Synthesis and Reactions of New Chiral Linear and Macrocyclic Tetra- and Penta-peptide Candidates

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A series of linear and macrocyclic pentapeptide derivatives have been prepared *via* the coupling of pyridine-2,6-dicarboxylic acid (**1**) or pyridine-2,6-dicarbonyl dichloride (**2**) with appropriate amino acid methyl esters. The coupling of **1** or **2** with aminoacid methyl esters gave the corresponding pyridine dipeptide methyl esters **3**, which were hydrolyzed with sodium hydroxide to the corresponding acids **4**. The latter compounds **4** were coupled with other amino acid methyl esters to afford the corresponding tetrapeptide esters **5**, which were hydrolyzed with sodium hydroxide to the corresponding acids **6**. Cyclization of tetrapeptide acids with L-lysine methyl ester or with aliphatic diamide derivatives afforded the corresponding cyclic pentapeptide methyl ester derivatives **7** and cyclic tetrapeptide diamines **8**, respectively. Finally, hydrolysis with 1 N sodium hydroxide or hydrazinolysis with hydrazine hydrate of methyl esters **7** afforded the corresponding acids **9a** – **e** and hydrazides **10a** – **e**, respectively.

Key words: Pyridine-2,6-dicarbonyl Dichloride, Amino Acids, Linear Piptides, Macrocyclic Pentapeptides

Introduction

Among the different areas of supramolecular and macrocyclic chemistry, the synthesis and complexing properties of azacrown compounds have been a subject of intensive exploration [1 – 7]. Synthesis of chemical modifications of existing antibacterial agents in order to generate novel macromolecules with better therapeutic properties is necessary because of the emergence of multidrug-resistant bacteria [8]. Peptides rarely function well as drugs due to their low bioavailability and rapid degradation within cells [9]. The conversion of these active peptides into peptidomimetics has been a successful approach for making new biologically active compounds [10]. In addition, we reported on the synthesis of some macrocyclic candidates from dipicolinic acid with amino acids and the screening of their biological activity [11 – 16]. On the other hand, the synthesis of chemosensors is an interesting approach providing accurate analytical tools in different analytical fields. In particular, 2,6-peptido-pyridines exhibited a general potential as ionophors [17] and were used for inventing novel thiocyanate-selective membrane sensors [18]. Recently, some new heterocyclic and peptide derivatives have been studied with respect to their anti-HIV [19], anti-inflammatory [20], anticoagulant [21], analgesic and anticonvulsant [22], anticancer [23], and antimicrobial activities [24 – 26]. In view of these observations and as continuation of our previous work [11 – 26] in macrocyclic and heterocyclic chemistry, we have synthesized some new macrocyclic

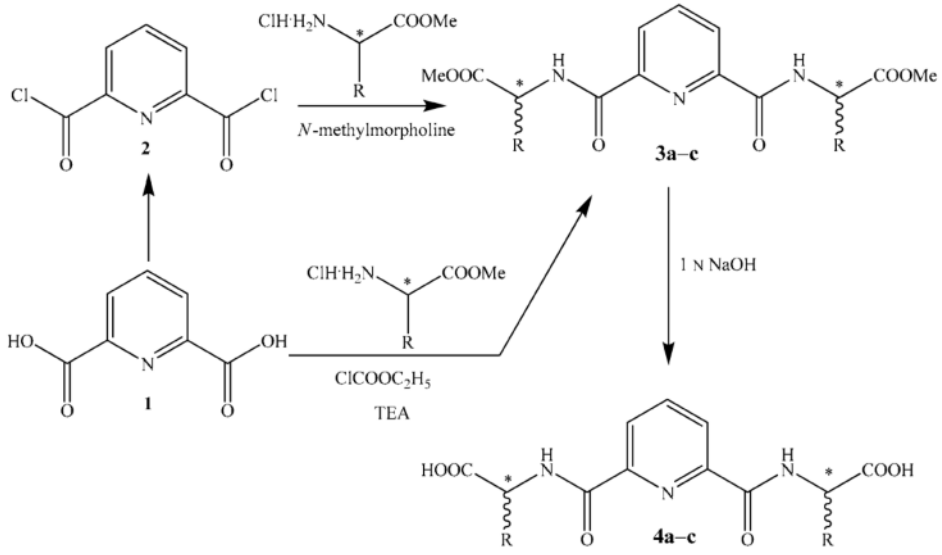
pentapeptides containing amino acid and pyridine moieties.

The versatile biological activities of the synthesized diasteromeric compounds will be a subject of future reports. For attributing the biological activity exclusively to one active diaesteromer, a resolution of the mixtures into their individual components will then be mandatory. Alternatively, synthesis and comparative studies of all L- or all D-peptide candidates could equally be envisioned.

Results and Discussion

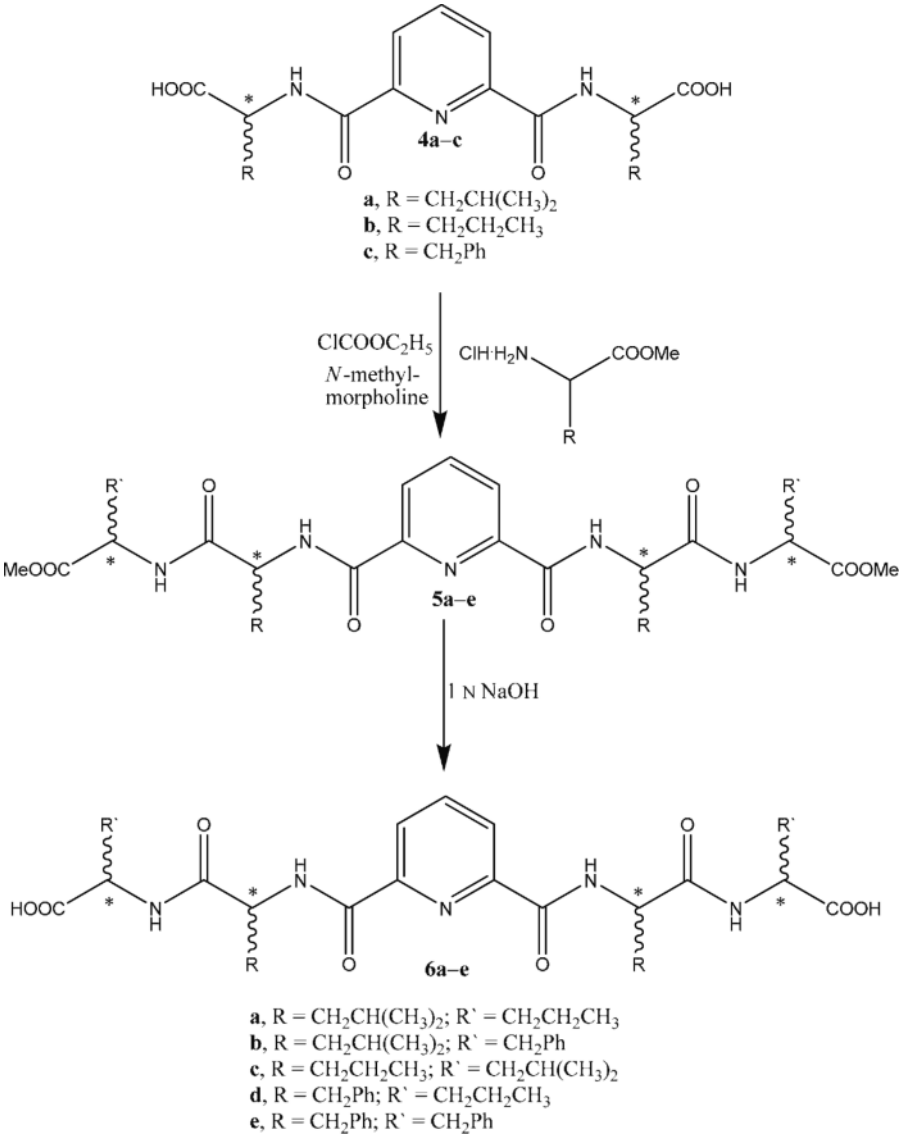
The synthesis of N^{α}-dipicolinoyl-bis-(amino acid) methyl esters **3a – c** was based on 2,6-pyridinedicarbonyl dichloride (**2**), which was obtained by conversion of 2,6-pyridine-dicarboxylic acid (**1**) *via* the reaction with thionyl chloride [27]. This acid chloride was then coupled, at low temperature, with amino acid methyl esters in the presence of triethylamine as organic base. Bis-esters **3a – c** were also prepared from 2,6-pyridinedicarboxylic acid (**1**) and amino acid esters in the presence ethyl chloroformate. Hydrolysis of the dipeptide methyl esters **3a – c** with 1 N sodium hydroxide in methanol afforded the corresponding N^{α}-dipicolinoyl-bis-amino acid derivatives **4a – c**, respectively (Scheme 1). The IR spectra of **3a – c** confirmed the presence of an aromatic ring, aliphatic hydrogens and an amide linkage in addition to the ester group. The amide linkage was confirmed by its three characteristic IR bands in the regions $\nu = 1680 - 1625$, $1548 - 1517$ and $1316 - 1240\ cm^{-1}$ (amide I, II and III, respectively). The presence of the ester group is supported by a band in the regions $1753 - 1740\ cm^{-1}$ ν (C=O), ester). In addition, an absorption band was observed at $3370 - 3335\ cm^{-1}$, attributed to hydrogen bonded amide ν (NH). Also, the IR spectra of **4a – c** showed the absence of ν (C=O, ester), and instead the presence of a band at $1738 - 1726\ cm^{-1}$ for ν (C=O, acid).

