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Synthesis of Chiral Macrocycles: I. Synthesis and Study of Cyclo (N^{α}-Dinicotinoyl)pentapeptide Candidates[1]

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Abstract—A series of linear tetrapeptides and macrocyclic pentapeptides has been synthesized starting with *N,N*-bis(1-carboxy-2-substituted)-3,5-diaminocarbonyl)pyridine and *N,N*-bis(1-hydrazonyl-2-substituted)-3,5-diaminocarbonyl)pyridine. Structures of newly synthesized compounds were elucidated by IR, ^{1}H and ^{13}C NMR, and MS spectral data and elemental analysis.

Keywords: synthesis, amino acids, 3,5-bis(tetrapeptide)pyridine, macrocyclic pentapeptide

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In the earlier publications [1–6] we presented synthesis of new macrocyclic peptide derivatives based on pyridinedicarboxylic acids and their biological activity. Synthesis and complexing ability of azacrown compounds have been the subject of intensive study [7–13]. Synthesis and chemical modification of existing antibacterial agents is important because of the emergence of multidrug-resistant bacteria [14]. Peptides rarely function well as drugs because of their low bioavailability and rapid degradation within cells [15].

In the current study we report synthetic approach to several linear tetrapeptide and macrocyclic pentapeptide derivatives based on *N,N*-bis[1-carboxy-2-(*p*-hydroxybenzyl)]-3,5-(diamino-carbonyl)pyridine (**III**) and hydrazide **IV** synthesized from the corresponding ester **II** [16] (Scheme 1).

Synthesis of N^{α}-dipicolinoyl-bis[dipeptide methyl ester] derivative (**V**) was based on the dipeptide acid **III** and dipeptide hydrazide **IV**. Treatment of L-phenylalanine methyl ester hydrochloride with dipeptide acid **III** (*Mixed anhydride method*) or dipeptide acid hydrazide (III) (*Azide method*) afforded the corresponding N^{α}-dinicotinoyl-bis[dipeptide methyl ester] derivative (**V**). The latter was hydrolyzed with NaOH in methanol to afford the corresponding N^{α}-dinicotinoyl-bis[dipeptide acid] derivative (**VI**). Hydrazinolysis of compound **V** with hydrazine hydrate in methanol gave the corresponding acid hydrazide derivative **VII** (Scheme 2). ^{1}H NMR spectrum of the product **V** contained the singlet (6H) at δ = 3.64 ppm (ester-CH_3). IR spectra of the compound **VI** demonstrated absence of ν(C=O, ester) and presence of the band at 1726 cm^{-1} (C=O, acid). ^{1}H NMR spectrum of **VI** demonstrated no singlet δ = 3.64 ppm (6H) (ester-CH_3), and appearance of the singlet δ = 11.74 ppm (2H) for carboxylic O<u>H</u> exchangeable with D_2O.

