Synthesis of Some New Chiral Tricyclic and Macrocyclic Pyridine Derivatives as Antimicrobial Agents

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A series of chiral macrocyclic pyridines has been prepared starting from N^2,N^2-(pyridine-2,6-dicarbonyl)diamino acid hydrazides **(2a-c)** and N,N-bis-(1-carboxy-2-substituted)-2,6-diaminocarbonyl)pyridines **(3a,b)**. The coupling of **(2a-c)** with 2,6-pyridine dicarbonyldichloride **(4)** gave the compounds **(5a-c).** Compounds **2a-c** were coupled with 2,6-diacetylpyridine **(6)** to yield compounds **(7a-c)** and with heterocyclic aldehydes **(8)** or **(10)** to give the compounds (**9a-c**) or (**11a-c**). In addition, the hydrazides **(2a-c)** were reacted with diformylcalix[4]arene **12** to afford the macrocyclic calix[4]arene hydrazone derivatives **(13a-c)** in reasonable yields. Finally, reaction of diaminocalix-[4]arene derivatives **(14a,b)** with hydrazides **2a,b** or acids **(3a,b),** using azide or mixed anhydride methods afforded macrocyclic calix[4]arene derivatives **15a,b** and **16a,b**, respectively. The structure assignments of the new compounds are based on chemical and spectroscopic evidence. The biological activity screening tests showed that many of the obtained compounds exhibit high antimicrobial activity comparable to ampicillin and chloramphenicol which are used as reference compounds

Key words: Pyridine-2,6-dicarboxamides, Chiral Tricyclic Pyridine, Amino Acids, Macrocyclic Calix[4]arene, Antimicrobial Agents

Introduction

Synthesis of chemical modifications of existing antibacterial agents in order to generate novel molecules with better therapeutic properties is necessary because of the emergence of multidrug resistant bacteria [1]. In continuation of our previous investigations [2,3], we have recently reported the synthesis and biological activity screening of some dipicolinic acid bis-L-amino acid hydrazide derivatives [3] and their corresponding acids [4]. The compounds of this kind have been given considerable attention as inhibitors of ribonucleoside diphosphate reductase [5]. Synthetic macrocyclic peptides are still subject of intensive research with respect to their therapeutic applications [6] as well as their binding properties [7].

Recently, peptidocalixarene derivatives have been studied as analogues of vancomycin-type antibiotics [8]. Therefore, it was interesting to synthesize some macrocyclic peptidocalixarenes with inversely positioned amide bonds based on well known distally substituted upper-rim diaminocalixarenes [9 – 13].

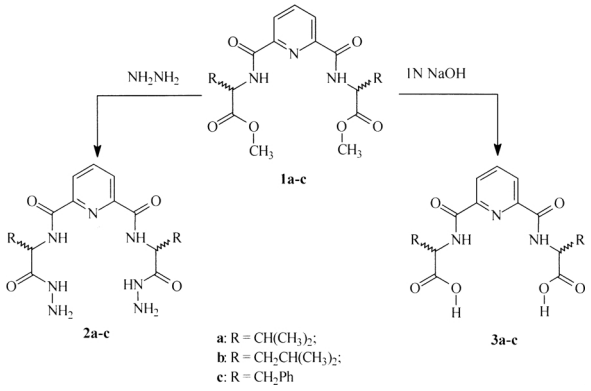
Results and Discussion

In the present work we report on the synthesis and preliminary biological activity screening of several macrocyclic derivatives based on N^2,$N^{2'}$-(pyridine-2,6-dicarbonyl)-diamino acid hydrazides **(2a-c)** and N,N'-bis(1-carboxy-2-substituted)-2,6-(diaminocarbonyl)pyridines **(3a-c)** which have been obtained from the corresponding esters **(1)** according to the published procedures [3, 4]. The syntheses of hydrazides **(2a-c)** and acids **(3a-c)** are shown in Scheme 1.

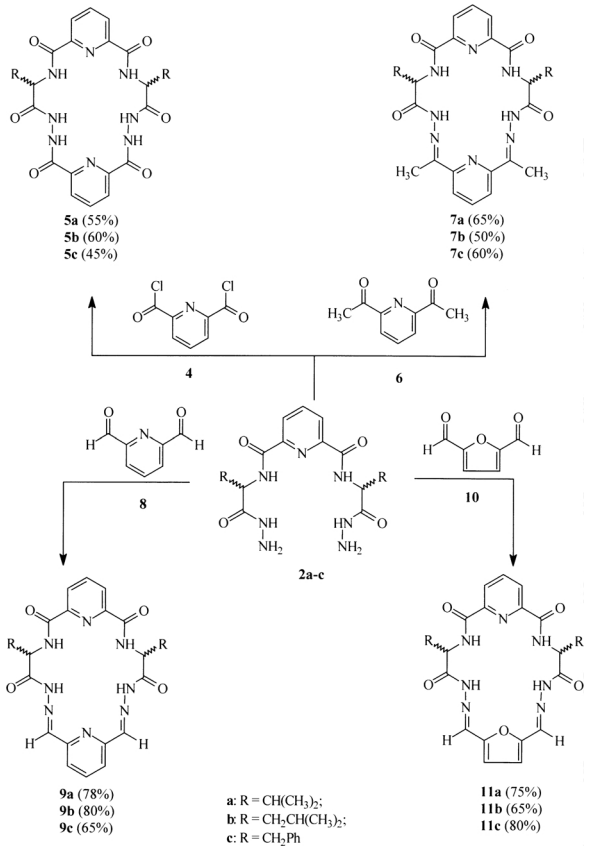
The structures of compounds **2a-c** and **3a-c** were identified by elemental analyses and spectroscopic data (IR, ^{1}H, ^{13}C NMR and mass spectra) in comparison with authentic samples [3, 4].

The hydrazides **2a-c** were treated with 2,6-pyridinedicarbonyl dichloride **(4)** [14, 15] in dichloromethane containing triethylamine at (-10 °C) according to the published procedure [16] affording **(5a-c)**, respectively (Scheme 2).

Treatment of **2a-c** with 2,6-diacetylpyridine **(6)** [17] in refluxing ethanol in the presence of triethyl-



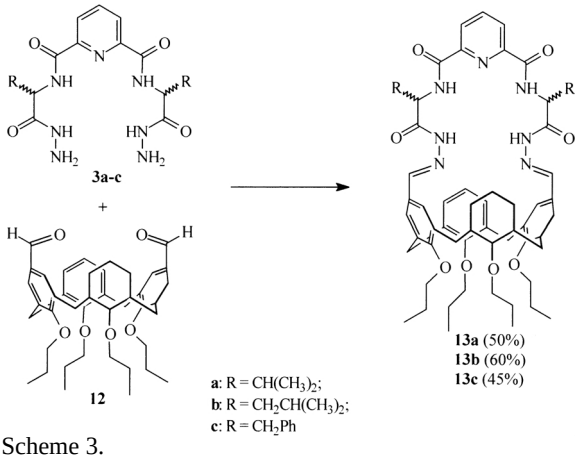
Scheme 1.