The synthesis of N^{α}-dipicolinoyl-bis[tetrapeptide methyl ester] derivatives **5a – e** was based on the dipeptide acids **4a – c**. Their treatment with amino acid methyl ester hydrochlorides in the presence of ethyl chloroformate in dichloromethane afforded the corresponding N^{α}-dipicolinoyl-bis[tetrapeptide methyl ester] derivatives **5a – e**, which were hydrolyzed with methanolic sodium hydroxide to afford the corresponding N^{α}-dipicolinoyl-bis[tetrapeptide] derivatives **6a – e** (Scheme 2). The ^{1}H NMR spectra of **5** revealed the presence of a singlet (6H) at $\delta = 3.6 - 3.7$ ppm for the ester-CH_3 protons. The IR spectra of **6** showed the



a, R = $CH_2CH(CH_3)_2$ [L-Leu]; **b**, R = $CH_2CH_2CH_3$ [DL-Nva]; **c**, R = CH_2Ph [L-Phe].

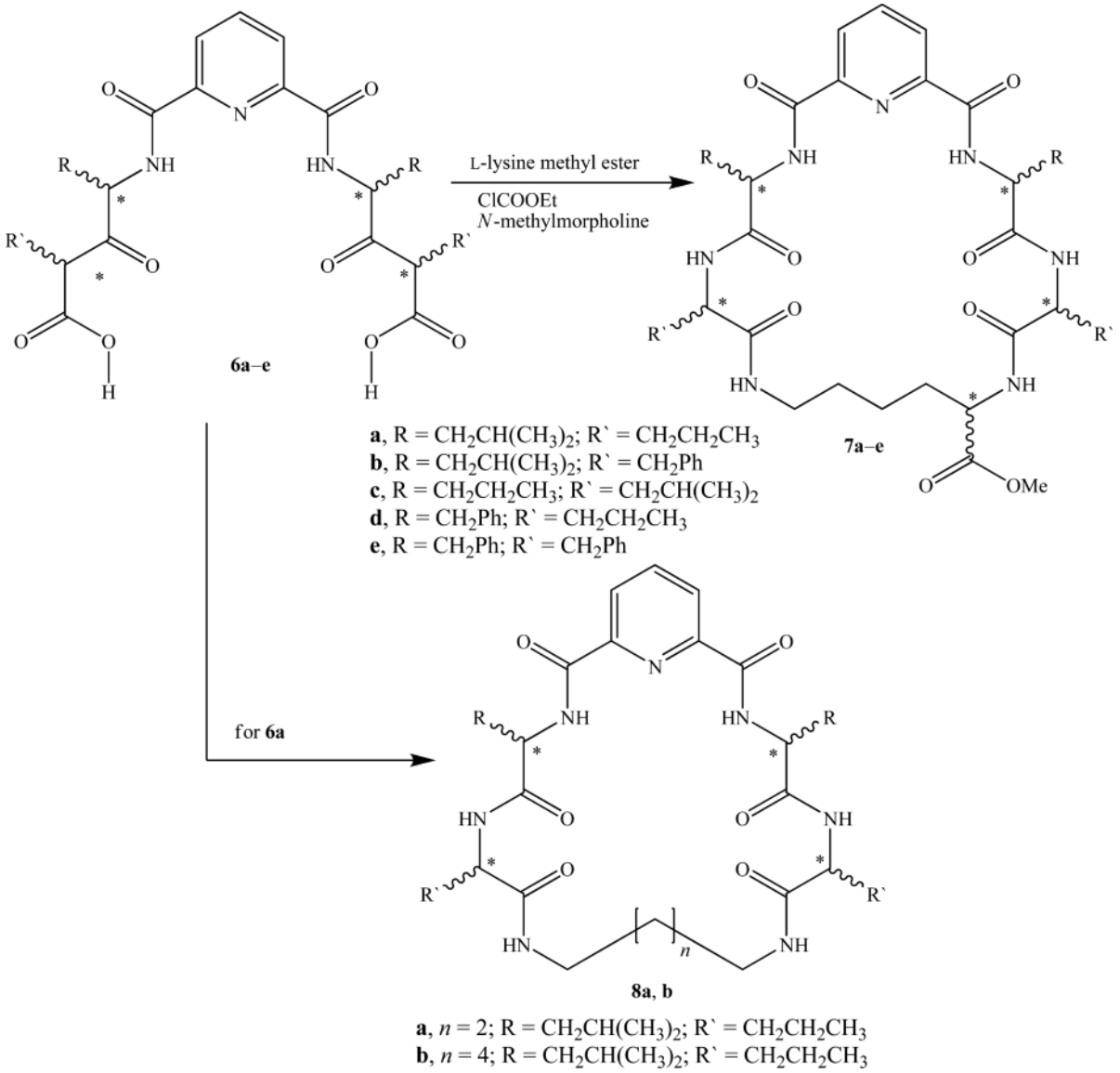
Scheme 1. Synthetic routes for compounds **3a–c** and **4a–c**.



Scheme 2. Synthetic routes for compounds **5a**–**e** and **6a**–**e**.

absence of ν (C=O, ester), and the presence of a band at 1738 – 1726 cm^{-1} for ν (C=O, acid). Also, the ^1H NMR spectra revealed the disappearance of the singlet (6H) at $\delta = 3.6 - 3.7$ ppm for ester-CH_3 protons, and the appearance of a singlet (2H) at $\delta = 9.5 - 9.8$ ppm for carboxylic (OH) protons which are exchangeable with D_2O.

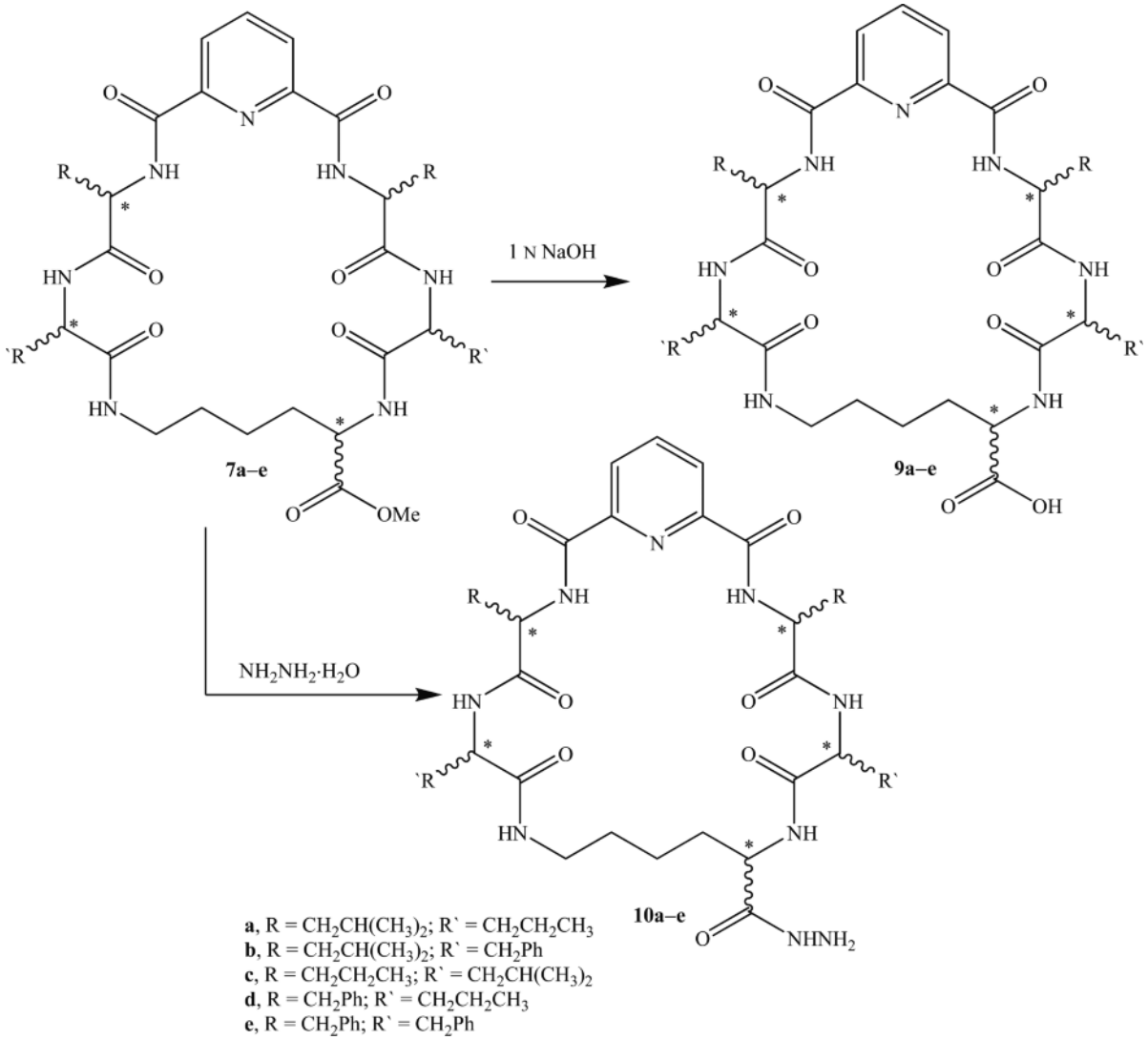
Cyclization of the tetrapeptides **6a** – **e** with L-lysine methyl ester by different methods afforded the corresponding cyclic pentapeptide esters **7a** – **e**. Also, tetrapeptides **6a** were cyclized with aliphatic diamines in the presence of ethyl chloroformate (mixed anhydride method) or in the presence of DCC (Method B) to afford the corresponding cyclo-(N^{α}-dipicolinoyl)-bis[L-Leu-DL-Nva]-aliphatic diamine **8a**, **b** (Scheme 3). The IR and ^1H NMR spectra of **7** supported the presence of the ester group by the observation of a band in the region 1753 – 1740 cm^{-1} ν (C=O) and the presence of a singlet (3H) at $\delta = 3.6 - 3.7$ ppm for ester-CH_3. Also, the IR spectra



Scheme 3. Synthetic routes for compounds **7a**–**e** and **8a**, **b**.

of **8** showed the absence of ν (C=O, acid), and the ^{1}H NMR spectra revealed the disappearance of the singlet (2H) at $\delta = 9.5-9.8$ ppm for the carboxylic protons.