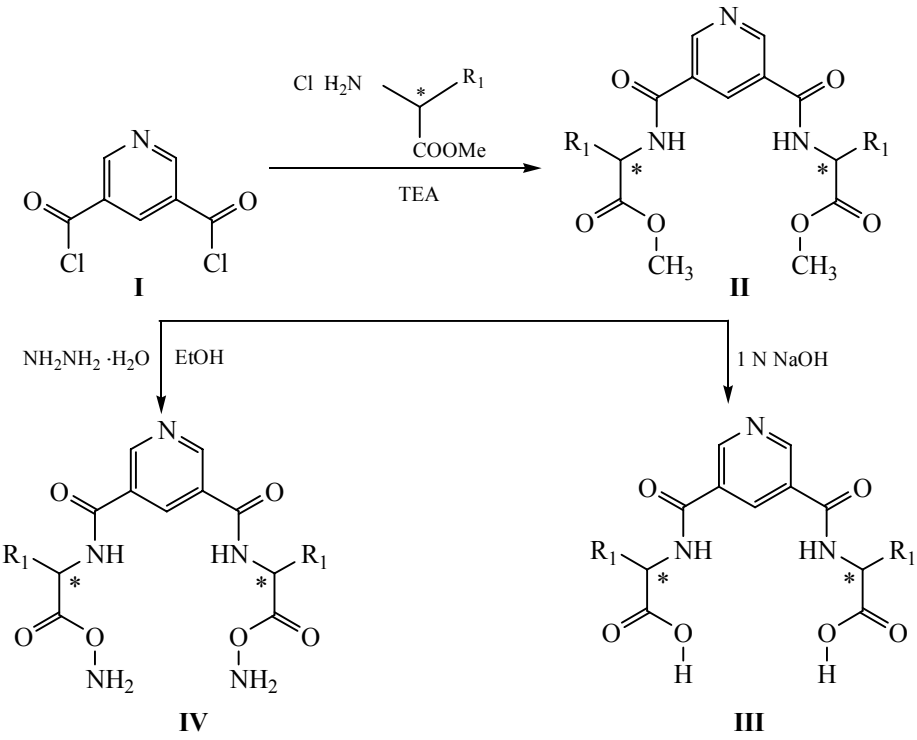
Cyclization of tetrapeptide acid **VI** or tetrapeptide bis-hydrazide **VII** with L-ornithine methyl ester or L-lysine methyl ester by different methods afforded the corresponding cyclic pentapeptide esters **VIII** and **IX** respectively. Tetrapeptides **VI** and **VII** were cyclized with aliphatic diamines by different methods to afford the corresponding cyclo-(N^{α}-dinicotinoyl)-bis[L-leu-L-phenylanyl]aliphatic diamines (**Xa, Xb**) respectively (Scheme 3). IR and ^{1}H NMR spectra of **VIII** and **IX** demonstrated the presence of the ester group registered at 1744 and 1748 cm^{-1} ν(C=O) and signals at δ = 3.58 and 3.62 ppm (ester-CH_3). IR spectra of **X** demonstrated absence of ν(C=O, acid) in **VI** and absence of ν(NH_2, hydrazide) in **VII**. ^{1}H NMR spectrum revealed disappearance of the singlet at δ = 11.74 ppm (2H) for the carboxylic protons in **VI**.

EXPERIMENTAL

Melting points were determined in open glass capillary tubes with an Electro Thermal Digital

[1] The text was submitted by the authors in English.

Scheme 1. Synthetic approach to starting compounds **III** and **IV** [16].



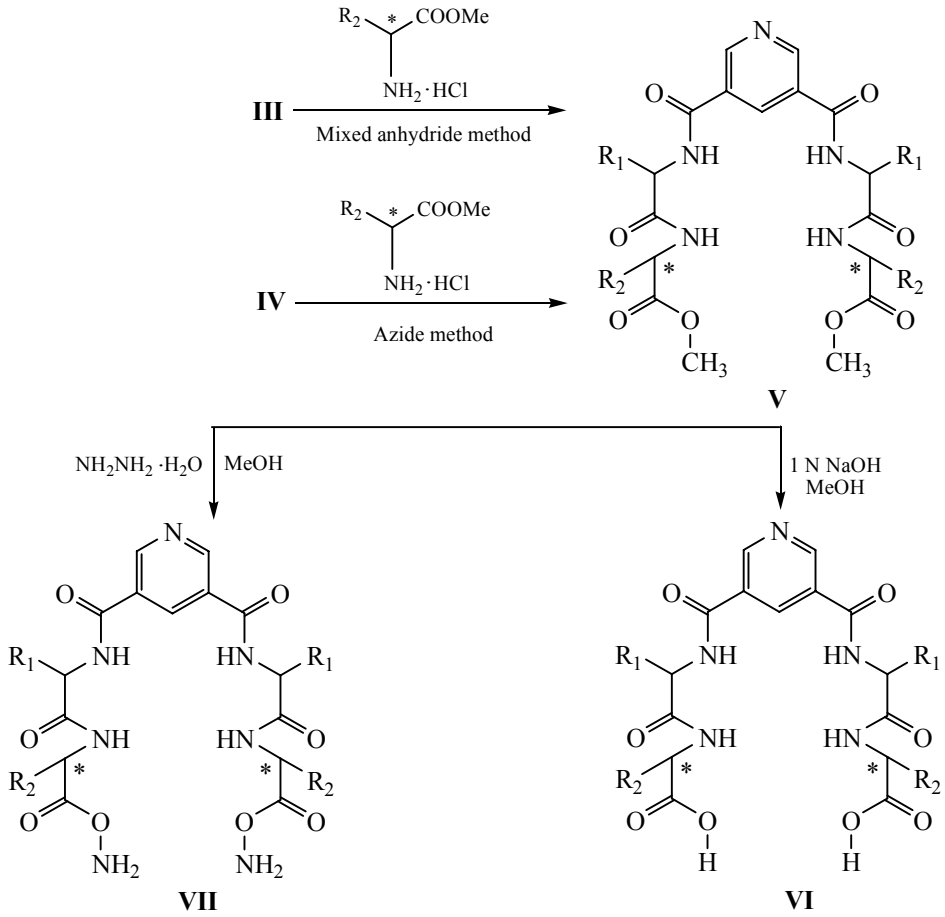
$R_1 = CH_2CH(CH_3)_2$.