Scheme 2.

amine/diethylamine gave compounds **(7a-c),** respectively [18] (Scheme 2).

In a similar way, the reaction of bishydrazide derivatives **2a-c** with aromatic dialdehydes, namely, 2,6-pyridinedicarboxaldehyde or 2,5-furanedicarboxaldehyde in refluxing ethanol afforded **(9a-c)** and **(11a-c)**, respectively (Scheme 2).



Scheme 3.

The reactions between calixarenes and bifunctional reagents can lead, through bridging, to macrocyclic molecules. Calixarenes have been receiving increasing attention in the field of supramolecular chemistry as building blocks for molecules with different properties [19, 20]. Thus, a new series of calix[4]arenes bridged at the upper rim with pyridino systems has been synthesized.

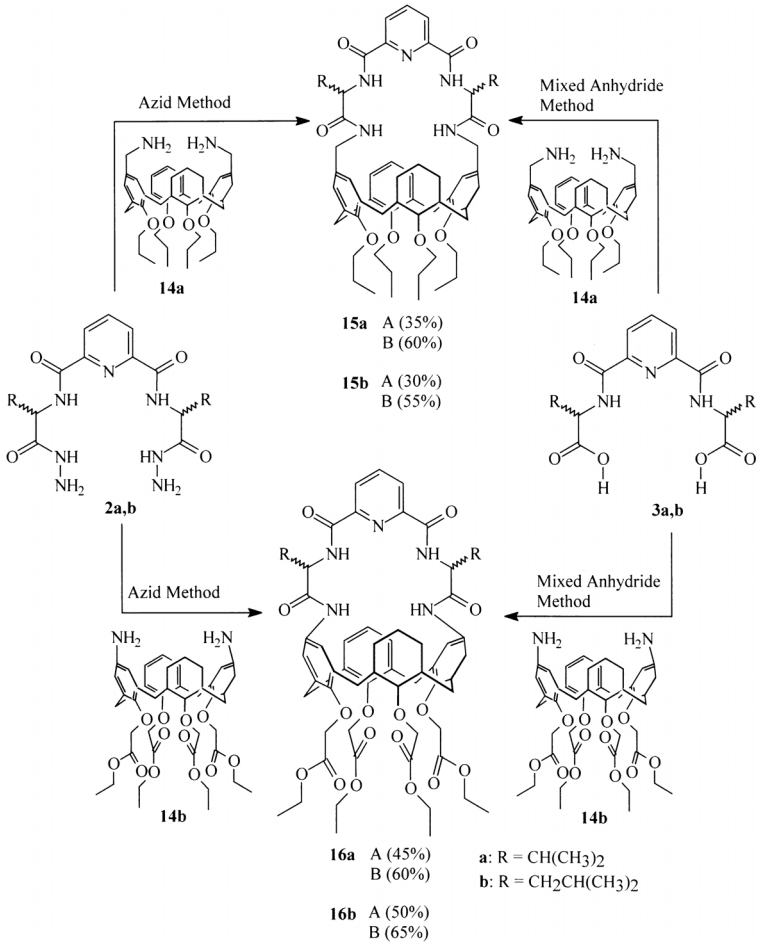
Condensation of hydrazides **2a-c** with 5,17-diformyl-25,26,27,28-tetra-*n*-propoxycalix[4]arene **(12)** [21, 22] in refluxing ethanol gave the corresponding macrocyclic calix[4]arene derivatives **(13a-c)**, respectively (Scheme 3).

The reaction of the azides prepared *in situ* from hydrazides **(2a-c)** with 5,17-bis-(aminomethyl)-25, 26,27,28-tetra-*n*-propoxycalix[4]arene **(14a)** [9] or 5,17-diamino-25,26,27,28-tetrakis[(ethoxycarbonyl) methoxy]calix[4]arene **(14b)** [10] afforded the corresponding chiral macrocyclic calixa[4]arene derivatives **(15a,b)** and **(16a,b)**, respectively (method A) [23] (Scheme 4).

Also, macrocyclic calix[4]arene derivatives **(15a,b)** and **(16a,b)** can be prepared by treating of N,N-bis(1-carboxy-2-substituted)-2,6-bis-(aminocarbonyl)pyridine **(3a,b)** [4] with ethyl chloroformate in the presence of triethylamine to give the corresponding mixed anhydrides, which were directly coupled with the same diaminocalix[4]arene derivatives **(14a,b)** [method B] [24]. The obtained products were identified by comparison with authentic samples from method A (Scheme 4).

Antimicrobial Activity

Preliminary biological activity screening of the synthesized compounds has been performed against



Scheme 4.

microorganisms representing Gram-positive bacteria (*Bacillus subtilis, Bacillus aureus* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*), yeast (*Candida albicans*) and fungi (*Aspergillus niger*), using the bioassay technique of antibiotics [25] specified in US pharmacopeia at 50 μg/ml. The most active compounds are: **11a** (*Bacillus subtilis*), **9b** (*Bacillus aureus*), **5b**, **9c** and **13a** (*Staphylococcus aureus*), **11c** (*Escherichia coli*), **5a** and **7a** (*Candida albicans*), **5a** and **11b** (*Aspergillus niger*). Ampicillin and chloramphenicol were used as standards. The results obtained are summarized in Table 1.

Experimental Section

Melting points are uncorrected and were recorded on an Electrothermal IA 9000 SERIES Digital Melting Point Apparatus. Analytical data were obtained from the Microanalytical unit, National Research Center, Cairo, Egypt. The IR spectra (KBr) were recorded on a FT IR-8201 PC Spectrophotometer (Shimadzu). The NMR spectra were measured with Jeol-GLM 270 MHz in DMSO-d_6 or $CDCl_3$ and the chemical shifts were recorded in δ-scale ppm relative to TMS as an internal standard. The mass spectra were taken at 70 eV with a Finnigan SSQ GC/MS Spectrometer using the Electron Ionization Technique (EI).

Starting materials **2, 3** and reagents **4, 6, 12** and **14** were prepared according to published procedures [3, 4, 9, 10, 17, 21, 22].