Finally, the methyl groups of the L-Lys-OMe esters of the cyclic pentapeptides **7a**–**e** were converted to carboxylic acid groups or hydrazides. Hydrolysis of the pentapeptide methyl ester derivatives **7a**–**e** with 1 N sodium hydroxide in methanol afforded the corresponding acid derivatives **9a**–**e**. Also, hydrazinolysis of **7a**–**e** with hydrazine hydrate in methanol afforded the corresponding cyclic pentapeptiedie hydrazide derivatives **10a**–**e** (Scheme 4). The IR spectra of **9** showed the absence of ν (C=O, ester) and the presence of a band at 1738–1726 cm^{-1} for ν (C=O, acid). The IR spectra of **10** showed the NH stretching vibrations of the amide and hydrazide groups as a broad band centered at 3370–3335 cm^{-1}.



Scheme 4. Synthetic routes for compounds **9a–e** and **10a–e**.

Experimental

Melting points were determined in open glass capillary tubes with an "Electro Thermal" Digital melting point apparatus, (model: IA9100) and are uncorrected. Elemental micro-analysis for carbon, hydrogen and nitrogen (Microanalytical Unit, NRC) was found within the acceptable limits of the calculated values. Infrared spectra (KBr) were recorded on a Nexus 670 FTIR Nicolet, Fourier Transform infrared spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were run in [D_6]DMSO on Jeol 270 MHz or 500 MHz instruments. Chemical shifts δ are given in ppm. Mass spectra were run on a MAT Finnigan SSQ 7000 spectrometer, using the electron impact technique (EI). Analytical thin layer chromatography (TLC) was performed on silica gel aluminum sheets, 60 F_{254} (E. Merck). The final compounds were purified on manually prepared silica gel glass plates using Fluka silica gel GF_{254}, with 13 % calcium sulfate as a binder. Specific optical rotations were measured with a A. Krawss, Optronic, P8000a polarimeter, in a 1 dm length observation tube, at the indicated conditions, and according to the equation: $[\alpha]_D^T = 100.\ \alpha/(cl)$, where: $\alpha =$ observed rotation angle, D = sodium line ($\lambda = 589$ nm), $c =$ concentration (g/100 mL), $l =$ path length in dm and $T =$ temperature (°C). The following solvent systems (by volume) were used as eluents for the development of the

plates: S: chloroform-methanol-acetic acid (85 : 10 : 5); S_1: S-petroleum ether (b. p. 40 – 60 °C) (1 : 1); S_2: S-petroleum ether (b. p. 40 – 60 °C) (3 : 2); S_3: S-petroleum ether (b. p. 40 – 60 °C) (1 : 2) and S_4: butanol-water-acetic acid-pyridine (120 : 48 : 12 : 40).

It is generally known that basic reaction media enhance racemization. However, under the reaction conditions employed in this work, especially short reaction times and temperatures below 0 °C, only negligible racemization was observed.

Synthesis of N^{α}-dipicolinoyl-bis[amino acid methyl esters] ***3a – c***

Method A: acid chloride method

2,6-Pyridinedicarbonyl dichloride (**2**) [27] (0.02 g, 1 mmol) was added drop by drop to a cold (−15 °C) and stirred dichloromethane solution (20 mL) of the corresponding free amino acid methyl ester (2 mmol), obtained by the addition of an equivalent amount of *N*-methylmorpholine (0.3 mL) to the amino acid methyl ester hydrochloride in stirred and cold (−15 °C) dichloromethane (20 mL). The reaction mixture was stirred for additional 3 h at the same temperature, then for 12 h at room temperature, washed with water, 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to dryness, and the obtained residue was solidified by trituration with *n*-hexane. The obtained solid was filtered off and crystallized from ethanol to give the esters **3a** [28] and **3b**, **c**, respectively.

Method B: mixed anhydride method

Ethyl chloroformate (0.2 mL, 2 mmol) was added to a stirred and cold (−15 °C) solution of 2,6-pyridinedicarboxylic acid (**1**) (0.17 g, 1 mmol) and *N*-methylmorpholine (0.2 mL, 2 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for additional 10 min, then the free amino acid methyl ester (2 mmol), dissolved in dichloromethane (20 mL, −15 °C) was added. Stirring was maintained for 3 h at −15 °C, then for 12 h at room temperature. The reaction mixture was then washed with water, 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and dried over anhydrous sodium sulfate. The solvent was evaporated to dryness, and the obtained oily residue was solidified by trituration with *n*-hexane. The obtained solid was collected by filtration and crystallized from ethanol-*n*-hexane to give esters **3a** [28] and **3b**, **c** as identified by melting point and TLC in comparison with authentic samples prepared according to method A.

3b: Yield, %: 55 [A], 87 [B]; m. p. 101 – 102 °C. – IR (KBr): $\nu = 3300$ (NH, str), 3033 (CH-Ar), 2960 (CH-aliph.), 1747 (C=O, ester), 1652, 1533, 1252 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 8.75$ (s, 2H, 2 NH, D_2O exchangeable), 8.40 – 8.35 (d, 2H, 3,5-pyridyl-H), 8.31 – 8.25 (t, 1H, 4-pyridyl-H), 4.60 – 4.55 (t, 2H, 2 C*H*NH), 3.75 (s, 6H, 2 OCH_3), 1.90 – 1.80 (m, 4H, 2C$H_2$$CH_2CH_3$), 1.40 – 1.30 (m, 4H, 2$CH_2CH_2$$CH_3$), 1.05 – 0.95 (m, 6H, 2 $CH_2CH_2CH_3$). – MS (EI, 70 eV): m/z (%) = 394 (14) $[M+1]^+$, 334 (100), 274 (40), 177 (3), 147 (2), 134 (8). – $C_{19}H_{27}N_3O_6$ (393): calcd. C 58.01, H 6.87, N 10.68; found C 57.95, H 6.76, N 10.55.

3c: Yield, %: 53 [A], 80 [B]; m. p. 115 – 117 °C. – $[\alpha]_D^{25} = -146.6$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3338$ (NH str.), 3028 (CH-Ar), 2945 (CH-aliph.), 1735 (C=O, ester), 1647, 1532, 1275 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 8.57$ (s, 2H, 2 NH, D_2O exchangeable), 8.35 – 8.30 (d, 2H, 3,5-pyridyl-H), 8.25 – 8.20 (t, 1H, 4-pyridyl-H), 7.45 – 7.33 (m, 10H, 2 Ar-H), 4.70 – 4.65 (t, 2H, 2 C*H*NH), 3.68 (s, 6H, 2 OCH_3), 3.40 – 3.35 (dd, 4H, 2 CH_2Ph). – MS (EI, 70 eV): m/z (%) = 489 (7) $[M]^+$, 430 (25), 398 (30), 327 (22), 162 (30), 91 (100). – $C_{27}H_{27}N_3O_6$ (489): calcd. C 66.26, H 5.52, N 8.59; found C 66.05, H 5.33, N 8.14.

Synthesis of N^{α}-dipicolinoyl-bis[amino acids] ***4a – c***

To a stirred and cold methanolic solution (−5 °C, 20 mL) of the corresponding dipeptide ester **3a – c** (1 mmol), 1 N sodium hydroxide (25 mL) was gradually added. The reaction mixture was stirred for 2 h at the same temperature, then for 3 h at room temperature. The solvent was concentrated under reduced pressure, and the remaining aqueous solution was cooled and acidified with 1 N hydrochloric acid to pH ∼ 3. The obtained solid was filtered off, washed with water, dried and crystallized from ethanol-water to give the corresponding dipeptides **4a** [28] and **4b**,**c**, respectively.

4b: Yield, 70 %; m. p. 90 – 93 °C. – IR (KBr): $\nu = 3307$ (NH, str.), 3048 (CH-Ar), 2960 (CH-aliph.), 1720 (C=O, acid), 1658, 1542, 1270 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 9.36$ (s, 2H, 2 OH, D_2O exchangeable), 8.48 (s, 2H, 2 NH, D_2O exchangeable), 8.15 – 8.05 (m, 3H, pyridyl-H), 4.55 – 4.50 (m, 2H, 2 C*H*NH), 1.90 – 1.80 (m, 4H, 2C$H_2$$CH_2CH_3$), 1.40 – 1.30 (m, 4H, 2$CH_2CH_2$$CH_3$), 1.10 – 0.98 (m, 6H, 2 $CH_2CH_2CH_3$). – MS (EI, 70 eV): m/z (%) = 362 (3) $[M–3]^+$, 350 (4), 334 (100), 274 (42), 134 (7), 78 (6). – $C_{17}H_{23}N_3O_6$ (365): calcd. C 55.89, H 6.30, N 11.51; found C 55.34, H 6.05, N 11.22.

