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Synthesis of Chiral Linear and Macrocyclic Candidates: II.[1] Synthesis and Investigation of 3,5-Bis-Linear and Macrocyclic Tetrapeptide Schiff Base Pyridine Derivatives[2]

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Abstract—A series of several linear and macrocyclic tetrapeptide derivatives based on N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninyl] acid hydrazide as starting material is synthesized. Treatment of acid hydrazide with cyclic alkanones gave the corresponding tetrapeptide cycloalkanone derivatives. Condensation of hydrazide with substituted acetophenone or acetylpyridine derivatives gave the corresponding Schiff base derivatives. Cyclization of acid hydrazide with 2,6-diacetylpyridine afforded the corresponding bicyclopyridine derivative. Reaction of acid hydrazide with acids anhydrides gave the corresponding bisimide carboxamide derivatives.

Keywords: synthesis, amino acids, bicyclotetrapeptide, macrocyclic tetrapeptide, Schiff bases

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Peptide-based drugs and neuromodulators, administered peripherally, fail to affect the target brain cells [2] because BBB, which is characterized by high electrical resistance and low paracellular diffusion [3], retards most of peptides from reaching the brain [4]. Heterocyclic compounds containing amino acids and peptides demonstrate biological [5] and moderate antibacterial activities in vitro against various Gram-positive and Gram-negative bacteria, fungi and yeast [6]. Some pyridazinone-based thio derivatives and pyridazine analogs were synthesized and their binding with three human formyl peptide receptor isoforms (FPR1, FPR2, and FPR3) was studied [7]. Previously we reported synthesis of some new amino acids, macrocyclic peptides derived from pyridine dicerboxylic acids with selected amino acids and their biological activity [8–13]. Synthesis and chemical modification of existing antibacterial agents is important because of emerge of multidrug-resistant bacteria [14].

In the present work we report synthesis of several linear and macrocyclic tetrapeptide derivatives based on N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninyl acid hydrazide] (**IV**) which was obtained from dipeptide ester **II** via the corresponding acid (**III**) [1] (Scheme 1).

Refluxing of N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninyl acid hydrazide] (**IV**) with cyclic alkanones (cyclopentanone, cyclohexanone or cycloheptanone) in glacial acetic acid gave the corresponding tetrapeptide cycloalkanone derivatives **Va–Vc**. Condensation of the same compound **IV** with substituted acetophenone or acetylpyridine derivatives in refluxed glacial acetic acid led to N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninylhydrazone] derivatives **VIa–VId** and **VIIa–VIIc**, respectively (Scheme 2).

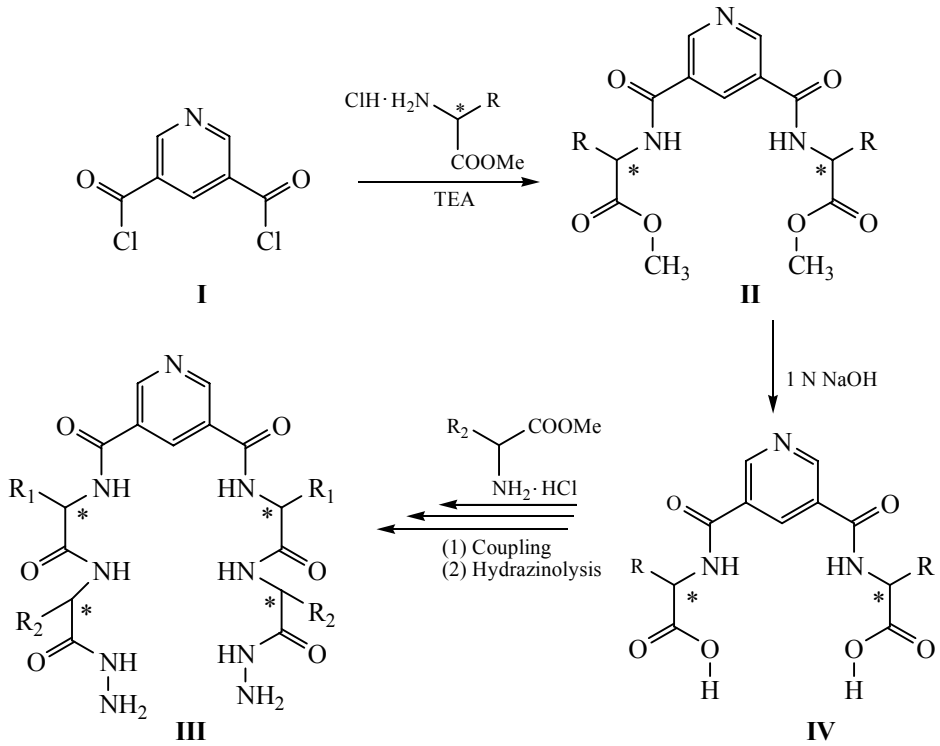
Cyclization of compound **IV** with 2,6-diacetylpyridine in refluxed acetic acid gave the corresponding cyclic product **VIII**. Reaction of compound **IV** with acids anhydrides, namely, phthalic, tetrachlorophthalic or 2,3-pyridinedicarboxylic, led to corresponding diimide derivatives **IXa, IXb,** and **X** (Scheme 3).