Synthesis of 4,18-disubstituted-3,6.7,15,16,19,25,26-octaaza-2,5,8,14,17,20-hexaoxotricyclo[3,19,1,$1^{9.13}$] hexacosa-1(24),9,11,13,21,23-hexaene (5a-c)

To a solution of N^2,$N^{2'}$-(pyridine-2,6-dicarbonyl) diaminoacid hydrazides **(2a-c)** [3] (1 mmol) in dichloromethane (50 ml) at (−10 °C) with stirring, 2,6-pyridine-dicarbonyl dichloride **(4)** [14,15] (0.204 g, 1 mmol) was added drop-wise at (−10 °C), followed by

Table 1. Antimicrobial activity of the new synthesized compounds.

Comp. No.	Inhibition zones (cm)					
	B. subtilis	*B. aureus*	*Staph. aureus*	*E. coli*	*C. albicans*	*Asp. niger*
5a	1.80	1.95	1.80	0.50	0.80	2.10
b	0.65	1.65	1.90	0.45	0.65	1.65
c	1.30	1.80	1.80	0.65	–	1.75
7a	1.25	1.95	1.75	0.70	0.80	1.80
b	0.85	2.00	1.65	0.65	–	1.90
c	0.85	1.65	1.45	0.55	–	1.65
9a	0.55	1.60	1.60	0.65	0.70	1.80
b	0.90	2.10	1.75	0.60	–	1.55
c	1.70	1.55	1.90	0.70	0.65	1.65
11a	1.90	1.60	1.40	0.55	–	1.80
b	1.65	1.45	1.55	0.70	–	2.10
c	1.50	1.65	1.60	0.80	0.75	2.00
13a	0.65	1.30	1.90	0.60	–	1.75
b	0.70	1.45	1.85	–	–	1.95
c	1.40	1.35	1.75	–	–	2.00
15a	0.80	1.40	0.75	0.75	–	1.85
b	0.95	1.50	0.85	–	–	1.80
16a	0.60	1.35	0.95	–	–	1.95
b	0.55	1.40	1.20	0.60	–	–
Ampicillin	1.15	2.50	1.30	0.75	–	2.30
Chloramphinicol	2.00	2.10	2.00	0.95	–	2.10

triethylamine (0.202 ml, 2 mmol) in order to keep the reaction mixture slightly alkaline (pH ∼ 8). The reaction mixture was stirred at (−10 °C) for 3 h, and 2 h at room temperature then washed with water (3 × 50 ml), 1N hydrochloric acid (3 × 50 ml), 1N sodium bicarbonate (3 × 50 ml) and with water several times, dried over anhydrous calcium chloride, evaporated under reduced pressure and purified by preparative thin layer chromatography on silica gel by using chloroform/ethanol (9:1, *v/v*) as eluent to yield the corresponding tricyclohexene derivatives **(5a-c)**, respectively.

4,18-Isopropyl-3,6.7,15,16,19,25,26-octaaza-2,5,8,14,17,20-hexaoxotricyclo[3,19,1,$1^{9,13}$]-hexacosa-1(24),9,11,13,21,23-hexaene (**5a**)

M. p. 210 – 212 °C (AcOEt). – $[\alpha]_D^{30}$ = + 40 (DMF). – IR (film): $\tilde{\nu}$ = 3380-3330 (NH), 1690 (C=O, amide) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.50 – 9.30 (s, 2H, 2NH), 8.70 – 8.65 (bs, 4H, 4NH), 8.30 – 8.00 (m, 6H, 2 pyr-H), 4.30 – 4.15 (t, 2H, 2CH), 2.30 – 2.10 (m, 2H, 2CH), 2.30 – 2.10 (m, 2H, 2CH), 1.10 – 1.00 (m, 12H, 4CH_3). – ^{13}C{^{1}H} NMR (270 MHz, DMSO-d_6): δ = 18.55, 18.95 (all *Me*), 30.25 (*CH*Me_2), 57.10 (*CH*NH), 124.15, 124.40, 139.32, 139.50, 148.35, 148.51 (all pyridine-*C*), 163.35, 165.45, 166.20 (all *CO*-NH). -MS (EI, 70 eV): *m/z* (%) = 524 (35) [M^+]; 331 (100) [M^+-$C_7H_7N_5O_2$]. -$C_{24}H_{28}N_8O_6$ (524.53): calcd. C 54.96, H 5.38, N 21.38; found C 54.90, H 5.34, N 21.25.

4,18-Isobutyl-3,6.7,15,16,19,25,26-octaaza-2,5,8,14,17,20-hexaoxotricyclo[3,19,1,$1^{9,13}$]-hexacosa-1(24),9,11,13,21,23-hexaene (**5b**)

M. p. 150 – 152 °C (CH_2Cl_2). – $[\alpha]_D^{30}$ = −10 (DMF). – IR (film): $\tilde{\nu}$ = 3400 – 3350 (NH), 1685 (C=O, amide) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.40 – 9.30 (bs, 2H, 2NH), 9.00 – 8.85 (bs, 4H, 4NH), 8.25 – 8.00 (m, 6H, 2 pyr-H), 4.60 – 4.40 (t, 2H, 2CH), 2.00 – 1.90 (m, 2H, 2CH), 1.65 – 1.50 (t, 4H, 2CH_2), 1.10 – 0.95 (m, 12H, 4CH_3). – ^{13}C{^{1}H} NMR (270 MHz, DMSO-d_6): δ = 17.35, 18.05 (all *Me*), 29.50 (*CH*Me_2), 40.90 (*CH*$_2$-CH), 56.90 (*CH*NH), 123.65, 123.95, 138.70, 138.90, 147.56, 148.0 (all pyridine-*C*), 163.60, 165.85, 166.80 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 552 (15) [M^+], 359 (100) [M^+-$C_7H_7N_5O_2$]. – $C_{26}H_{32}N_8O_6$ (552.59): calcd. C 56.51, H 5.84, N 20.30; found C 56.90, H 5.78, N 20.25.