4c: Yield: 87 %; m. p. 120 – 122 °C. – $[\alpha]_D^{25} = -89.6$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3339$ (NH, str.), 3030 (CH-Ar), 2929 (CH-aliph.), 1727 (C=O, acid), 1648, 1534, 1225 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 9.42$ (s, 2H, 2 OH, D_2O exchangeable), 8.65 (s, 2H, 2 NH, D_2O exchangeable), 8.25 – 8.15 (m, 3H, pyridyl-H), 7.25 – 7.10 (m, 10H, 2 Ar-H), 4.75 – 4.70 (t, 2H,

2 C*H*NH), 3.30 – 3.25 (dd, 4H, 2 CH_2Ph). – MS (EI, 70 eV): m/z (%) = 460 (10) $[M–1]^+$, 373 (48), 313 (30), 148 (62), 105 (36), 91 (100). –$C_{25}H_{23}N_3O_6$ (461): calcd. C 65.08, H 4.99, N 9.11; found C 64.91, H 4.86, N 9.03.

*Synthesis of N^{α}-dipicolinoyl-bis[dipeptide methyl ester] derivatives **5a – e** by the mixed anhydride method*

Ethyl chloroformate (0.2 mL, 2 mmol) was added to a stirred and cold (−15 °C) dichloromethane solution (20 mL) of the corresponding N^{α}-dipicolinoyl-*bis*[amino acid] **4a – c** (1 mmol), containing *N*-methylmorpholine (0.2 mL, 2 mmol). The reaction mixture was stirred for additional 10 min, then a cold dichloromethane solution (20 mL) of the free amino acid methyl ester of L-Leu, DL-Nva, or L-Phe (2 mmol), was added. Stirring was maintained for 3 h at −15 °C, then for 12 h at room temperature. The reaction mixture was washed with water, 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to dryness, and the obtained oily residue was solidified by trituration with a dry ether-*n*-hexane mixture. The obtained solid was collected by filtration and crystallized from ethanol-*n*-hexane to give the corresponding esters **5a** [29] and **5b – e**, respectively.

5b: Yield: 66 %; m. p. 95 – 97 °C. – $[\alpha]_D^{25}$ = −58.6 (c = 0.5, MeOH). – IR (KBr): ν = 3309 (NH, str.), 3028 (CH-Ar), 2957 (CH-aliph.), 1743 (C=O, ester), 1660,1530,1214 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 8.80, 8.52 (2s, 4H, 4 NH, D_2O exchangeable), 8.25 – 8.20 (t, 1H, 4-pyridyl-H), 8.15 – 8.10 (d, 2H, 3,5 pyridyl-H), 7.20 – 7.10 (m, 10H, 2Ar-H), 4.50 – 4.40 (m, 4H, 4 C*H*NH), 3.64 (s, 6H, 2 OCH_3), 2.80 – 2.70 (dd, 4H, 2 CH_2Ph), 1.80 – 1.70 (m, 2H, 2$CH_2CH(CH_3)_2$), 1.50 – 1.40 (m, 4H, 2$CH_2CH(CH_3)_2$), 0.90 – 0.80 (m, 12H, 2$CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 716 (2) $[M+1]^+$, 508 (7), 376 (47), 302 (74), 162 (100), 78 (68). – $C_{39}H_{49}N_5O_8$ (715): calcd. C 65.45, H 6.85, N 9.79; found C 65.12, H 6.56, N 9.44.

5c: Yield: 78 %; m. p. 99 – 100 °C. – $[\alpha]_D^{25}$ = −18.6 (c = 0.5, MeOH). – IR (KBr): ν = 3297 (NH str.), 3032 (CH-Ar), 2960 (CH-aliph.), 1746 (C=O, ester), 1653, 1539, 1208 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 8.58 (s, 4H, 4 NH, D_2O exchangeable), 8.40 – 8.30 (m, 3H, pyridyl-H), 4.60 – 4.55 (t, 2H, 2 C*H*NH), 4.30 – 4.25 (t, 2H, 2 C*H*NH), 3.65 (s, 6H, 2 OCH_3), 1.90 – 1.80 (m, 2H, 2$CH_2CH(CH_3)_2$), 1.70 – 1.60 (m, 4H, 2CH_2), 1.55 – 1.45 (m, 4H, 2 CH_2), 1.30 – 1.20 (m, 4H, 2 $CH_2CH_2CH_3$), 0.90 – 0.80 (m, 18H, 2 $CH_2CH_2CH_3$, 2$CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 619 (2) $[M]^+$, 447 (81), 348 (60), 302 (18), 274 (95), 158 (100). – $C_{31}H_{49}N_5O_8$ (619): calcd. C 60.09, H 7.91, N 11.31; found C 59.88, H 7.14, N 11.02.

5d: Yield: 80 %; m. p. 92 – 94 °C. – $[\alpha]_D^{25}$ = −140 (c = 0.5, MeOH). – IR (KBr): ν = 3302 (NH, str.), 3040 (CH-Ar), 2959 (CH-aliph.), 1744 (C=O, ester), 1658, 1531, 1208 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 8.65 (s,4H,4NH,D_2O exchangeable), 8.40 – 8.30 (m, 3H, pyridyl-H), 7.40 – 7.30 (m, 10H, 2Ar-H), 4.30 – 4.20 (t, 2H, 2 C*H*NH), 4.05 – 3.95 (t, 2H, 2 C*H*NH), 3.61 (s, 6H, 2 OCH_3), 3.20 – 3.10 (dd, 4H, 2 CH_2Ph), 1.70 – 1.60 (m, 4H, 2$CH_2CH_2CH_3$), 1.40 – 1.30 (m, 4H, 2 $CH_2CH_2CH_3$), 1.10 – 0.95 (m, 6H, 2 $CH_2CH_2CH_3$). – MS (EI, 70 eV): m/z (%) = 687 (8) $[M]^+$, 540 (33), 382 (100), 322 (38), 91 (48), 78 (30). – $C_{37}H_{45}N_5O_8$ (687): calcd. C 64.63, H 6.55, N 10.19; found C 64.45, H 6.25, N 10.03.

5e: Yield: 64 %; m. p. 142 – 144 °C. – $[\alpha]_D^{25}$ = −127.4 (c = 0.5, MeOH). – IR (KBr): ν = 3289 (NH, str.), 3028 (CH-Ar), 2946 (CH-aliph.), 1741 (C=O, ester), 1656, 1531, 1213 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 8.85 and 8.65 (2s, 4H, 4 NH, D_2O exchangeable), 8.40 – 8.35 (t, 1H, 4-pyridyl), 8.20 – 8.15 (d, 2H, 3,5-pyridyl), 7.45 – 7.35 (m, 20H, 4Ar-H), 4.80 – 4.70 (t, 2H, 2 C*H*NH), 4.60 – 4.50 (t, 2H, 2 C*H*NH), 3.65 (s, 6H, 2 OCH_3), 3.10 – 2.95 (m, 8H, 4CH_2Ph). – MS (EI, 70 eV): m/z (%) = 783 (2) $[M]^+$, 749 (6), 489 (50), 398 (38), 168 (26), 91 (100). – $C_{45}H_{45}N_5O_8$ (783): calcd. C 68.97, H 5.75, N 8.94; found C 68.15, H 5.42, N 8.65.

*Synthesis of N^{α}-dipicolinoyl-bis[dipeptide] derivatives **6a – e***

To a stirred and cold methanolic solution (−5 °C, 20 mL) of the corresponding tetrapeptide ester **5a – e** (1 mmol), sodium hydroxide (1 N, 25 mL) was gradually added. The reaction mixture was stirred for 2 h at the same temperature then for 3 h at room temperature. The solvent was distilled off under reduced pressure, and the remaining aqueous solution was cooled and acidified with 1 N hydrochloric acid to pH ∼ 3. The obtained solid was filtered off, washed with water, dried and crystallized from ethanol–water to give the corresponding tetrapeptides **6a** [29] and **6b – e**.

6b: Yield: 73 %; m. p. 124 – 126 °C. – $[\alpha]_D^{25}$ = −66.2 (c = 0.5, MeOH). – IR (KBr): ν = 3310 (NH, str.), 3035 (CH-Ar), 2957 (CH-aliph.), 1720 (C=O, acid), 1655, 1528, 1218 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 10.53 (s, 2 H, 2 OH, D_2O exchangeable), 9.15 and 9.05 (2s, 4H, 4 NH, D_2O exchangeable), 8.35 – 8.25 (m, 3H, pyridyl-H), 7.20 – 7.10 (m, 10H, 2Ar-H), 4.50 – 4.45 (t, 2H, 2 C*H*NH), 4.40 – 4.35 (t, 2H, 2 C*H*NH), 3.10 – 3.05 (dd, 2H, CH_2Ph), 2.90 – 2.80 (dd, 2H, CH_2Ph), 1.80 – 1.70 (m, 2H, 2 $CH_2CH(CH_3)_2$), 1.50 – 1.40 (m, 4H, 2 CH_2CH$(CH_3)_2$), 0.90 – 0.80 (m, 12H, 2 $CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 687 (5) $[M]^+$, 634 (2), 489 (70),

327 (48), 162 (36), 91 (100). – $C_{37}H_{45}N_5O_8$ (687): calcd. C 64.62, H 6.55, N 10.19; found C 64.15, H 6.38, N 10.03.