EXPERIMENTAL

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

[1] For communication I, see [1].
[2] The text was submitted by the authors in English.

Scheme 1. Synthetic route for the starting compound **IV**.



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

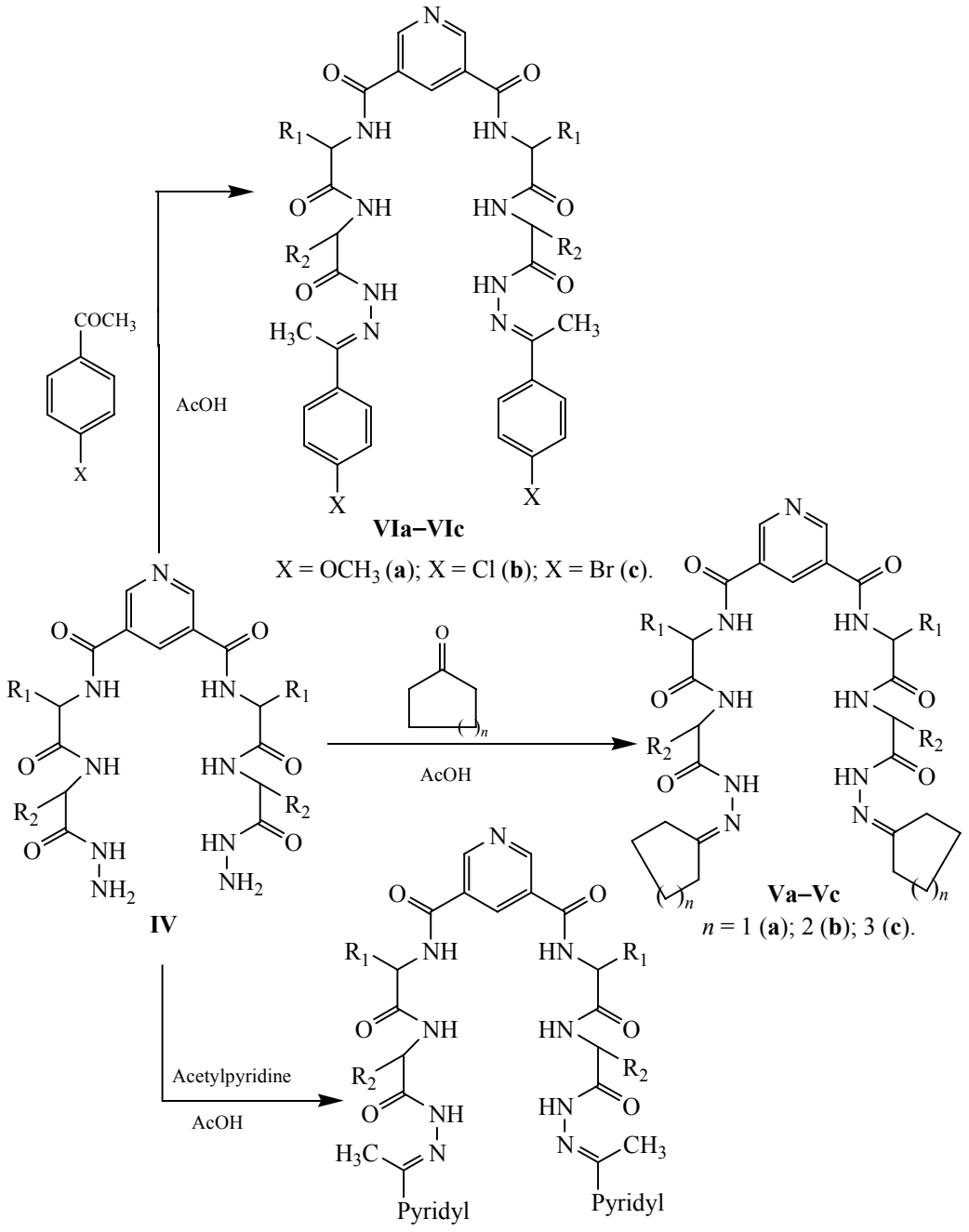
point apparatus (model IA9100). CHN elemental microanalysis was carried out with a Microanalytical Unit, NRC. FT-IR spectra (KBr) were recorded on a Nexus 670 FTIR Nicolet spectrophotometer. ^1H and ^{13}C NMR spectra were measured in DMSO-d_6 on a Jeol 500 MHz and 125 MHz spectrometers. MS spectra were measured on a MAT Finnigan SSQ 7000 spectrometer using EI technique. TLC was performed on silica gel aluminum sheets, 60 F_{254} (E. Merck).