4,18-Benzyl-3,6.7,15,16,19,25,26-octaaza-2,5,8,14,17,20-hexaoxotricyclo[3,19,1,$1^{9,13}$]-hexacosa-1(24),9,11,13,21,23-hexaene (**5c**)

M. p. 179 – 181 °C (ether). – $[\alpha]_D^{30}$ = −30 (DMF). – IR (film): $\tilde{\nu}$ = 3390 – 3320 (NH), 1685 (C=O, amide) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.45 – 9.25 (bs, 2H, 2NH), 9.00 – 8.90 (bs, 4H, 4NH), 8.35 – 8.10 (m, 6H, 2 pyr-H), 7.55 – 7.25 (m, 10H, 2Ph-H), 4.55 – 4.40 (t, 2H, 2CH), 2.55 – 2.45 (d, 4H, 2CH_2). – ^{13}C{^{1}H} NMR (270 MHz, DMSO-d_6): δ = 42.60 (*CH*$_2$-Ph), 56.85 (*CH*NH), 123.35, 123.75, 138.45, 138.52, 147.50, 147.95 (all pyridine-*C*), 127.16, 127.45, 128.25, 128.70, 130.65, 131.30, 134.60, 134.80 (all Ph-*C*), 163.55, 165.60, 166.55 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 620 (18) [M^+], 427 (80) [M^+-$C_7H_7N_5O_2$], 243 (100) [427-2PhCH$_3$]. −$C_{32}H_{28}N_8O_6$ (620.62): calcd. C 61.93, H 4.55, N 18.07; found C 61.88, H 4.48, N 18.02.

Synthesis of 4,18-disubstituted-8,19-dimethyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,$1^{9,13}$]hexacosa-1(24),7,9,11,13,15,21,23-octaene (7a-c)

A mixture of bis-hydrazides **(2a-c)** (1 mmol) and 2,6-diacetylpyridine **(6)** [17] (0.163 g, 1 mmol) in absolute ethanol (100 ml) was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure, the solid formed was collected by filtration, washed with ether and purified by crystallization to give the tricyclooctaene derivatives **(7a-c)**, respectively.

4,18-Isopropyl-8,19-dimethyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,$1^{9,13}$]-hexacosa-1(24),7,9,11,13,15,21,23-octaene (**7a**)

M. p. 260 – 262 °C (dioxane). – $[\alpha]_D^{30}$ = −55 (DMF). – IR (film): $\tilde{\nu}$ = 3460 – 3380 (NH), 1665 (C=O, amide), 1625 (C=N) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.35

(s, 2H, 2NH), 8.60 – 8.55 (d, 2H, 2NH), 8.35 – 8.15 (m, 6H, 2 pyr-H), 4.35 – 4.20 (t, 2H, 2CH), 2.40 – 2.15 (m, 2H, 2CH), 2.00 (s, 6H, 2 CH_3), 1.00 – 0.80 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 16.25, 18.35, 18.85 (all *Me*), 32.00 (*CH*Me_2), 56.45 (*CH*NH), 123.10, 123.60, 137.95, 138.55, 147.60, 147.65 (all pyridine-*C*), 146.85 (*C*=N), 171.35, 163.60 (all *CO*-NH). -MS (EI, 70 eV): *m/z* (%) = 520 (16) [M^+], 288 (60) [M^+-$C_{12}H_{12}N_2O_3$], 232 (100) [$C_{12}H_{12}N_2O_3$]. – $C_{26}H_{32}N_8O_4$ (520.59): calcd. C 59.99, H 6.20, N 21.54; found C 59.95, H 6.17, N 21.49.

4,18-Isobutyl-8,19-dimethyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,1^{9,13}]hexacosa-1(24),7,9,11,13,15,21,23-octaene (**7b**)

M. p. 248 – 250 °C (AcOH). – $[\alpha]_D^{30}$ = +40 (DMF). – IR (film): $\tilde{\nu}$ = 3540 – 3400 (NH), 1670 (C=O, amide), 1630 (C=N) cm^{-1}. – ^1H NMR (270 MHz, DMSO-d_6): δ = 9.60 (s, 2H, 2NH), 8.70 (s, 2H, 2NH), 8.40 – 8.10 (m, 6H, 2 pyr-H), 4.35 – 4.15 (m, 2H, 2CH), 3.60 (t, 4H, $2CH_2$), 2.3 (s, 6H, $2CH_3$), 2.25 – 2.10 (m, 2H, 2CH), 1.00 – 0.80 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 15.15, 18.50, 19.05 (all *Me*), 31.50 (*CH*Me_2), 41.52 (CH_2-CH), 56.85 (*CH*NH), 23.18, 123.90, 138.40, 138.75, 147.65, 147.76 (all pyridine-*C*), 146.35 (*C*=N), 171.50, 163.65 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 548 (26) [M^+], 359 (35) [M^+-$C_9H_{11}N_5$], 246 (100) [M^+-$C_{15}H_{22}N_6O$]. – $C_{28}H_{36}N_8O_4$ (548.64): calcd. C 61.30, H 6.62, N 20.44; found C 61.26, H 6.58, N 20.36.

4,18-Benzyl-8,19-dimethyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,1^{9,13}]hexacosa-1(24),7,9,11,13,15,21,23-octaene (**7c**)

M. p. 266 – 268 °C (AcOH). – $[\alpha]_D^{30}$ = +45 (DMF). – IR (film): $\tilde{\nu}$ = 3520 – 3350 (NH), 1675 (C=O, amide), 1640 (C=N) cm^{-1}. -^1H NMR (270 MHz, DMSO-d_6): δ = 9.50 (s, 2H, 2NH), 9.00 – 8.90 (t, 2H, 2NH), 8.30 – 8.10 (m, 6H, 2 pyr-H), 7.70 – 7.20 (m, 10H, 2Ph-H), 4.60 (t, 2H, 2CH), 3.35 (d, 4H, $2CH_2$), 2.30 (s, 6H, $2CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 18.25 (*Me*), 42.68 (CH_2-Ph), 56.75 (*CH*NH), 123.00, 123.56, 138.18, 138.78, 147.60, 147.88 (all pyridine-*C*), 127.30, 127.60, 128.55, 128.70, 130.45, 131.70, 134.15, 134.50 (all Ph-*C*), 147.00 (*C*=N), 172.10, 163.45 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 616 (12) [M^+], 336 (45) [M^+-$C_{16}H_{12}N_2O_3$], 280 (100) [$C_{16}H_{12}N_2O_3$]. – $C_{34}H_{32}N_8O_4$ (616.60): calcd. C 66.29, H 5.23, 18.19; found C 66.25, H 5.20, N 18.16.

Synthesis of tri- and macrocyclic hydrazone derivatives 9a-c, 11a-c and 13a-c

A solution of bis-hydrazides **(2a-c)** (1 mmol) and aromatic aldehydes, namely, 2,6-pyridinedicarboxaldehyde **(8)**, 2,5-furanedicarboxaldehyde **(10)** or 5,17-diformyl-25,26,27,28-tetra-*n*-propoxy-calix[4]arene **(12)** [21,22] (1 mmol) in absolute ethanol (100 ml) was refluxed for 6 – 8 h. The solvent was evaporated under reduced pressure, the obtained residues were triturated with petroleum ether or *n*-hexane and crystallized from the proper solvent to afford the corresponding tricyclohydrazone and macrocyclic calix[4]arene hydrazone derivatives **9a-c**, **11a-c** and **13a-c**, respectively.