6c: Yield: 75 %; m. p. 118 – 120 °C. – $[\alpha]_D^{25} = -20.8$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3315$ (NH, str.), 3048 (CH-Ar), 2961 (CH-aliph.), 1722 (C=O, acid), 1653, 1531, 1236 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 9.53$ (s, 2H, 2 OH, D_2O exchangeable), 8.75 and 8.62 (2s, 4H, 4 NH, D_2O exchangeable), 8.40 – 8.30 (m, 3H, pyridyl-H), 4.70 – 4.40 (m, 4H, 4C*H*NH), 1.90 – 1.80 (m, 2H, 2 $CH_2CH(CH_3)_2$), 1.70 – 1.60 (m, 4H, 2CH_2), 1.55 – 1.50 (m, 4H, 2 CH_2), 1.40 – 1.30 (m, 4H, 2 $CH_2CH_2CH_3$), 0.90 – 0.80 (m, 18H, 2 $CH_2CH_2CH_3$ and 2 $CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 588 (2) $[M]^+$, 447 (8), 348 (14), 274 (8), 158 (100), 78 (12). – $C_{29}H_{45}N_5O_8$ (591): calcd. C 58.88, H 7.61, N 11.84; found C 58.49, H 7.53, N 11.45.

6d: Yield: 76 %; m. p. 113 – 115 °C. – $[\alpha]_D^{25} = -64.6$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3317$ (NH, str.), 3043 (CH-Ar), 2961 (CH-aliph.), 1727 (C=O, acid), 1656, 1530, 1232 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 9.55$ (s, 2H, 2 OH, D_2O exchangeable), 8.85 and 8.80 (2s, 4H, 4 NH, D_2O exchangeable), 8.20 – 8.10 (m, 3H, pyridyl-H), 7.40 – 7.30 (m, 10H, 2 Ar-H), 4.75 – 4.70 (t, 2H, 2 C*H*NH), 4.65 – 4.60 (t, 2H, 2 C*H*NH), 4.20 – 4.10 (dd, 4H, 2 CH_2Ph), 1.80 – 1.70 (m, 4H, 2 $CH_2CH_2CH_3$), 1.40 – 1.30 (m, 4H, 2 $CH_2CH_2CH_3$), 1.10 – 0.95 (m, 6H, 2 $CH_2CH_2CH_3$). – MS (EI, 70 eV): m/z (%) = 659 (4) $[M]^+$, 582 (52), 408 (36), 241 (60), 131 (52), 56 (100). – $C_{35}H_{41}N_5O_8$ (659): calcd. C 63.73, H 6.22, N 10.62; found C 63.52, H 6.13, N 10.39.

6e: Yield: 65 %; m. p. 116 – 118 °C. – $[\alpha]_D^{25} = -108.4$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3309$ (NH, str.), 3028 (CH-Ar), 2948 (CH-aliph.), 1725 (C=O, acid), 1655, 1528, 1219 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 9.85$ (s, 2H, 2 OH, D_2O exchangeable), 8.85 and 8.80 (2s, 4H, 4 NH, D_2O exchangeable), 8.35 – 8.30 (d, 2H, 3,5-pyridyl-H), 8.05 – 8.00 (t, 1H,4-pyridyl-H), 7.50 – 7.30 (m, 20H, 4 Ar-H), 4.75 – 4.70 (t, 2H, 2 C*H*NH), 4.45 – 4.40 (t, 2H, 2 C*H*NH), 3.10 – 2.85 (m, 8H, 4 CH_2Ph). – MS (EI, 70 eV): m/z (%) = 752 (3) $[M–3]^+$, 681 (2), 549 (4), 284 (8), 168 (7), 91 (100). – $C_{43}H_{41}N_5O_8$ (755): calcd. C 68.34, H 5.43, N 9.27; found C 68.05, H 5.28, N 9.17.

Synthesis of cyclo-(N^α-dipicolinoyl)-bis-[dipeptide]-L-Lys-OMe (cyclic pentapeptide methyl esters) ***7a – e***

Method A: mixed anhydride method

Ethyl chloroformate (0.2 mL, 2 mmol) was added to a stirred and cold (−15 °C) dichloromethane solution (20 mL) of the corresponding N^α-dipicolinoyl-*bis*[dipeptide] **6a – e** (1 mmol), containing *N*-methylmorpholine (0.2 mL, 2 mmol). The reaction mixture was stirred for additional 20 min, then a cold (−15 °C) dichloromethane solution (20 mL) of the free L-lysine methyl ester (1 mmol) was added. Stirring was maintained for 3 h at −15 °C, then for 12 h at room temperature. The reaction mixture was washed with water, 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to dryness, and the obtained oily residue was solidified by trituration with dry ether-*n*-hexane mixture. The crude product was purified by preparative thin layer chromatography using S_3 as eluent to give the corresponding cyclic pentapeptide methyl esters **7a** [29] and **7b – e**.

Method B: DCC method

A cold (−5 °C) tetrahydrofuran solution (20 mL) of the free L-lysine methyl ester (1 mmol) was added to a stirred dry tetrahydrofuran solution (−5 °C, 20 mL) of the corresponding N^α-dipicolinoyl-*bis*[dipeptide] **6a – e** (1 mmol). Dicyclohexylcarbodiimide (0.42 g, 2 mmol) was then added in portions to the reaction mixture over 20 min at the same temperature. Stirring was maintained for 20 h at room temperature. The reaction mixture was then diluted with acetonitrile (20 mL), and the formed dicyclohexylurea was filtered off and washed with acetonitrile (2 × 10 mL). The filtrate was kept in the refrigerator overnight, and the newly formed dicyclohexylurea was then filtered off. Tetrahydrofuran was evaporated to dryness, and the obtained residue was dissolved in dichloromethane, washed with 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness, and the obtained oily residue was solidified by trituration with dry ether-*n*-hexane mixture. In case of **7c** and **7d**, the obtained solid was collected by filtration and crystallized from ethanol-*n*-hexane, while for **7a**, **b** and **e**, the crude products were purified by preparative thin layer chromatography (S_3). The cyclic pentapeptide methyl esters **7a – e** were identified by melting point and TLC in comparison with authentic samples prepared according to method A.

Method C: active ester method

To a stirred cold (−5 °C) dry tetrahydrofuran solution (20 mL) of N^α-dipi-colinoyl-*bis*-[L-Leu-DL-Nva] (**6a**) (0.59 g, 1 mmol) containing *N*-hydroxysuccinimide (0.24 g, 2 mmol), dicyclohexylcarbodiimide (0.42 g, 2 mmol) was added to the reaction mixture in portions over 20 min at the same temperature. Free L-lysine methyl ester (1 mmol) was then added. Stirring was maintained for 20 h at room temperature. The reaction mixture was then diluted with acetonitrile (20 mL), and the formed dicyclohexylurea was filtered off and washed with acetonitrile (2×10 mL). The filtrate was

kept in the refrigerator overnight, and the newly formed dicyclohexylurea was filtered off. Tetrahydrofuran was evaporated to dryness, and the obtained residue was dissolved in dichloromethane, washed with 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness, and the obtained oily residue was solidified by trituration with dry ether-*n*-hexane mixture. The crude product was purified by preparative thin layer chromatography (S_3) to give the corresponding cyclic pentapeptide methyl ester **7a** as identified by melting point and TLC in comparison with an authentic sample prepared according to method A.

Method D: azide method

To a stirred methanolic solution (20 mL) of N^{α}-dipicolinoyl-*bis*[L-Leu-DL-Nva-OMe] (**5a**) (1.24 g, 2 mmol), anhydrous hydrazine hydrate (0.7 mL, 20 mmol) was added. The reaction mixture was refluxed for 3 h, after which the solvent was evaporated. The obtained residue was triturated with ether, filtered off and crystallized from methanol-ether to afford the corresponding dihydrazide derivative (yield 80 %, m. p. 130 – 132 °C). A cold mixture (−15 °C) of the dihydrazide derivative (0.62 g, 1 mmol) in hydrochloric acid (6 N, 2 mL) and glacial acetic acid (1 mL) was stirred for 10 min, then an aqueous solution of sodium nitrite (5 M, 2 mL) was added. Stirring was maintained for 30 min at the same temperature, after which the reaction mixture was extracted with ether (60 mL), washed with cold water, 5 % sodium bicarbonate and water, and then dried over anhydrous sodium sulfate. The cold ethereal azide solution (−15 °C) was added to free L-lysine methyl ester (1 mmol). Stirring was maintained for 5 h at the same temperature, then for 20 h at room temperature. The reaction mixture was washed with water, 5 % potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. Ether was evaporated to dryness, and the obtained oily residue was solidified by trituration with a dry ether-*n*−hexane mixture. The crude product was purified by preparative thin layer chromatography (S_3) to give the corresponding cyclic pentapeptide methyl ester **7a** as identified by melting point and TLC in comparison with an authentic sample prepared according to method A.