melting point apparatus (IA9100). HCN microanalysis was carried out with Microanalytical Unit, NRC. IR spectra (KBr) were recorded on a Nexus 670 FTIR Nicolet, Fourier Transform spectrometer. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 by a Jeol 500 MHz spectrometer. Mass spectra were recorded on a MAT Finnigan SSQ 7000 spectrometer using the electron impact technique (EI). Analytical TLC was performed on silica gel aluminum sheets, 60 F_{254} (E. Merck).

***N*$^{\alpha}$-Dinicotinoyl-bis[L-leucyl-L-phenylalanine methyl ester] (V).** *Method A* (mixed anhydride). To a suspension of diacid **III** (1 mmol) in dichloromethane (25 mL, –20°C) containing triethylamine (0.2 g, 2 mmol), ethyl chloroformate (22 g, 2 mmol) was added upon stirring. The reaction mixture was stirred for 20 min and then L-phenylalanine methyl ester (2 mmol) was added. The reaction mixture was stirred at (–20°C) for 6 hrs and then overnight at room temperature. The resulting mixture was washed with water, 1N hydrochloric acid, 1 N sodium bicarbonate and water then dried over anhydrous calcium chloride. The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization from ethanol/ether to give the corresponding title compound ester derivatives **V**.

Method B (azide method). The cold mixture (–5°C) of dihydrazide **IV** (1 mmol), 5 N hydrochloric acid (1.2 mL), glacial acetic acid (2.4 mL) and water (10 mL) was stirred for 10 min followed by addition of aqueous sodium nitrite (0.138 g, 2 mmol in 6 mL of water) in one portion and the mixture stirred for 30 min. The synthesized 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 azide solution was added in one portion to cold solution (−5°C) of L-phenyl alanine methyl ester (2 mmol) in dry dichloromethane (25 mL). The reaction mixture was stirred at the same temperature for 3 h, then overnight at room temperature, washed with 1 N hydrochloric acid, 1 N aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give the corresponding dimethyl ester **V** (mp, TLC). Yield 92% [A], 62% [B], mp 186–188°C. IR spectrum, ν, cm^{-1}: 3370 (NH), 3087 (CH-Ar), 2968 (CH-aliph.), 1755 (C=O, ester), 1656, 1538, 1255

Scheme 2. Synthetic approach to compounds **V, VI**, and **VII**.