4,17-Isopropyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,1^{9,13}]hexacosa-1(24),7,9,11,13,15,21,23-octaene (**9a**)

M. p. 232 – 234 °C (dioxane). – $[\alpha]_D^{30}$ = −35 (DMF). – IR (film): $\tilde{\nu}$ = 3450 – 3350 (NH), 1675 (C=O, amide), 1630 (C=N) cm^{-1}. – ^1H NMR (270 MHz, DMSO-d_6): δ = 9.40 (s, 2H, 2NH), 8.55 (d, 2H, 2NH), 8.45 – 8.25 (m, 6H, 2 pyr-H), 5.35 (s, 2H, CH=N), 4.35 – 4.15 (t, 2H, 2CH), 2.20 – 2.00 (m, 2H, 2CH), 1.10 – 0.95 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 17.25, 18.15 (all *Me*), 31.10 (*CH*Me_2), 54.85 (*CH*NH), 123.55, 124.65, 139.85, 140.00, 148.36, 148.70 (all pyridine-*C*), 147.90 (*CH*=N), 171.05, 164.10 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 492 (18) [M^+], 331 (100) [M^+-$C_7H_7N_5$]. – $C_{24}H_{28}N_8O_4$ (492.53): calcd. C 58.53, H 5.73, N 22.77; found C 58.46, H 5.7, N 22.74.

4,17-Isobutyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,1^{9,13}]hexacosa-1(24),7,9,11,13,15,21,23-octaene(**9b**)

M. p. 256 – 258 °C (EtOH). – $[\alpha]_D^{30}$ = +25 (DMF). – IR (film): $\tilde{\nu}$ = 3500 – 3400 (NH), 1665 (C=O, amide), 1625 (C=N) cm^{-1}. – ^1H NMR (270 MHz, DMSO-d_6): δ = 9.45 (s, 2H, 2NH), 8.75 (s, 2H, 2NH), 8.35 – 8.10 (m, 6H, 2 pyr-H), 4.60 (s, 2H, CH=N), 4.30 – 4.10 (m, 2H, 2CH), 3.50 (t, 4H, $2CH_2$), 2.20 – 2.10 (m, 2H, 2CH), 1.00 – 0.90 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 17.35, 17.85 (all *Me*), 31.50 (*CH*Me_2), 41.01 (CH_2-CH), 55.90 (*CH*NH), 123.40, 123.95, 139.25, 139.75, 147.85, 148.00 (all pyridine-*C*), 146.80 (*CH*=N), 172.00, 163.65 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 520 (18) [M^+], 274 (30) [M^+-$C_{13}H_{14}N_2O_3$], 246 (50) [M^+-$C_{13}H_{18}N_6O$], 188 (100) [246-C_4H_{10}]. – $C_{26}H_{32}N_8O_4$ (520.59): calcd. C 59.99, H 6.20, N 21.54; found C 59.96, H 6.18, N 21.49.

4,17-Benzyl-3,6.7,15,16,19,25,26-octaaza-2,5,17,20-tetraoxotricyclo[3,19,1,1^{9,13}]hexacosa-1(24),7,9,11,13,15,21,23-octaene(**9c**)

M. p. > 300 °C (AcOH). – $[\alpha]_D^{30}$ = +10 (DMF). – IR (film): $\tilde{\nu}$ = 3460 – 3350 (NH); 1680 (C=O, amide), 1645 (C=N) cm^{-1}. – ^1H NMR (270 MHz, DMSO-d_6): δ = 9.30 (s, 2H, 2NH), 8.80 (s, 2H, 2NH), 8.30 – 8.10 (m, 6H, 2 pyr-H), 7.70 – 7.20 (m, 10H, 2Ph-H), 4.80 (s, 2H, 2CH=N), 4.35 (t, 2H, 2CH), 3.50 (d, 4H, $2CH_2$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 42.60 (CH_2-Ph), 55.85 (*CH*NH),

124.55, 125.00, 139.60, 139.85, 148.65, 148.90 (all pyridine-*C*), 127.27, 127.52, 128.78, 129.82, 130.52, 131.75, 134.24, 134.56 (all Ph-*C*), 147.50 (*CH*=N), 172.45, 163.90 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 588 (23) [M^+], 280 (10) [M^+-$C_{16}H_{16}N_6O$], 188 (100) [280-$PhCH_3$]. – $C_{32}H_{28}N_8O_4$ (588.62): calcd. C 65.36, H 4.80, N 19.05; found C 65.32, H 4.75, N 19.00.

4,18-Isopropyl-3,6.7,14,15,18,24-heptaaza-2,5,16, 19,25-pentaoxotricyclo[3,18,1,1^{9,12}]pentacosa-1(23),7,9,11,13,20,22-heptaene (**11a**)

M. p. 296 – 298 °C (AcOH). – $[\alpha]_D^{30}$ = −35 (DMF). – IR (film): $\tilde{\nu}$ = 3500 – 3400 (NH), 1665 (C=O, amide), 1635 (C=N) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.10 (s, 2H, 2NH), 8.50 (d, 2H, 2NH), 8.30 – 8.15 (m, 3H, pyr-H), 7.50-7.20 (d, 2H, furan-H), 5.20 (s, 2H, CH=N), 4.30 – 4.10 (t, 2H, 2CH), 2.25 – 2.10 (m, 2H, 2CH), 1.10 – 0.90 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 14.15, 16.25 (all *Me*), 31.70 (*CH*Me_2), 56.00 (*CH*NH), 124.00, 137.65, 147.36 (all pyridine-*C*), 129.00, 134.25 (all furan-*C*), 147.45 (*CH*=N), 171.90, 163.65 (all *CO*-NH). - MS (EI, 70 eV): *m/z* (%) = 481 (25) [M^+], 331 (100) [M^+-$C_6H_6N_4O$]. – $C_{23}H_{27}N_7O_5$ (481.51): calcd. C 57.37, H 5.56, N 20.38; found: C 57.33, H 5.62, N 20.35.