7a: Yield 20 % [A] (lit. [29]: 60), 61 [B], 45 [C], 17 [D] (lit. [35]: 29); m. p. 145 – 147 °C [lit. [29]: 148 – 150°C]. – $[\alpha]_D^{25} = -70$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3254$ (NH, str.), 3033 (CH-Ar), 2931 (CH-aliph.), 1751 (C=O, ester), 1644, 1530, 1235 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.65$ and 8.00 (2s, 6H, 6NH, D_2O exchangeable), 8.30 – 8.20 (m, 3H, pyridyl-H), 4.50 – 4.40 (m, 4H, 4C*H*NH), 4.25 – 4.20 (t, 1H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.55 (s, 3H, OCH_3), 3.25 – 3.20 (m, 2H, $NHCH_2CH_2$), 1.90 – 1.80 (m, 2H, $2CH_2CH(CH_3)_2$), 1.70 – 1.60 (m, 4H, 2 CH_2), 1.50 – 1.40 (m, 8H, 4 CH_2), 1.30 – 1.20 (m, 6H, 3 CH_2), 1.05 – 0.90 (m, 18H, 2 $CH_2CH_2CH_3$ and $2CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 716 (5) $[M+1]^+$, 571 (11), 475 (60), 302 (20), 156 (25), 91 (100). – $C_{36}H_{57}N_7O_8$ (715): calcd. C 60.42, H 7.97, N 13.71; found C 60.15, H 7.69, N 13.28.

7b: Yield 18 % [A], 55 [B]; m. p. 108 – 110 °C. – $[\alpha]_D^{25} = -52$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3306$ (NH, str.), 3045 (CH-Ar), 2955 (CH-aliph.), 1743 (C=O, ester), 1656, 1525, 1220 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.60$ (s, 6H, 6 NH, D_2O exchangeable), 8.30 – 8.20 (m, 3H, pyridyl-H), 7.15 – 6.95 (m, 10H, 2Ar-H), 4.80 – 4.70 (m, 4H, 4 C*H*NH), 4.10 – 4.05 (t, 1H, $NHCH_2CH_2CH_2$-CH_2CHNH), 3.65 (s, 3H, OCH_3), 3.40 – 3.35 (m, 2H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.10 – 3.00 (dd, 4H, $2CH_2Ph$), 1.90 – 1.80 (m, 2H, $2CH_2CH(CH_3)_2$), 1.70 – 1.60 (m, 4H, 2 CH_2), 1.45 – 1.40 (m, 4H, 2 CH_2), 1.30 – 1.20 (m, 2H, CH_2), 0.95 – 0.85 (m, 12H, $2CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 811 (2) $[M]^+$, 554 (3), 509 (35), 302 (92), 186 (64), 91 (100). – $C_{44}H_{57}N_7O_8$ (811): calcd. C 65.10, H 7.02, N 12.08; found C 64.95, H 6.89, N 11.93.

7c: Yield, 15 % [A], 64 [B]; m. p. 95 – 98 °C. – $[\alpha]_D^{25} = -46$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3315$ (NH, str.), 3035 (CH-Ar), 2958 (CH-aliph.), 1742 (C=O, ester), 1655, 1533, 1236 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.85$ and 8.00 (2s, 6H, 6 NH, D_2O exchangeable), 8.30 – 8.20 (m, 3H, pyridyl-H), 4.50 – 4.40 (m, 4H,4C*H*NH), 4.15 – 4.10 (t, 1H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.65 (s, 3H, OCH_3), 3.30 – 3.25 (m, 2H, $NHCH_2CH_2CH_2$-CH_2CHNH), 2.00 – 1.90 (m, 2H, $2CH_2CH(CH_3)_2$), 1.70 – 1.60 (m, 4H, $2CH_2$), 1.50 – 1.40 (m, 8H, 4 CH_2), 1.30 – 1.20 (m, 6H, 3 CH_2), 1.05 – 0.90 (m, 18H, 2 $CH_2CH_2CH_3$ and $2CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 716 (5) $[M+1]^+$, 595 (7), 302 (10), 268 (32), 91 (100), 78 (40). – $C_{36}H_{57}N_7O_8$ (715): calcd. C 60.42, H 7.97, N 13.71; found C 60.21, H 7.69, N 13.45.

7d: Yield 13 % [A], 40 [B]; m. p. 117 – 119 °C. – $[\alpha]_D^{25} = -61$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3313$ (NH, str.), 3052 (CH-Ar), 2959 (CH-aliph.), 1736 (C=O, ester), 1655, 1527, 1233 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.90$ and 8.00 (2s, 6H, 6 NH, D_2O exchangeable), 8.30 – 8.20 (m, 3H, pyridyl-H), 7.30 – 7.20 (m, 10H, 2Ar-H), 4.10 – 4.00 (m, 4H, 4C*H*NH), 3.95 – 3.90 (t, 1H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.67 (s, 3H, OCH_3), 3.45 – 3.40 (m, 2H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.20 – 3.10 (dd, 4H, 2 CH_2Ph), 1.50 – 1.40 (m, 8H, 4 CH_2), 1.30 – 1.20 (m, 6H, 3 CH_2), 1.15 – 0.95 (m, 6H, 2 $CH_2CH_2CH_3$). – MS (EI, 70 eV): m/z (%) = 782 (25) $[M+1]^+$, 632 (20), 503 (45), 349 (40), 91 (100), 78 (40). –

$C_{42}H_{53}N_7O_8$ (783): calcd. C 64.37, H 6.77, N 12.52; found C 64.22, H 6.43, N 12.09.

7e: Yield 16% [A], 48 [B]; m. p. 140–142 °C. – $[\alpha]_D^{25} = -58$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3299$ (NH, str.), 3028 (CH-Ar), 2956 (CH-aliph.), 1745 (C=O, ester), 1655, 1529, 1216 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.85$ and 8.00 (2s, 6H, 6 NH, D_2O exchangeable), 8.30–8.20 (m, 3H, pyridyl-H), 7.20–7.05 (m, 20H, 4 Ar-H), 4.90–4.80 (m, 4H, 4 C*H*NH), 4.25–4.20 (t,1H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.75 (s, 3H, OCH_3), 3.40–3.35 (m, 2H, $NHCH_2CH_2CH_2CH_2CHNH$), 3.20–3.10 (m, 8H, 4 CH_2Ph), 1.45–1.40 (m, 4H, 2 CH_2), 1.30–1.25 (m, 2H, CH_2). – MS (EI, 70 eV): m/z (%) = 879 (0.5) $[M]^+$, 759 (2), 263 (44), 120 (54), 91 (100), 78 (22). – $C_{50}H_{53}N_7O_8$ (879): calcd. C 68.26, H 6.03, N 11.15; found C 68.15, H 5.97, N 10.98.

*Synthesis of cyclo-(N^{α}-dipicolinoyl)-bis[L-Leu-DL-Nva]-aliphatic diamines **8a**, **b***

Method A: mixed anhydride method

Ethyl chloroformate (0.2 mL, 2 mmol) was added to a stirred and cold (−15 °C) dichloromethane (20 mL) solution of N^{α}-dipicolinoyl-bis-[L-Leu-DL-Nva] (**6a**) (0.59 g, 1 mmol) containing *N*-methylmorpholine (0.2 mL, 2 mmol). The reaction mixture was stirred for additional 20 min, then a cold dichloromethane solution (20 mL) of 1,4-diaminobutane (0.09 g, 1 mmol) or 1,6-diaminohexane (0.12 g, 1 mmol) was added. Stirring was maintained for 3 h at −15 °C, then for 12 h at room temperature. The reaction mixture was washed with water, 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness, and the obtained oily residue was solidified by trituration with a dry ether-*n*-hexane mixture. The crude product was purified by preparative thin layer chromatography using (S_3) as eluent to give the corresponding cyclic derivatives **8a**,**b**.

Method B: DCC method

A cold (−5 °C) tetrahydrofuran solution (20 mL) of 1,4-diaminobutane (0.09 g, 1 mmol) or 1,6-diaminohexane (0.12 g, 1 mmol) was added to a stirred dry tetrahydrofuran solution (−5 °C, 20 mL) of N^{α}-dipicolinoyl-bis[L-Leu-DL-Nva] (**6a**) (0.59 g, 1 mmol). Dicyclohexyl- carbodiimide (0.42 g, 2 mmol) was then added to the reaction mixture, in portions, over 20 min at the same temperature. Stirring was maintained for 20 h at room temperature. The reaction mixture was then diluted with acetonitrile (20 mL), and the formed dicyclohexylurea was filtered off and washed with acetonitrile (2 × 10 mL). The filtrate was kept in the refrigerator overnight, and the newly formed dicyclohexylurea was filtered off. Tetrahydrofuran was evaporated to dryness, and the obtained residue was dissolved in dichloromethane, washed with 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness, and the obtained oily residue was solidified by trituration with dry ether-*n*-hexane mixture. The obtained solid was collected by filtration and crystallized from ethanol-*n*−hexane to give the cyclic derivatives **8a**,**b** as identified by melting point and TLC in comparison with authentic samples prepared according to method A.