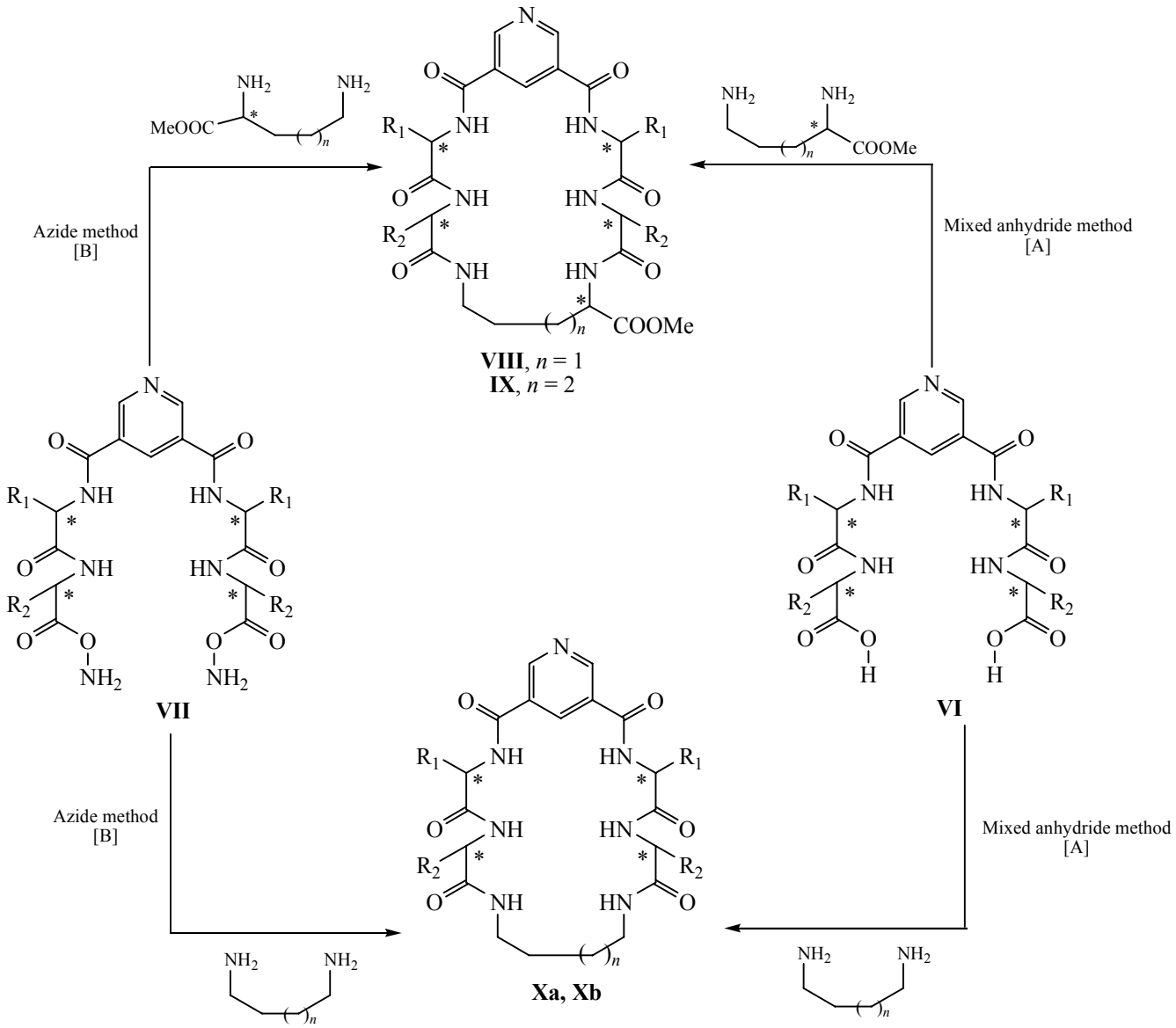


$R_1 = CH_2CH(CH_3)_2$; $R_2 = CH_2Ph$.

(C=O, amide I, II and III). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm:1.02–0.92 m (12H, $4CH_3$), 1.68–1.72 m (4H, $2CH_2$), 2.30–2.35 m (2H, 2CH), 3.36 d (4H, $2CH_2$), 3.64 s (6H, $2OCH_3$), 4.18–4.25 m (2H, 2CH), 4.56–4.65 m (2H, 2CH), 6.98–7.45 m (10H, 2Ph-H), 8.40 s, 9.01 s (3H, pyr-H) and 8.65 s, 8.85 s (4H, 4NH, exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.54, 18.65 (4C, $4CH_3$), 23.75 (2C, 2CH), 40.93 (2C, $2CH_2$), 42.14 (2C, $2CH_2$), 52.56, 52.82 (4C, 4CH), 55.65 (2C, $2OCH_3$), 124.15, 128.35, 129.45, 138.62 (12C, 2Ph), 131.64, 140.08, 152.16 (5C, pyr-C), 163.74, 168.95 (4C, 4CO-amide), 172.45 (2C, 2CO-ester). Mass spectrum: *m/z* 716 $[M]^+$. Found, %: C 65.32; H 6.80; N 9.70. $C_{39}H_{49}N_5O_8$. Calculated, %: C 65.44; H 6.90; N 9.78.