Synthesis of N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninyl cycloalkanone hydrazone] (Va–Vc). A mixture of compound **IV** (1 mmol) and one of cycloalkanones: cyclopentanone, cyclohexanone or cycloheptanone (2 mmol), in glacial acetic acid (30 mL) was refluxed for 6 h. The reaction mixture was poured onto ice, thus obtained precipitate was filtered off, washed with water, dried, and crystallized from AcOH/H_2O to give the corresponding Schiff bases derivatives **Va–Vc**, respectively.

Compound Va. Yield 76%, mp 210–212°C. $[\alpha]_D^{25}$ = –96 (c = 0.5, DMF). FT-IR, ν, cm^{-1}: 3456–3375 (NH), 3092 (CH-Ar), 2976 (CH-aliph.), 1655, 1536, 1254 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.94–0.85 m (2H, $4CH_3$), 1.25–1.37 m (16H, CH_2), 1.65–1.76 m (4H, $2CH_2$), 2.15–2.25 m (2H, 2CH), 3.40 d (4H, $2CH_2$), 4.22–4.35 m (2H, 2CH), 4.56–4.67 m (2H, 2CH), 6.98–7.48 m (10H, 2Ph-H), 8.35 s, 9.01 s (3H, pyr-H), 8.67 s, 8.76 s, 9.18 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 17.32, 18.54 (4C, $4CH_3$), 26.12, 32.22, 187.04 (10C, cyclopentyl ring), 23.75 (2C, 2CH), 40.10 (2C, $2CH_2$), 42.26 (2C, CH_2), 52.45, 53.06 (4C, 4CH), 124.15, 128.23, 129.36, 138.65 (12C, 2Ph–C), 131.62, 140.14, 152.18 (5C, pyr-C), 163.70, 169.12 (4C, 4 CO-amide), 178.43 (2C, 2CO-hydrazone). MS (EI, 70 eV): m/z (%) = 848 (14) $[M]^+$. Found, %: C 66.50; H 7.20; N 14.80. $C_{47}H_{61}N_9O_6$. Calculated, %: C 66.57; H 7.25; N 14.86.