8a: Yield 14% [A], 46 [B]; m. p. 92–93 °C. – $[\alpha]_D^{25} = -41$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3310$ (NH, str.), 3028 (CH-Ar), 2959 (CH-aliph.), 1661, 1529, 1247 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.85$ and 8.00 (2s, 6H, 6NH D_2O exchangeable), 8.40–8.30 (m, 3H, pyridyl-H), 4.10–4.00 (m, 4H, 4 C*H*NH), 3.45–3.30 (m, 4H, $NHCH_2CH_2CH_2CH_2NH$), 1.90–1.80 (m, 2H, 2 $CH_2CH(CH_3)_2$), 1.70–1.60 (m, 4H, 2 CH_2), 1.40–1.30 (m, 8H, 4 CH_2), 1.30–1.20 (m, 4H, 2 CH_2), 1.05–0.85 (m, 18H, 2 $CH_2CH_2CH_3$ and 2 $CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 647 (2) $[M+3]^+$, 606 (5), 302 (3), 267 (100), 185 (25), 78 (30). – $C_{33}H_{53}N_7O_6$ (643): calcd. C 61.59, H 8.24, N 15.24; found C 61.34, H 8.12, N 15.03.

8b: Yield 18% [A], 49 [B]; m. p. 136–138 °C. – $[\alpha]_D^{25} = -20.2$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3315$ (NH, str.), 3045 (CH-Ar), 2959 (CH-aliph.), 1660, 1530, 1249 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.75$ and 8.00 (2s, 6H, 6NH, D_2O exchangeable), 8.40–8.30 (m, 3H, pyridyl-H), 4.20–4.10 (m, 4H, 4 C*H*NH), 3.40–3.30 (m, 4H, $NHCH_2CH_2CH_2CH_2CH_2NH$), 1.90–1.80 (m, 2H, 2 $CH_2CH(CH_3)_2$), 1.70–1.60 (m, 4H, 2 CH_2), 1.40–1.30 (m, 8H, 4 CH_2), 1.30–1.20 (m, 8H, 4 CH_2), 1.00–0.80 (m, 18H, 2 $CH_2CH_2CH_3$ and 2 $CH_2CH(CH_3)_2$). – MS (EI, 70 eV): m/z (%) = 671 (2) $[M]^+$, 601 (3), 302 (5), 143 (45), 78 (2), 56 (100). – $C_{35}H_{57}N_7O_6$ (671): calcd. C 62.59, H 8.49, N 14.61; found C 62.28, H 8.32, N 14.19.

*Synthesis of cyclo-(N^{α}-dipicolinoyl)-bis [dipeptide]-L-Lys(cyclic pentapeptides) **9a**–**e***

To a stirred and cold methanolic solution (−5 °C, 20 mL) of the corresponding cyclic pentapeptide methyl ester **7a**–**e** (1 mmol), sodium hydroxide (1 N, 25 mL) was gradually added. The reaction mixture was stirred for 2 h at the same temperature, then for 3 h at room temperature. The solvent was distilled off under reduced pressure, and the remaining aqueous solution was cooled and acidified with 1 N hydrochloric acid to pH ∼ 3. The obtained solid was filtered off, washed with water, dried and crystallized from ethanol-water to give the corresponding cyclic pentapeptides **9a**–**e**.

9a: Yield: 71 %; m. p. 155 – 158 °C. – $[\alpha]_D^{25} = -113.2$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3323$ (NH, str.), 3045 (CH-Ar), 2959 (CH-aliph.), 1722 (C=O, acid), 1653, 1534, 1240 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 12.50$ (s, 1H, OH, D_2O exchangeable), 8.85 and 8.20 (2s, 6H, 6NH, D_2O exchangeable), 8.40 – 8.35 (m, 3H, pyridyl-H), 4.70 – 4.60 (m, 4H, 4 C*H*NH), 4.25 – 4.20 (t, 1H, NHCH$_2$CH$_2$CH$_2$CH$_2$C*H*NH), 3.15 – 3.10 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 1.90 – 1.80 (m, 2H, 2 CH$_2$C*H*(CH$_3$)$_2$), 1.70 – 1.60 (m, 4H, 2 CH$_2$), 1.45 – 1.40 (m, 8H, 4 CH$_2$), 1.30 – 1.20 (m, 6H, 3 CH$_2$), 0.95 – 0.85 (m, 18H, 2 CH$_2$CH$_2$C*H*$_3$ and 2 CH$_2$CH(C*H*$_3$)$_2$). – MS (EI, 70 eV): m/z (%) = 701 (7) $[M]^+$, 572 (12), 430 (44), 304 (68), 199 (22), 125 (100). – $C_{35}H_{55}N_7O_8$ (701): calcd. C 59.91, H 7.85, N 13.98; found C 59.57, H 7.63, N 13.18.

9b: Yield: 56 %; m. p. 146 – 148 °C. – $[\alpha]_D^{25} = -2.8$ ($c = 0.5$, MeOH). – IR (KBr): ν = 3326 (NH, str.), 3033 (CH-Ar), 2930 (CH-aliph.), 1721 (C=O, acid), 1653, 1537, 1230 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 12.55$ (s, 1H, OH, D_2O exchangeable), 8.65 and 8.22 (2s, 6H, 6 NH, D_2O exchangeable), 8.35 – 8.30 (m, 3H, pyridyl-H), 7.30 – 7.20 (m, 10H, 2Ar-H), 4.60 – 4.50 (m, 4H,4 C*H*NH), 4.10 – 4.05 (t, 1H, NHCH$_2$CH$_2$CH$_2$-CH$_2$C*H*NH), 3.55 – 3.50 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 3.20 – 3.10 (dd, 4H, 2C*H*$_2$Ph), 1.95 – 1.85 (m, 2H, 2 CH$_2$C*H*(CH$_3$)$_2$), 1.80 – 1.70 (m, 4H, 2 CH$_2$), 1.45 – 1.40 (m, 4H, 2 CH$_2$), 1.35 – 1.30 (m, 2H, CH$_2$), 0.95 – 0.85 (m, 12H, 2 CH$_2$CH(C*H*$_3$)$_2$). – MS (EI, 70 eV): m/z (%) = 797 (5) $[M]^+$, 755 (20), 477 (15), 302 (60), 231 (26), 91 (100). – $C_{43}H_{55}N_7O_8$ (797): calcd. C 64.74, H 6.90, N 12.29; found C 64.62, H 6.45, N 12.03.

9c: Yield: 60 %; m. p. 140 – 143 °C. – $[\alpha]_D^{25} = -85$ ($c = 0.5$, MeOH). – IR (KBr): ν = 3326 (NH, str.), 3044 (CH-Ar), 2930 (CH-aliph.), 1721 (C=O, acid), 1653, 1537, 1230 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 12.50$ (s, 1H, OH, D_2O exchangeable), 8.85 and 8.00 (2s, 6H, 6 NH, D_2O exchangeable), 8.40 – 8.30 (m, 3H, pyridyl-H), 4.60 – 4.50 (m, 4H, 4 C*H*NH), 4.25 – 4.20 (t, 1H, NHCH$_2$CH$_2$CH$_2$CH$_2$C*H*NH), 3.20 – 3.15 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 1.90 – 1.80 (m, 2H, 2 CH$_2$C*H*(CH$_3$)$_2$), 1.70 – 1.60 (m, 4H, 2 CH$_2$), 1.45 – 1.35 (m, 8H, 4 CH$_2$), 1.25 – 1.15 (m, 6H, 3 CH$_2$), 0.95 – 0.85 (m, 18H, 2 CH$_2$CH$_2$C*H*$_3$ and 2 CH$_2$CH(C*H*$_3$)$_2$). – MS (EI, 70 eV): m/z (%) = 701 (1) $[M]^+$, 678 (2), 318 (85), 236 (45), 154 (66), 56 (100). – $C_{35}H_{55}N_7O_8$ (701): calcd. C 59.91, H 7.85, N 13.98; found C 59.76, H 7.48, N 13.29.

9d: Yield: 60 %; m. p. 148 – 150 °C. – $[\alpha]_D^{25} = -45.4$ ($c = 0.5$, MeOH). – IR (KBr): ν = 3325 (NH, str.), 3028 (CH-Ar), 2930 (CH-aliph.), 1723 (C=O, acid), 1655, 1528, 1241 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 12.55$ (s, 1H, OH, D_2O exchangeable), 9.25 and 8.00 (2s, 6H, 6 NH D_2O exchangeable), 8.40 – 8.30 (m, 3H, pyridyl-H), 7.30 – 7.20 (m, 10H, 2 Ar-H), 4.40 – 4.30 (m, 4H, 4 C*H*NH), 4.25 – 4.20 (t, 1H, CH$_2$C*H*NH), 3.45 – 3.40 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 3.00 – 2.90 (dd, 4H, 2 C*H*$_2$Ph), 1.60 – 1.50 (m, 8H, 4 CH$_2$), 1.30 – 1.20 (m, 6H, 3 CH$_2$), 0.95 – 0.85 (m, 6H, 2 CH$_2$CH$_2$C*H*$_3$). – MS (EI, 70 eV): m/z (%) = 768 (5) $[M–1]^+$, 688 (10), 524 (23), 304 (10), 143 (27), 56 (100). – $C_{41}H_{51}N_7O_8$ (769): calcd. C 63.98, H 6.63, N 12.74; found C 63.15, H 6.43, N 12.31.