***N*$^{\alpha}$-Dinicotinoyl-bis[L-leucyl-L-phenylalanine] derivative (VI).** To a stirred cold methanol solution (–5°C, 20 mL) of the corresponding tetrapeptide ester (**V**) (1 mmol), NaOH (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 ca 3. The obtained solid was filtered off, washed with water, dried and recrystallized from ethanol/water to give the corresponding tetrapeptide diacid (**VI**). Yield 90%, mp 232–234°C. IR spectrum, ν, cm^{-1}: 4560–3378 (OH, NH), 3085 (CH-Ar), 2972 (CH-aliph.), 1726 (C=O, acid), 1655, 1534, 1256 (C=O, amide I, II and III). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 0.96-0.82 m (12H, $4CH_3$), 1.69-1.70 m (4H, $2CH_2$), 2.14–2.32 m (2H, 2CH), 3.40 d (4H, $2CH_2$), 4.24–4.28 m (2H, 2CH), 4.36–4.52 m (2H, 2CH), 7.00–7.42 m (10H, 2Ph-H), 8.45, 9.06 m (3H, pyr-H), 8.65 s, 8.82 s (4H, 4NH, exchangeable with D_2O), 11.74 s (2H, 2OH, exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.95, 18.62 (4C, $4CH_3$), 33.70 (2C, 2CH), 39.85 (2C, $2CH_2$), 41.96 (2C, $2CH_2$), 52.55, 53.10 (4C, 4CH), 124.22, 128.25, 129.42, 138.65 (12C, 2Ph-C), 131.55, 140.12, 152.15 (5C, pyr-C),

Scheme 3. Synthetic approach to compounds **VIII, IX**, **Xa,** and **Xb**.



$R_1 = CH_2CH(CH_3)_2$, $R_2 = CH_2Ph$.

164.08, 169.12 (4C, 4CO-amide), 171.45 (2C, 2CO-acid). Mass spectrum: *m/z* 688 $[M]^+$. Found, %: C 64.50; H 6.50; N 10.10. $C_{37}H_{45}N_5O_8$. Calculated, %: C 64.61; H 6.59; N 10.18.

***N*$^{\alpha}$-Dinicotinoyl-bis[L-leucyl-L-phenylalanine] hydrazide (VII).** To a solution of *N*$^{\alpha}$-dinicotinoyl-bis-[L-leucyl-L-phenylalaninyl]methyl ester (**V**) (1 mmol) in methanol (20 mL), anhydrous hydrazine hydrate (0.35 mL, 10 mmol) was added. The reaction mixture was refluxed for 3 h, the solvent was evaporated under reduced pressure, thus obtained residue was triturated with ether, filtered off and recrystallized from ethanol/ether to give the corresponding title compound **VII**. Yield 90%, mp 250–252°C. IR spectrum, ν, cm^{-1}: 3460–3350 br (NH_2, NH), 3076 (CH-Ar), 2985 (CH-aliph.), 1654, 1532, 1255 (C=O, amide I, II and III). ^1H NMR spectrum (DMSO-d_6), δ_H, ppm: 0.98–0.86 m (12H, $4CH_3$), 1.67–1.74 m (4H, $2CH_2$), 2.17-2.26 m (2H, 2CH), 3.40 d (4H, $2CH_2$), 4.05 br.s (4H, $2NH_2$, exchangeable with D_2O), 4.24–4.32 m (2H, 2CH), 4.54–4.68 m (2H, 2CH), 6.99–7.45 m (10H, 2Ph-H), 8.36, 9.00 m (3H, pyr-H), 8.65 s, 8.78 s, 9.16 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum

(DMSO-d_6), δ_C, ppm: 17.35, 18.56 (4C, $4CH_3$), 33.74 (2C, 2CH), 40.05 (2C, $2CH_2$), 42.25 (2C, CH_2), 52.43, 53.03 (4C, 4CH), 124.13, 128.21, 129.37, 138.67 (12C, 2Ph-C), 131.58, 140.10, 152.10 (5C, pyr-C), 163.73, 169.02 (4C, 4CO-amide), 170.43 (2C, 2CO-hydrazide). Mass spectrum: *m/z* 716 $[M]^+$. Found, %: C 62.00; H 6.78; N 17.53. $C_{37}H_{49}N_9O_6$. Calculated, %: C 62.08; H 6.90; N 17.61.

Cyclic pentapeptide methyl esters VIII and IX. *Method A* (mixed anhydride method). Ethyl chloroformate (0.2 mL, 2 mmol) was added to a stirred cold (–15°C) dichloromethane solution (20 mL) of the corresponding N^{α}-dinicotinoyl-bis[dipeptide] **VI** (1 mmol), containing triethylamine (2 mmol). The reaction mixture was stirred for additional 20 min then free L-ornithine or L-lysine methyl ester (1 mmol) in dichloromethane solution (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 washed with water, 1 N sodium bicarbonate, 1 N potassium hydrogen sulfate and water then dried over anhydrous calcium chloride. 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 TLC using methanol–benzene eluent (1 : 9 by volume) to give the corresponding cyclic pentapeptide methyl esters **VIII** and **IX** respectively.