4,18-Isobutyl-3,6.7,14,15,18,24-heptaaza-2,5,16, 19,25-pentaoxotricyclo[3,18,1,1^{9,12}]pentacosa-1(23),7,9,11,13,20,22-heptaene(**11b**)

M. p. 210 – 212 °C (EtOH). – $[\alpha]_D^{30}$ = – 15 (DMF). – IR (film): $\tilde{\nu}$ = 3450 – 3400 (NH), 1680 (C=O, amide), 1630 (C=N) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.15 (s, 2H, 2NH), 8.65 (s, 2H, 2NH), 8.40 – 8.20 (m, 3H, pyr-H), 7.70 – 7.30 (d, 2H, furan-H), 5.30 (s, 2H, CH=N), 4.35 – 4.15 (m, 2H, 2CH), 3.40 (t, 4H, $2CH_2$), 2.15 – 2.00 (m, 2H, 2CH), 1.20 – 1.00 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 15.60, 18.10 (all *Me*), 31.65 (*CH*Me_2), 41.00 (CH_2-CH), 55.24 (*CH*NH), 123.80, 137.90, 147.65 (all pyridine-*C*), 128.55, 134.65 (all furan-*C*), 147.25 (*CH*=N), 172.10, 164.01 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 509 (32) [M^+], 246 (100) [M^+-$C_{12}H_{17}N_5O_2$]. – $C_{25}H_{31}N_7O_5$ (509.56): calcd. C 58.93, H 6.13, N 19.26; found C 58.86, H 6.10, N 19.22.

4,18-Benzyl-3,6.7,14,15,18,24-heptaaza-2,5,16, 19,25-pentaoxotricyclo[3,18,1,1^{9,12}]pentacosa-1(23),7,9,11,13,20,22-heptaene (**11c**)

M. p. 194 – 196 °C (MeOH). – $[\alpha]_D^{30}$ = +20 (DMF). – IR (film): $\tilde{\nu}$ = 3400 – 3350 (NH); 1670 (C=O, amide), 1640 (C=N) cm^{-1}. –^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.10 (s, 2H, 2NH), 8.70 (s, 2H, 2NH), 8.45 – 8.25 (m, 3H, pyr-H), 7.80 – 7.65 (m, 10H, 2Ph-H), 7.50 – 7.30 (d, 2H, furan-H), 4.95 (s, 2H, 2CH=N), 4.40 (t, 2H, 2CH), 3.45 (d, 4H, $2CH_2$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 42.75 (CH_2-Ph), 56.02 (*CH*NH), 123.95, 138.65, 147.90 (all pyridine-*C*), 127.30, 128.70, 129.85, 130.55, 134.30, 134.60 (all Ar-*C*), 147.45 (*CH*=N), 171.90, 163.60 (all *CO*-NH). – MS (EI, 70 eV): *m/z* (%) = 577 (42) [M^+], 427 (100) [M^+-$C_6H_6N_4O$]. – $C_{31}H_{27}N_7O_5$ (577.59): calcd. C 64.52, H 4.71, N 16.99; found C 64.48, H 4.68, N 16.95.

Macrocyclic calix[4]arene hydrazone **13a**

M. p. > 300 °C (AcOH). – $[\alpha]_D^{30}$ = +30 (DMF). – IR (film): $\tilde{\nu}$ = 3500 – 3450 (NH), 1680 (C=O, amide), 1625 (C=N) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.90 (s, 2H, 2NH), 8.60 (d, 2H, 2NH), 8.30 – 8.10 (m, 3H, pyr-H), 7.15 – 7.05 (m, 6H, calix-H), 6.30 (s, 4H, calix-H), 5.10 (s, 2H, CH=N), 4.35, 3.20 (2d, J = 12.6 Hz, 8H, Ar-CH_2-Ar-calix) [12], 4.25 – 4.10 (t, 2H, 2CH), 3.90, 3.25 (2t, 8H, $4OCH_2$), 2.20 – 2.00 (m, 2H, 2CH), 1.90 – 1.80 (m, 8H, $4CH_2$), 1.25 – 1.15 (m, 12H, $4CH_3$), 1.10 – 0.95 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 14.10, 14.35, 17.55, 18.60 (all Me), 30.85 (OCH_2CH_2), 31.35 ($CHMe_2$), 56.85 (CHNH), 60.45 (OCH_2), 71.50 (Ar-CH_2-Ar), 123.50, 139.00, 148.20 (all pyridine-C), 125.20, 128.10, 128.40, 129.9, 133.40, 151.90, 153.25, 169.20 (all Ar-C), 147.65 (CH=N), 171.50, 164.45 (all CO-NH). – MS (EI, 70 eV): *m/z* (%) = 1006 (23) [M^+], 232 (100) [M^+-$C_{47}H_{59}N_5O_5$]. – $C_{59}H_{71}N_7O_8$ (1006.27): calcd. C 70.42, H 7.11, N 9.74; found C 70.36, H 7.10, N 9.70.

Macrocyclic calix[4]arene hydrazone **13b**

M. p. > 300 °C (AcOH). – $[\alpha]_D^{30}$ = +60 (DMF). – IR (film): $\tilde{\nu}$ = IR 3400 – 3350 (NH), 1665 (C=O, amide), 1630 (C=N) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.75 (s, 2H, 2NH), 8.60 (d, 2H, 2NH), 8.25 – 8.05 (m, 3H, pyr-H), 7.25 – 7.10 (m, 6H, calix-H), 6.45 (s, 4H, calix-H), 5.30 (s, 2H, CH=N), 4.40, 3.25 (2d, J = 12.6 Hz, 8H, Ar-CH_2-Ar-calix), 4.30 – 4.15 (t, 2H, 2CH), 4.00, 3.85 (2t, 8H, $4OCH_2$), 2.25 – 2.05 (m, 2H, 2CH), 1.85 – 1.70 (m, 8H, $4CH_2$), 1.65 – 1.50 (t, 4H, $2CH_2$), 1.20 – 1.10 (m, 12H, $4CH_3$), 0.95 – 0.90 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 14.10, 14.60, 17.65, 18.00 (all Me), 31.20 (OCH_2CH_2), 31.40 ($CHMe_2$), 41.15 (CH_2-CH), 55.90 (CHNH), 60.60 (OCH_2), 71.55 (Ar-CH_2-Ar), 124.15, 138.85, 148.25 (all pyridine-C), 124.65, 128.15, 128.60, 128.90, 133.45, 151.85, 153.35, 168.95 (all Ar-C), 147.35 (CH=N), 171.95, 164.85 (all CO-NH). – MS (EI, 70 eV): *m/z* (%) = 1034 (9) [M^+], 246 (100) [M^+-$C_{48}H_{61}N_5O_5$]. – $C_{61}H_{75}N_7O_8$ (1034.30): calcd. C 70.85, H 7.31, N 9.48; found C 70.80, H 7.28, N 9.45.