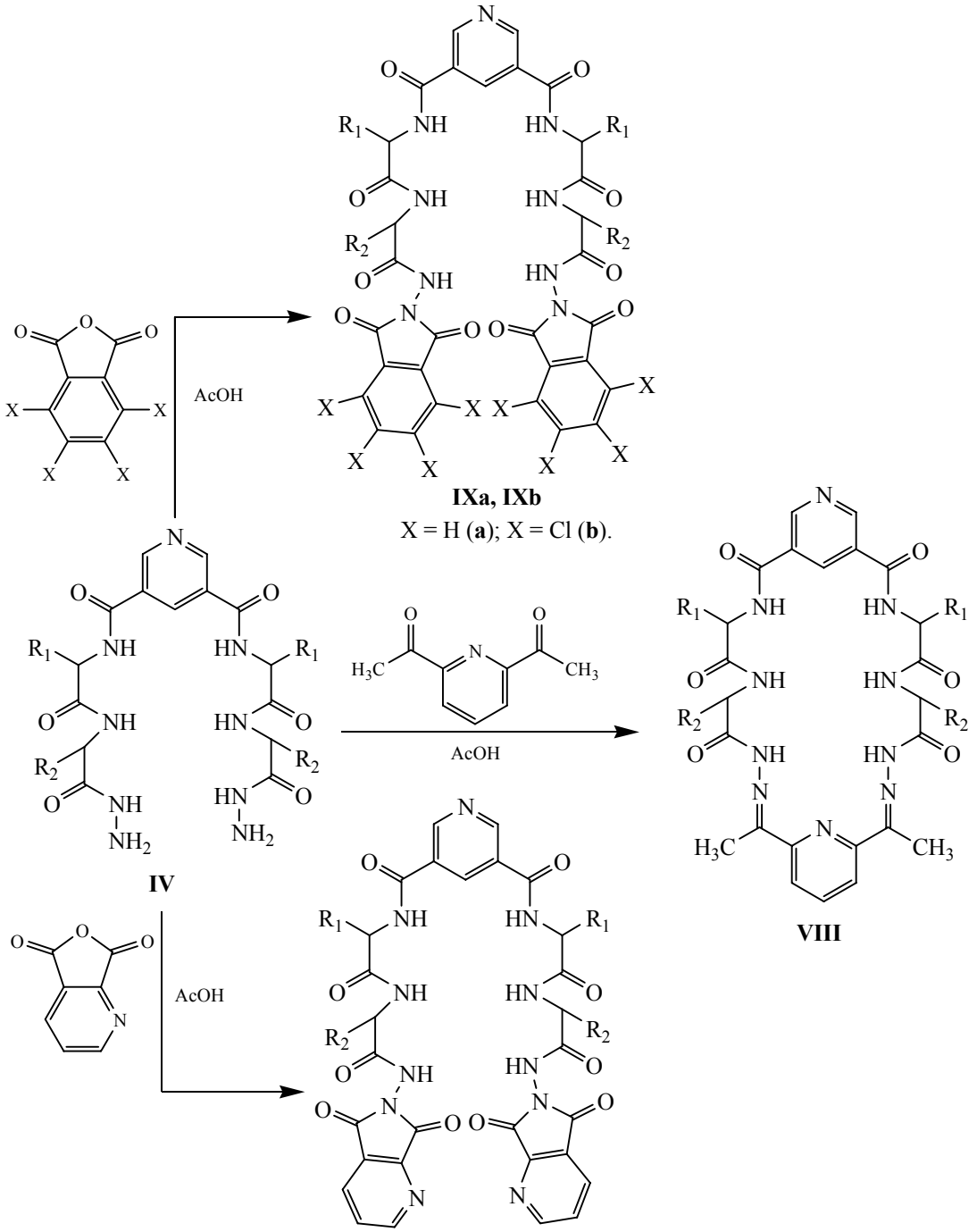
Compound Vb. Yield 75%, mp 186–188°C. $[\alpha]_D^{25}$ = –106 (c = 0.5, DMF). FT-IR, ν, cm^{-1}: 3445–3394 (NH), 3084 (CH-Ar), 2980 (CH-aliph.), 1656, 1537, 1256 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.86–0.95 m (12H, $4CH_3$), 1.24–1.42 m (20H, CH_2), 1.66–1.75 m (4H, $2CH_2$), 2.14–2.22 m (2H, 2CH), 3.44 d (4H, $2CH_2$), 4.26–4.36 m (2H, 2CH), 4.55–4.65 m (2H, 2CH), 7.02–7.56 m (10H,