Method B (azide method). The cold mixture (–15°C) of dihydrazide derivative (**VII**) (1 mmol) in hydrochloric acid (6 N, 2 mL) and glacial acetic acid (1 mL) was stirred for 10 min followed by addition of aqueous solution of sodium nitrite (5 M, 2 mL). 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 then dried over anhydrous sodium sulfate. Cold ethereal azide solution (–15°C) was added to free L-ornithine or 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 then dried over anhydrous sodium sulfate. Ether was evaporated to dryness and thus obtained oily residue was solidified by trituration with dry ether–*n*-hexane mixture to give the corresponding cyclic pentapeptide methyl esters **VIII** and **IX**, respectively (mp, TLC).

Cyclo-(N^{α}-dinicotinoyl)bis[L-Leucyl-L-phenylalaninyl]-L-ornithine (VIII). Yield 72% [A], 55% [B], mp 192–194°C. IR spectrum, ν, cm^{-1}: 3375 (NH), 3072 (CH-Ar), 2968 (CH-aliph.), 1744 (C=O, ester), 1654, 1537, 1256 (C=O, amide I, II and III). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 0.80–1.90 m (12H, $4CH_3$), 1.24–1.46 m (4H, $2CH_2$), 1.60–1.75 m (4H, $2CH_2$), 2.30–2.35 m (2H, 2CH), 3.00–3.20 m (2H, CH_2), 3.36 d (4H, $2CH_2$), 3.58 s (3H, OCH_3), 3.90–4.05 m (4H, 4CH), 4.38–4.44 m (1H, CH), 7.12–7.30 m (10H, 2Ph-H), 8.42 s, 9.05 s (3H, pyr-H), 8.88 s, 8.96 s, 9.22 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.65, 18.97 (4C, $4CH_3$), 28.30, 30.35, 38.00 (3C, $4CH_2$), 23.85 (2C, 2CH), 41.99, 42.05 (4C, $4CH_2$), 52.36, 52.80 (4C, 4CH), 54.48 (1C, CH_3-ester), 60.50 (1C, CH-ester), 124.32, 128.30, 129.42, 138.74 (12C, 2Ph-C), 131.48, 140.10, 152.15 (5C, pyr-C), 163.81, 169.15, 170.64 (6C, 6CO, amide), 173.89 (1C, CO-ester). Mass spectrum: *m/z* 798 $[M]^+$. Found, %: C 64.62; H 6.84; N 12.20. $C_{43}H_{55}N_7O_8$. Calculated, %: C 64.72; H 6.95; N 12.29.

Cyclo-(N^{α}-dinicotinoyl)bis[L-leucyl-L-phenylalaninyl]-L-lysine (IX). Yield 78% [A], 58% [B], mp 186–188°C. IR spectrum, ν, cm^{-1}: 3365 (NH), 3082 (CH-Ar), 2977 (CH-aliph.), 1748 (C=O, ester), 1656, 1533, 1253 (C=O, amide I, II and III). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm:0.95–0.88 m (12H, $4CH_3$), 1.23–1.45 m (4H, $2CH_2$), 1.61–1.76 m (4H, $2CH_2$), 2.28–2.36 m (2H, 2CH), 3.02–3.22 m (4H, $2CH_2$), 3.35 d (4H, $2CH_2$), 3.62 s (3H, OCH_3), 3.91–4.04 m (4H, 4CH), 4.38–4.46 m (1H, CH), 7.08–7.45 m (10H, 2Ph-H), 8.32 s, 9.01 s (3H, pyr-H), 8.85 s, 8.97 s, 9.18 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.64, 18.96 (4C, CH_3), 22.57, 28.32, 30.31, 38.02 (4C, $4CH_2$), 23.82 (2C, 2CH), 41.96 (2C, $2CH_2$), 42.15 (2C, $2CH_2$), 52.40, 52.85 (4C, 4CH), 54.43 (1C, OCH_3), 60.52 (1C, CH-ester), 124.35, 128.32, 129.41, 138.77 (12C, 2Ph-C), 131.74, 140.12, 151.98 (5C, pyr-C), 163.75, 169.32 170.68 (6C, 6CO, amide), 173.85 (1C, CO, ester). Mass spectrum: *m/z* 812 $[M]^+$. Found, %: C 65.00; H 7.00; N 12.00. $C_{44}H_{57}N_7O_8$. Calculated, %: C 65.09; H 7.08; N 12.08.