Macrocyclic calix[4]arene hydrazone **13c**

M. p. 260 – 262 °C (MeOH). – $[\alpha]_D^{30}$ = −10 (DMF). – IR (film):$\tilde{\nu}$ = 3600 – 3500 (NH), 1675 (C=O, amide), 1620 (C=N) cm^{-1}. – ^{1}H NMR (270 MHz, DMSO-d_6): δ = 9.15 (s, 2H, 2NH), 8.75 (d, 2H, 2NH), 8.25 – 8.05 (m, 3H,

pyr-H), 7.40 – 7.20 (m, 10H, 2Ph-H), 7.15 – 7.00 (m, 6H, calix-H), 6.25 (s, 4H, calix-H), 5.40 (s, 2H, CH=N), 4.55 (t, 2H, 2CH), 4.35, 3.20 (2d, J = 12.6 Hz, 8H, Ar-CH_2-Ar-calix), 3.80, 3.20 (2t, 8H, 4OCH_2), 3.65 (t, 4H, 2Ph-CH_2), 1.85 – 1.70 (m, 8H, 4CH_2), 1.10 – 0.85 (m, 12H, 4CH_3). – $^{13}C\{^1H\}$ NMR (270 MHz, DMSO-d_6): δ = 14.15, 14.50 (Me), 31.25 (OCH_2CH_2), 42.35 (CH_2-Ph), 56.00 (CHNH), 61.05 (OCH_2), 71.95 (Ar-CH_2-Ar), 123.75, 138.25, 148.15 (all pyridine-C), 124.85, 127.15, 128.00, 128.45, 128.65, 129.85, 130.55, 133.15, 134.60, 151.60, 153.25, 169.35 (all Ar-C), 147.55 (CH=N), 172.00, 163.95 (all CO-NH). – MS (EI, 70 eV): *m/z* (%) = 1102 (10) [M^+], 427 (100) [M^+-$C_{42}H_{50}N_4O_4$]. – $C_{67}H_{71}N_7O_8$ (1102.34): calcd. C 79.54, H 6.49, N 8.89; found: C 79.50, H 6.44, N 8.83.

Synthesis of macrocyclic calix[4]arene tetramide pyridine derivatives 15a,b and 16a,b

Method A: [azide method]

A solution of N^2,$N^{2'}$-(pyridine-2,6-dicarbonyl)diamino-acid hydrazides **(2a,b)** [3] (1 mmol) in cold (−5 °C) mixture of 5N hydrochloric acid (2 ml), glacial acetic acid (3 ml) and water (10 ml) was stirred for 15 min. Aqueous sodium nitrite (0.2 g, 2 ml water) was added in one portion and the mixture was stirred for 0.5 h. The azide formed *in situ* was extracted with cold dichloromethane (60 ml). The organic layer was washed with (ice-cold) water, 3% sodium hydrogen carbonate, water and dried over anhydrous calcium chloride. This azide solution was added in one portion to a cold solution (−5 °C) of diaminocalix[4]arenes (1 mmol), namely, 5,17-bis(aminomethyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene **(14a)** [9] or 5,17-diamino-25,26,27,28-tetrakis(ethoxycarbonyl)methoxycalix[4]arene **(14b)** [10] in dry dichloromethane (25 ml) with stirring. The reaction mixture was stirred at −5 °C for 3 h then at room temperature for 20 h, washed with water, 0.5 N hydrochloric acid, water and dried over anhydrous calcium chloride. The solvent was evaporated under reduced pressure, the crude products were purified by preparative chromatography on silica gel by using chloroform/ethanol (9:1, *v/v*) as eluent to give the corresponding macrocyclic calix[4]arene derivatives **15a,b** and **16a,b**, respectively.

Method B: [mixed anhydride method]

A mixture of N,N-bis(1-carboxy-2-substituted)-2,6-aminocarbonyl)pyridines **(2a,b)** [4] (1 mol) in dry dichloromethane (50 ml), ethyl chloroformate (0.216 g, 2 mmol) and triethylamine (0.202 g, 2 mmol) was stirred at (−15 °C) for 15 min. Diaminocalix[4]arene derivatives **(14a,b)** (1 mmol) in dry dichloromethane (25 ml) were added dropwise at (−15 °C). The reaction mixture was stirred at the same temperature for 3 h, then washed with water, 0.5 N hydrochloric acid, water and dried over anhydrous calcium chloride. The solvent was evaporated under reduced pressure, the crude products were purified by preparative chromatography on silica gel using chloroform/ethanol (9:1, v/v) as eluent to give macrocyclic calix[4]arenes **15a,b** and **16a,b**, respectively. The obtained products were identified by m.p. and TLC in comparison with authentic samples from method A.

Macrocyclic pyridotetrapropoxycalix[4]arene derivative **15a**

M. p. 186 – 188 °C (*n*-hexane). – $[\alpha]_D^{30}$ = −50 (DMF). – IR (film): $\tilde{\nu}$ = 3450 – 3380 (NH), 1665 (C=O, amide) cm^{-1}. – ^1H NMR (270 MHz, $CDCl_3$): δ = 8.85 (s, 2H, 2NH), 8.55 (d, 2H, 2NH), 8.25 – 8.00 (m, 3H, pyr-H), 7.15 – 7.00 (m, 6H, calix-H), 6.40 (s, 4H, calix-H), 4.80 (d, 2H, 2CH), 4.40, 3.35 (2d, *J* = 12.6 Hz, 8H, Ar-C*H*$_2$-Ar-calix) [12], 3.80, 3.30 (2t, 8H, 4OCH_2), 3.70 (s, 4H, calix-C*H*$_2$-N), 2.15-2.05 (m, 2H, 2CH), 1.90 – 1.80 (m, 8H, 4CH_2), 1.25 – 1.05 (m, 12H, 4CH_3), 1.00 – 0.85 (m, 12H, 4CH_3). – $^{13}C\{^1H\}$ NMR (270 MHz, $CDCl_3$): δ = 13.95, 14.15, 17.55, 18.00 (all *Me*), 30.25 (*CH*Me_2), 31.25 (OCH_2CH_2), 40.50 (*CH*$_2$-NH), 57.00 (*CH*NH), 60.95 (O*CH*$_2$), 71.15 (Ar-*CH*$_2$-Ar), 124.15, 138.32, 139.55 (all pyridine-*C*), 124.65, 127.85, 128.20, 128.75, 132.85, 151.70, 153.40, 169.35 (all Ar-*C*), 164.95, 164.15 (all *CO*-NH). - MS (EI, 70 eV): *m/z* (%) = 980 (35) [M^+], 331 (100) [M^+-$C_{42}H_{52}N_2O_4$]. – $C_{59}H_{73}N_5O_8$ (980.20): calcd. C 72.29, H 7.50, N 7.14; found C 72.26, H 7.46, N 7.10.