Scheme 2. Synthetic routes for compounds **Va–Vc, VIa–Vic,** and **VIIa–VIIc**.



2Ph-H), 8.44 s, 9.08 s (3H, pyr-H), 8.65 s, 8.85 s, 9.15 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 17.44, 18.62 (4C, $4CH_3$), 24.15, 26.86, 28.18, 161.22 (12C, cyclohexyl ring), 23.78 (2C, 2CH), 40.10 (2C, $2CH_2$), 42.27 (2C, CH_2), 52.47, 53.07 (4C, 4CH), 124.18, 128.25, 129.35, 138.64 (12C, 2Ph-C), 131.65, 140.18, 152.32 (5C, pyr-C), 163.76, 169.30 (4C, 4CO-amide), 178.54 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 876 (12) $[M]^+$. Found, %: C 67.10; H 7.40; N 14.32. $C_{49}H_{65}N_9O_6$. Calculated, %: C 67.18; H 7.48; N 14.39.

Scheme 3. Synthetic routes for compounds **VIII, IXa, IXb,** and **X**.



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

Compound Vc. Yield 82%, mp 201–203°C. $[\alpha]_D^{25}$ = –98 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3438–3356 (NH), 3088 (CH-Ar), 2990 (CH-aliph.), 1654, 1536, 1256 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.87–0.97 m (12H, $4CH_3$), 1.22–1.40 m (24H, CH_2), 1.68–1.75 m (4H, $2CH_2$), 2.14–2.26 m (2H, 2CH), 3.39 d (4H, $2CH_2$), 4.24–4.36 m (2H, 2CH), 4.55–4.65 m (2H, 2CH), 6.99–7.49 m (10H, 2Ph-H), 8.42 s, 9.07 s (3H, pyr-H), 8.66 s, 8.76 s, 9.16 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum,

δ_C, ppm: 17.33, 18.53 (4C, $4CH_3$), 24.12, 26.82, 29.28, 184.01 (14C, cyclohexyl ring), 23.68 (2C, 2CH), 40.15 (2C, $2CH_2$), 42.24 (2C, CH_2), 52.43, 53.05 (4C, 4CH), 124.16, 128.25, 129.38, 138.67 (12C, 2Ph-C), 131.68, 140.22, 152.16 (5C, pyr-C), 163.65, 169.10 (4C, 4CO-amide), 178.45 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 904 (32) $[M]^+$. Found, %: C 67.69; H 7.60; N 13.88. $C_{51}H_{69}N_9O_6$. Calculated, %: C 67.75; H 7.69; N 13.94.

General procedure for synthesis of N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninyl hydrazone] (Schiff base) VIa–Vc and VIIa–VIIc. A mixture of compound **IV** (1 mmol) and acetophenone or acetylpyridine derivatives, namely, 4-methoxy-, 4-chloro-, 4-bromo-acetophenone or 2-acetylpyridine, 3-acetylpyridine or 4-acetyl-pyridine (2 mmol) in ethanol (30 mL), in presence of diethylamine and triethylamine (4 mL, 2 : 2) was refluxed for 3–6 h. The reaction mixture was evaporated under reduced pressure, the obtained residue was solidified in *n*-hexane. The obtained precipitate was filtered off, washed with *n*-hexane, dried, and crystallized from the proper solvents to give corresponding hydrazone compounds **VIa–VIc** and **VIIa–VIIc**, respectively.