Synthesis of cyclo-(N^{α}-dinicotinoyl)bis[L-Leucyl-L-phenylalaninyl]aliphatic diamines (Xa, Xb). *Method A* (mixed anhydride method). To a suspension of diacid **VI** (1 mmol) in cold and stirred dichloromethane (25 mL, –20°C) containing triethylamine (0.2 g, 2 mmol), ethyl chloroformate (22 g, 2 mmol) was added. Stirring was continued for 20 min, then either 1,4-butane diamine or 1,6-hexane diamine

(1 mmol) was added. The reaction mixture was stirred at (–20°C) for 6 hrs and then overnight at room temperature. The resulting mixture was washed with water, 1 N hydrochloric acid, 1 N sodium bicarbonate and water then dried over anhydrous calcium chloride. The solvent was evaporated under reduced pressure, and the crude product was purified by crystallization from ethanol to give the corresponding cyclic peptides **Xa, Xb**, respectively.

Method B (azide method). An aqueous solution of sodium nitrite (10%, 0.13 g, 2 mmol) was added to cold (–5°C) stirred solution of dihydrazide (**VII**) (1 mmol) in 5 N HCl (3 mL) and acetic acid (3 mL). Stirring of the mixture was continued for 30 min followed by extraction with ether and washing with water, $NaHCO_3$, and water, then dried over anhydrous sodium sulfate. Cold ether solution (–5°C) was added to cold (–5°C) dichloromethane solution of either 1,4-butanediamine or 1,6-hexanediamine (1 mmol, 10 mL dichloromethane). Stirring of cold mixture was lasted for 5 h and at room temperature for 2 hrs. The reaction mixture was washed with 1 N hydrochloric acid, water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crude products **Xa, Xb**, that upon preparative TLC were determined to be identical with those obtained via the mixed anhydride method.

Cyclo-(N^{α}-dinicotinoyl)bis[L-Leucyl-L-phenylalaninyl]-1,4-butanediamine (Xa). Yield 82% [A], 54% [B], mp 188–190°C. IR spectrum, ν, cm^{-1}: 3365 (NH), 3058 (CH-Ar), 2975 (CH-aliph.), 1660, 1530, 1246 (C=O, amide I, II and III). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 1.05–0.85 m (12H, $4CH_3$), 1.22–1.35 m (4H, $2CH_2$), 1.38–1.42 m (4H, $2CH_2$), 1.62–1.74 m (4H, $2CH_2$), 2.28–2.36 m (2H, 2CH), 3.35 d (4H, $2CH_2$Ph), 4.10–4.00 m (4H, 4CH), 6.95–7.42 m (10H, 2Ph-H), 8.42 s, 9.10 s (3H, pyr-H), 8.78 s, 8.95 s, 9.18 s (6H, 6NH, exchangeable with D_2O). Mass spectrum: *m/z* 740 $[M]^+$. Found, %: C 66.44; H 7.15; N 13.20. $C_{41}H_{53}N_7O_6$. Calculated, %: C 66.55; H 7.22; N 13.25.

Cyclo-(N^{α}-dinicotinoyl)bis[L-Leucyl-L-phenylalaninyl]-1,6-hexanediamine (Xb). Yield 86% [A], 55% [B], mp 204–206°C. IR spectrum, ν, cm^{-1}: 3358 (NH, str.), 3085 (CH-Ar), 2966 (CH-aliph.), 1662, 1532, 1247 (C=O, amide I, II and III). ^{1}H NMR spectrum (DMSO-d_6), δ_H, ppm: 1.00–0.80 m (12H, $4CH_3$), 1.20–1.28 m (4H, $2CH_2$), 1.30–1.36 m (4H, $2CH_2$), 1.40–1.48 m (4H, $2CH_2$), 1.70–1.60 m (4H, $2CH_2$), 2.28–2.36 m (2H, 2CH), 3.42 d (4H, $2CH_2$), 4.10–4.22 m (4H, 4CH), 6.98–7.46 m (10H, 2Ph-H), 8.40 and 9.02 (2s, 3H, pyridyl-H), 8.74 s, 8.95 s, 9.18 s (6H, 6NH, exchangeable with D_2O). Mass spectrum: *m/z* 768 $[M]^+$. Found, %: C 67.16; H 7.40; N 12.70. $C_{43}H_{57}N_7O_6$. Calculated, %: C 67.25; H 7.48; N 12.77.

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