Macrocyclic pyridotetrapropoxycalix[4]arene derivative **15b**

M. p. 175 – 177 °C (*n*-hexane). – $[\alpha]_D^{30}$ = +25 (DMF). – IR (film): $\tilde{\nu}$ = 3400 – 3350 (NH), 1675 (C=O, amide) cm^{-1}. – ^1H NMR (270 MHz, $CDCl_3$): δ = 8.80 (bs, 2H, 2NH), 8.40 (bs, 2H, 2NH), 8.30 – 8.10 (m, 3H, pyr-H), 7.35-7.10 (m, 6H, calix-H), 6.55 (s, 4H, calix-H), 4.90 – 4.80 (q, 2H, 2CH), 4.50, 3.30 (2d, *J* = 12.6 Hz, 8H, Ar-CH_2-Ar-calix), 3.85, 3.35 (2t, 8H, 4OCH_2), 3.65 (s, 4H, calix-CH_2-N), 2.25 – 2.15 (m, 2H, 2CH), 1.90 – 1.60 (m, 12H, 6CH_2), 1.15 – 1.05 (m, 12H, 4CH_3), 0.95 – 0.85 (m, 12H, 4CH_3). – $^{13}C\{^1H\}$ NMR (270 MHz, $CDCl_3$): δ = 13.90, 14.10, 17.60, 18.10 (all Me), 30.35 ($CHMe_2$), 31.25 (OCH_2CH_2), 40.65 (CH_2-NH), 41.10 (CH_2-CH), 56.85 (CHNH), 61.00 (OCH_2), 71.35 (Ar-CH_2-Ar), 123.95, 138.50, 139.65 (all pyridine-C), 124.15, 127.55, 128.00, 128.55, 132.70, 151.60, 153.25, 168.90 (all Ar-C), 164.45, 163.90 (all CO-NH). – MS (EI, 70 eV): *m/z* (%) = 1008 (15) [M^+], 359 (100) [M^+-$C_{42}H_{52}N_2O_4$]. – $C_{61}H_{77}N_5O_8$ (1008.20): calcd. C 72.81, H 7.71, N 6.96; found C 72.75, H 7.65, N 6.90.

Macrocyclic pyridotetracarboethoxymethylcalix[4]arene derivative **16a**

M. p. 195 – 197 °C (*n*-hexane). – $[\alpha]_D^{30}$ = +20 (DMF). – IR (film): $\tilde{\nu}$ = 3350 – 3320 (NH), 1745 (C=O, ester), 1670

(C=O, amide) cm^{-1}. – ^1H NMR (270 MHz, $CDCl_3$): δ = 9.00 (s, 2H, 2NH), 8.70 (d, 2H, 2NH), 8.35 – 8.25 (m, 3H, pyr-H), 7.60 – 7.50 (m, 6H, calix-H), 6.70 (s, 4H, calix-H), 4.90 and 3.40 (2d, J = 12.6 Hz, 8H, Ar-CH_2-Ar-calix), 4.85, 4.65 (s, 8H $4OCH_2CO$), 4.55 (d, 2H, 2CH), 4.25 – 4.15 (m, 8H, $4CH_2$), 2.20 – 2.00 (m, 2H, 2CH), 1.30 (t, 12H, $4CH_3$), 1.00 – 0.90 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, $CDCl_3$): δ = 14.10, 14.20, 17.55, 18.00 (all Me), 31.65 (OCH_2CH_3), 31.75 ($CHMe_2$), 40.50 (CH_2-NH), 57.00 (CHNH), 61.00 (OCH_2), 70.95 (Ar-CH_2-Ar), 123.90, 138.45, 140.15 (all pyridine-C), 124.55, 128.35, 128.70, 129.25, 133.85, 152.15, 154.00, 169.60 (all Ar-C), 170.60, 170.35, 164.00, 163.95 (all C=O). – MS (EI, 70 eV): *m/z* (%) = 1128 (18) [M^+], 232 (100) [M^+-$C_{49}H_{57}N_3O_{13}$]. – $C_{61}H_{69}N_5O_{16}$ (1128.25): calcd. C 64.94, H 6.16, N 6.20; found C 64.90, H 6.10, N 6.14.

Macrocyclic pyridotetracarboethoxymethylcalix[4]arene derivative **16b**

M. p. 140 – 142 °C (*n*-hexane). – $[\alpha]_D^{30}$ = +30 (DMF). – IR (film): ν = 3400 – 3320 (NH), 1749 (C=O, ester), 1680 (C=O, amide) cm^{-1}. $-^1H$ NMR (270 MHz, $CDCl_3$): δ = 8.80 – 8.40 (bs, 4H, 4NH), 8.20 – 8.00 (m, 3H, pyr-H), 7.70 – 7.50 (m, 6H, calix-H), 6.80 (s, 4H, calix-H), 4.85, 4.65 (2s, 8H, $4OCH_2CO$), 4.70 – 4.60 (q, 2H, 2CH), 4.55 and 3.30 (2d, J = 12.6 Hz, 8H, Ar-CH_2-Ar-calix), 4.30 – 4.15 (m, 8H, $4CH_2$), 2.35 (m, 12H, $4CH_3$), 1.80 – 1.60 (m, 4H, $2CH_2$), 1.25 (t, 12H, $4CH_3$), 1.10 – 0.95 (m, 12H, $4CH_3$). – $^{13}C\{^1H\}$ NMR (270 MHz, $CDCl_3$): δ = 13.85, 14.00, 17.35, 17.65 (all Me), 31.70 (OCH_2CH_3), 31.25 ($CHMe_2$), 40.70 (CH_2-CH), 41.15 (CH_2-NH), 56.35 (CHNH), 60.65 (OCH_2), 71.05 (Ar-CH_2-Ar), 124.00, 137.95, 141.05 (all pyridine-C), 124.35, 128.45, 128.90, 129.15, 134.00, 152.10, 153.85, 169.90 (all Ar-C), 171.15, 170.65, 164.10, 163.85 (all C=O). – MS (EI, 70 eV): *m/z* (%) = 1156 (22) [M^+], 246 (100) [M^+-$C_{50}H_{59}N_3O_{13}$]. – $C_{63}H_{73}N_5O_{16}$ (1156.30): calcd. C 65.44, H 6.82, N 6.05; found C 65.40, H, 6.78, N 6.00.

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