9e: Yield: 71 %; m. p. 151 – 153 °C. – $[\alpha]_D^{25} = -16.6$ ($c = 0.5$, MeOH). – IR (KBr): ν = 3325 (NH, str.), 3028 (CH-Ar), 2929 (CH-aliph.), 1720 (C=O, acid), 1656, 1528, 1230 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.75$ and 8.10 (2s, 6H, 6 NH, D_2O exchangeable), 8.40 – 8.35 (m, 3H, pyridyl-H), 7.20 – 7.10 (m, 20H, 4 Ar-H), 4.70 – 4.60 (m, 4H, 4 C*H*NH), 4.15 – 4.10 (t,1H, CH$_2$C*H*NH), 3.55 – 3.50 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$-CH$_2$CHNH), 3.00 – 2.90 (m, 8H, 4 C*H*$_2$Ph), 1.50 – 1.40 (m, 4H, 2 CH$_2$), 1.30 – 1.25 (m, 2H, CH$_2$). – MS (EI, 70 eV): m/z (%) = 865 (20) $[M]^+$, 498 (52), 370 (13), 205 (21), 91 (100). – $C_{49}H_{51}N_7O_8$ (865): calcd. C 67.97, H 5.89, N 11.33; found C 67.48, H 5.12, N 11.01.

Synthesis of
cyclo-(N^{α}-dipicolinoyl)-bis[dipeptide]-L-Lys-NHNH$_2$
(cyclic pentapeptide hydrazides) ***10a – e***

To a stirred methanolic solution (20 mL) of the corresponding cyclic pentapeptide methyl ester **7a – e** (1 mmol), anhydrous hydrazine hydrate (0.35 mL, 10 mmol) was added. The reaction mixture was refluxed for 3 h, after which the solvent was evaporated. The obtained residue was triturated with ether, filtered off and crystallized from methanol-ether to afford the corresponding cyclic hydrazides **10a – e**.

10a: Yield: 66 %; m. p. 165 – 167 °C. – $[\alpha]_D^{25} = -24.8$ ($c = 0.5$, MeOH). – IR (KBr): ν = 3318 (NH, str.), 3028 (CH-Ar), 2931 (CH-aliph.), 1657, 1531, 1240 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.85$, 8.75 and 8.00 (3s, 7H, 7NH, D_2O exchangeable), 8.30 – 8.25 (m, 3H, pyridyl-H), 4.70 – 4.60 (m, 4H, 4 C*H*NH), 4.15 – 4.10 (t, 1H, NHCH$_2$CH$_2$-CH$_2$CH$_2$C*H*NH), 3.45 (bs, 2H, NH$_2$, D_2O exchangeable), 3.20 – 3.15 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$-CH$_2$CHNH), 1.90 – 1.80 (m, 2H, 2 CH$_2$C*H*(CH$_3$)$_2$), 1.70 – 1.60 (m, 4H, 2 CH$_2$), 1.50 – 1.40 (m, 8H, 4 CH$_2$), 1.30 – 1.20 (m, 6H, 2 CH$_2$), 1.05 – 0.85 (m, 18H, 2 CH$_2$CH$_2$C*H*$_3$ and 2CH$_2$-CH(C*H*$_3$)$_2$). – MS (EI, 70 eV): m/z (%) = 716 (2) $[M+1]^+$, 603 (5), 266 (12), 185 (100), 102 (18), 78 (5). – $C_{35}H_{57}N_9O_7$ (715): calcd. C 58.74, H 7.97, N 17.62; found C 58.35, H 7.43, N 17.36.

10b: Yield: 52 %; m. p. 130 – 132 °C. – $[\alpha]_D^{25} = -22.2$ ($c = 0.5$, MeOH). – IR (KBr): ν = 3325 (NH, str.), 3035 (CH-Ar), 2959 (CH-aliph.), 1657, 1530, 1242 (C=O, amide I, II and III) cm^{-1}. – ^1H NMR

(500 MHz, [D$_6$]DMSO): δ = 9.50 and 8.20 (2s, 7H, 7 NH, D$_2$O exchangeable), 8.40 – 8.35 (m, 3H, pyridyl-H), 7.20 – 7.10 (m, 10H, 2 Ar-H), 4.50 – 4.40 (m, 4H, 4 C*H*NH), 4.20 – 4.015 (t, 1H, NHCH$_2$CH$_2$CH$_2$CH$_2$C*H*NH), 3.45 (bs, 2H, NH$_2$, D$_2$O exchangeable), 3.30 – 3.25 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 2.90 – 2.80 (dd, 4H, 2 C*H*$_2$Ph), 1.80 – 1.70 (m, 2H, 2 CH$_2$C*H*(CH$_3$)$_2$), 1.60 – 1.50 (m, 4H, 2 CH$_2$), 1.45 – 1.40 (m, 4H, 2 CH$_2$), 1.35 – 1.30 (m, 2H, CH$_2$), 0.95 – 0.85 (m, 12H, 2 CH$_2$CH(C*H*$_3$)$_2$). – MS (EI, 70 eV): m/z (%) = 811 (9) [M]$^+$, 720 (7), 373 (10), 187 (60), 131 (46), 91 (100). – C$_{43}$H$_{57}$N$_9$O$_7$ (811): calcd. C 63.62, H 7.03, N 15.53; found C 63.42, H 6.91, N 15.23.

10c: Yield: 67 %; m. p. 116 – 118 °C. – $[\alpha]_D^{25}$ = −11.0 (c = 0.5, MeOH). – IR (KBr): ν = 3300 (NH, str.), 3053 (CH-Ar), 2958 (CH-aliph.), 1657, 1529, 1240 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.85 and 8.10 (2s, 7 H, 7 NH, D$_2$O exchangeable), 8.35 – 8.30 (m, 3H, pyridyl-H), 4.50 – 4.40 (m, 4H, 4 C*H*NH), 4.05 – 4.00 (t, 1H, NHCH$_2$CH$_2$CH$_2$-CH$_2$C*H*NH), 3.45 (bs, 2H, NH$_2$, D$_2$O exchangeable), 3.05 – 3.00 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$-CHNH), 1.90 – 1.80 (m, 2H, 2CH$_2$C*H*(CH$_3$)$_2$), 1.60 – 1.50 (m, 4H, 2 CH$_2$), 1.40 – 1.30 (m, 8H, 4 CH$_2$), 1.20 – 1.10 (m, 6H, 3 CH$_2$), 0.95 – 0.85 (m, 18H, 2 CH$_2$CH$_2$C*H*$_3$ and 2 CH$_2$CH(C*H*$_3$)$_2$). – MS (EI, 70 eV): m/z (%) = 715 (6) [M]$^+$, 654 (5), 348 (26), 330 (75), 225 (82), 78 (100). – C$_{35}$H$_{57}$N$_9$O$_7$ (715): calcd. C 58.74, H 7.97, N 17.62; found C 58.23, H 7.35, N 17.21.

10d: Yield: 58 %; m. p. 136 – 138 °C. – $[\alpha]_D^{25}$ = −47.6 (c = 0.5, MeOH). – IR (KBr): ν = 3302 (NH, str.), 3045 (CH-Ar), 2932 (CH-aliph.), 1658, 1528, 1233 (C=O, amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.90, 8.85 and 8.00 (3s, 7H, 7 NH, D$_2$O exchangeable), 8.30 – 8.25 (m, 3H, pyridyl-H), 7.30 – 7.20 (m, 10H, 2 Ar-H), 4.90 – 4.80 (m, 4H, 4 C*H*NH), 4.15 – 4.10 (t, 1H, NHCH$_2$CH$_2$CH$_2$CH$_2$C*H*NH), 3.45 (bs, 2H, NH$_2$, D$_2$O exchangeable), 3.30 – 3.25 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 3.15 – 3.10 (dd, 4H, 2 C*H*$_2$Ph), 1.50 – 1.40 (m, 8H, 4 CH$_2$), 1.30 – 1.20 (m, 6H, 3 CH$_2$), 0.95 – 0.85 (m, 6H, 2 CH$_2$CH$_2$C*H*$_3$). – MS (EI, 70 eV): m/z (%) = 784 (6) [M+1]$^+$, 706 (7), 316 (33), 276 (50), 149 (100), 78 (80). – C$_{41}$H$_{53}$N$_9$O$_7$ (783): calcd. C 62.83, H 6.77, N 16.09; found C 62.51, H 6.65, N 15.89.

10e: Yield: 74 %; m. p. 184 – 186 °C. – $[\alpha]_D^{25}$ = −53.8 (c = 0.5, MeOH). – IR (KBr): ν = 3298 (NH stretching), 3028 (CH-Ar), 2930 (CH-aliph.), 1657, 1528, 1230 (C=O amide I, II and III) cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.90, 8.80 and 8.00 (3s, 7H, 7 NH, D$_2$O exchangeable), 8.40 – 8.35 (m, 3H, pyridyl-H), 7.20 – 7.10 (m, 20H, 4 Ar-H), 4.80 – 4.70 (m, 4H, 4 C*H*NH), 4.10 – 4.05 (t, 1H, NHCH$_2$CH$_2$CH$_2$CH$_2$C*H*NH), 3.55 – 3.50 (m, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$CHNH), 3.45 (bs, 2H, NH$_2$ D$_2$O exchangeable), 3.30 – 3.20 (m, 8H, 4 C*H*$_2$Ph), 1.50 – 1.40 (m, 4H, 2CH$_2$), 1.30 – 1.25 (m, 2H, CH$_2$). – MS (EI, 70 eV): m/z (%) = 879 (3) [M]$^+$, 749 (4), 279 (19), 192 (50), 91 (47), 56 (100). – C$_{49}$H$_{53}$N$_9$O$_7$ (879): calcd. C 66.89, H 6.03, N 14.33; found C 66.49, H 5.92, N 14.06.

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