Compound VIa. Yield 62%, mp 198–200°C (dioxane–*n*-hexane). $[\alpha]_D^{25}$ = –105 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3477–3343 (NH), 3083 (CH-Ar), 2975 (CH-aliph.), 1656, 1532, 1252 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.86–0.98 m (18H, $6CH_3$), 1.60–1.75 m (4H, $2CH_2$), 2.20–2.28 m (2H, 2CH), 3.42 d (4H, $2CH_2$), 3.64 s (6H, 2 OCH_3), 4.25–4.36 m (2H, 2CH), 4.62–4.72 m (2H, 2CH), 6.88–7.54 m (18H, 4Ph-H), 8.32 s, 9.08 s (3H, pyr-H), 8.65 s, 8.78 s, 9.22 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.54, 17.22, 18.65 (6C, $6CH_3$), 23.78 (2C, 2CH), 40.24 (2C, $2CH_2$), 42.36 (2C, CH_2), 52.48, 53.12 (4C, 4CH), 55.78 (2C, $2OCH_3$), 114.05, 124.32, 125.65, 128.28, 129.42, 129.75, 138.68, 162.85 (24C, 4Ph-C), 131.65, 140.25, 152.26 (5C, pyr-C), 168.15 (2C, 2C=N), 163.84, 169.40 (4C, 4CO-amide), 178.46 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 980 (42) $[M]^+$. Found, %: C 67.32; H 6.60; N 12.80. $C_{55}H_{65}N_9O_8$. Calculated, %: C 67.40; H 6.68; N 12.86.

Compound VIb. Yield 65%, mp 175–177°C (DMF–H_2O). $[\alpha]_D^{25}$ = –100 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3445–3332 (NH), 3085 (CH-Ar), 2978 (CH-aliph.), 1654, 1536, 1253 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.82–0.95 m (18H, $6CH_3$), 1.65–1.78 m (4H, $2CH_2$), 2.22–2.30 m (2H, 2CH), 3.45 d (4H, $2CH_2$), 4.24–4.35 m (2H, 2CH), 4.65–4.76 m (2H, 2CH), 6.92–7.68 m (18H, 4Ph-H), 8.45 s, 9.11 s (3H, pyr-H), 8.72 s, 8.82 s, 9.25 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.48, 17.35, 18.78 (6C, 6 CH_3), 23.75 (2C, 2CH), 40.22 (2C, $2CH_2$), 42.48 (2C, CH_2), 52.42, 53.10 (4C, 4CH), 124.12, 128.28, 128.85, 129.36, 130.03, 131.88, 132.05, 138.65 (24C, 4Ph-C), 131.62, 140.28, 152.25 (5C, pyr-C), 168.08 (2C, 2C=N), 163.80, 169.47 (4C, 4CO-amide), 178.40 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 989 (18) $[M]^+$. Found, %: C 64.30; H 5.92; Cl 7.10; N 12.70. $C_{53}H_{59}Cl_2N_9O_6$. Calculated, %: C 64.36; H 6.01; Cl 7.17; N 12.75.

Compound VIc. Yield 72%, mp 185–187°C (AcOH–H_2O). $[\alpha]_D^{25}$ = –132 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3452–3318 (NH), 3090 (CH-Ar), 2974 (CH-aliph.), 1655, 1532, 1250 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.89–0.98 m (18H, $6CH_3$), 1.60–1.75 m (4H, $2CH_2$), 2.25–2.36 m (2H, 2CH), 3.44 d (4H, $2CH_2$), 4.22–4.36 m (2H, 2CH), 4.66–4.78 m (2H, 2CH), 6.98–7.54 m (18H, 4Ph-H), 8.32 s, 9.15 s (3H, pyr-H), 8.70 s, 8.86 s, 9.24 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.55, 17.44, 18.74 (6C, 6 CH_3), 23.81 (2C, 2CH), 40.28 (2C, $2CH_2$), 42.52 (2C, CH_2), 52.46, 53.18 (4C, 4CH), 124.33, 125.00, 128.24, 129.38, 130.95, 131.07, 132.86, 138.66 (24C, 4Ph-C), 131.65, 140.33, 152.28 (5C, pyr-C), 168.12 (2C, 2C=N), 163.84, 169.52 (4C, 4 CO-amide), 178.45 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 1078 (8) $[M]^+$. Found, %: C 59.00; H 5.44; N 11.60. $C_{53}H_{59}Br_2N_9O_6$. Calculated, %: C 59.06; H 5.52; N 11.69.

