 9.38 (m, 2H,  $2 \times NH$ , exchangeable with  $D_2O$ ). –  $^{13}C$  {H} NMR (270 MHz, DMSO- $d_6$ ):  $\delta$  = 27.86, 30.45, 38.44 ( $CH_2$ ), 51.86 ( $CHNH$ ), 146.96 ( $CH=N$ ), 125.15, 125.31, 137.22, 137.24, 148.25, 148.44 (pyr-*C*), 123.89, 127.98, 129.34, 139.45 (Ar-*C*), 163.64, 169.58 ( $CONH$ ), 171.95 ( $CO$ -hydrazone). – MS (EI, 70 eV):  $m/z$  (%) = 799 [ $M^+$ , 10], 524 [ $M^+ - 2 Cl-C_6H_4CN$ , 100], 436 [ $524 - 2 H_2N-CO$ , 6], 245 [ $C_{11}H_7N_3O_4$ , 18]. –  $C_{38}H_{36}Cl_2N_{10}O_6$  (799.67): calcd. C 57.07, H 4.54, N 17.52; found C 56.98, H 4.48, N 17.46.

#### Antimicrobial assay

The antimicrobial activity was measured at a concentration 50  $\mu$ mL of the tested compounds using the bioassay sensitivity technique of antibiotics specified in the US Pharmacopoeia [27]. The degree of inhibition is measured in comparison with that of Chloramphenicol<sup>®</sup> taken as standard.

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- [1] L. Fabbri, A. Poggi, *Chem. Soc. Rev.* **197** (1995).
- [2] D. Diamond, M. A. McKerver, *Chem. Soc. Rev.* **25**, 15 (1996).
- [3] E. J. Iorio, Y. Shao, C. T. Chen, H. Wagner, W. C. Still, *Bioorg. Med. Chem. Lett.* **11**, 1635 (2001).
- [4] H. Hioki, M. Lubo, H. Yoshida, M. Bando, Y. Ohnishi, M. Kodama, *Tetrahedron Lett.* **43**, 7949 (2002).
- [5] S. Knoblauch, O. M. Falana, J. Nam, D. M. Roundhill, H. Hennig, K. Zeckert, *Inorg. Chim. Acta* **300–302**, 328 (2000).
- [6] F. C. J. M. Van Veggel, W. Verboom, D. N. Reinhoudt, *Chem. Rev.* **94**, 281 (1994).
- [7] D. M. Roundhill, in: D. M. Roundhill, J. P. Fackler (Jr.) (eds), *Optoelectronic Properties of Inorganic Compounds*, Chapt. 9, pp. 317–347, Plenum, New York (1999).
- [8] A. W. Czarnik, *Acc. Chem. Res.* **27**, 302 (1994).
- [9] S. S. M. Hassan, M. H. Abou-Ghaila, A. E. Amr, A. H. K. Mohamed, *Talanta* **60**, 81 (2003).
- [10] S. S. M. Hassan, M. H. Abou-Ghaila, A. E. Amr, A. H. K. Mohamed, *Anal. Chem. Acta* **482**, 9 (2003).
- [11] A. E. Amr, A. M. Mohamed, A. A. Ibrahim, *Z. Naturforsch.* **58b**, 861 (2003).
- [12] A. Casnati, M. Fabbi, N. Pelizzi, A. Pochini, F. Sansone, R. Ungaro, E. DiModugno, G. Tarzia, *Bioorg. Med. Chem. Lett.* **6**, 2699 (1996).
- [13] E. Pinkhossik, I. Stibor, V. Havlicek, *J. Org. Chem.* **61**, 1182 (1996).
- [14] A. E. Amr, *Z. Naturforsch.* **60b**, 90 (2005).
- [15] M. H. Abou-Ghaila, A. E. Amr, M. M. Abdallah, *Z. Naturforsch.* **58b**, 903 (2003).
- [16] A. E. Amr, H. H. Sayed, M. M. Abdulla, *Arch. Pharm. Chem. Life Sci.* **338**, 433 (2005).
- [17] E. A. Amr, N. A. Abdel-Latif, M. M. Abdulla, *Bioorg. Med. Chem.* **14**, 373 (2006).
- [18] A. G. Hammam, A. F. M. Fahmy, A. E. Amr, A. M. Mohamed, *Ind. J. Chem.* **42B**, 1985 (2003).
- [19] M. Abo-Ghaila, A. E. Amr, *Amino Acids* **26**, 283 (2004).
- [20] A. Attia, O. I. Abdel-Salam, A. E. Amr, I. Stibor, M. Budesinsky, *Egypt. J. Chem.* **43**(2), 187 (2000).
- [21] A. E. Amr, O. I. Abdel-Salam, A. Attia, I. Stibor, *Collect. Czech. Chem. Commun.* **64**, 288 (1999).
- [22] A. B. Roderick, M. F. Henry, *J. Am. Chem. Soc.* **75**, 975 (1953).
- [23] E. A. Nils, O. S. Taito, *J. Am. Pharm. Assoc.* **39**, 460 (1950).
- [24] J. Supniewski, T. Bany, J. Krupinska, *Bull. Acad. Polon. Sci.* **3**, 55 (1955).
- [25] J. R. Vaughan, *J. Am. Chem. Soc.* **73**, 3547 (1951).
- [26] E. Pinkhossik, I. Stibor, A. Cosnati, R. Ungaro, *J. Org. Chem.* **62**, 8654 (1997).
- [27] A. A. Abou-Zeid, Y. M. Shehata, *Ind. J. Pharm.* **31**(3), 72 (1969).