Compound VIIa. Yield 56%, mp 215–217°C (DMF–H_2O). $[\alpha]_D^{25}$ = –116 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3454–3324 (NH), 3088 (CH-Ar), 2974 (CH-aliph.), 1655, 1534, 1253 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.88–0.99 m (18H, $6CH_3$), 1.64–1.78 m (4H, $2CH_2$), 2.26–2.32 m (2H, 2CH), 3.44 d (4H, $2CH_2$), 4.26–4.35 m (2H, 2CH), 4.65–4.75 m (2H, 2CH), 6.90–7.52 m (10H, 2Ph-H), 7.64–8.55 m (10H, pyr-H), 9.09 s (1H, pyr-H-4), 8.68 s, 8.84 s, 9.16 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.65, 17.33, 18.62 (6C, $6CH_3$), 23.76 (2C, 2CH), 40.25 (2C, $2CH_2$), 42.38 (2C, CH_2), 52.52, 53.18 (4C, 4CH), 124.22, 128.24, 129.35, 138.65 (12C, 2Ph-C), 145.32 (2C, 2C=N), 122.95, 126.01, 131.65, 135.86, 140.25, 148.67, 152.26, 154.45 (15C, 3 pyr-C), 163.82, 169.33 (4C, 4CO-

amide), 178.55 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 922 (14) $[M]^+$. Found, %: C 66.35; H 6.38; N 16.62. $C_{51}H_{59}N_{11}O_6$. Calculated, %: C 66.43; H 6.45; N 16.71.

Compound VIIb. Yield 62%, mp 232–234°C (AcOH–H_2O). $[\alpha]_D^{25}$ = –128 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3455–3351 (NH), 3078 (CH-Ar), 2992 (CH-aliph.), 1652, 1538, 1250 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.82–0.96 m (18H, $6CH_3$), 1.65–1.72 m (4H, $2CH_2$), 2.18–2.35 m (2H, 2CH), 3.46 d (4H, $2CH_2$), 4.23–4.38 m (2H, 2CH), 4.64–4.77 m (2H, 2CH), 6.86–7.65 m (10H, 2Ph-H), 7.75–8.64 m (8H, pyr-H), 9.05 s, 9.24 s (3H, pyr-H), 8.72 s, 8.87 s, 9.18 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.60, 17.45, 18.67 (6C, $6CH_3$), 24.05 (2C, 2CH), 40.32 (2C, $2CH_2$), 42.46 (2C, CH_2), 52.54, 53.34 (4C, 4CH), 124.25, 128.34, 129.45, 138.60 (12C, 2Ph-C), 123.56, 126.05, 131.62, 136.85, 140.28, 150.86, 151.25, 152.25 (15C, 3 pyr-C), 168.45 (2C, 2C=N), 164.02, 169.45 (4C, 4CO-amide), 178.68 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 922 (32) $[M]^+$. Found, %: C 66.37; H 6.35; N 16.60. $C_{51}H_{59}N_{11}O_6$. Calculated, %: C 66.43; H 6.45; N 16.71.

Compound VIIc. Yield 72%, mp 208–210°C (EtOH–H_2O). $[\alpha]_D^{25}$ = –142 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3432–3360 (NH), 3082 (CH-Ar), 2980 (CH-aliph.), 1656, 1535, 1252 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.90–0.98 m (18H, $6CH_3$), 1.66–1.77 m (4H, $2CH_2$), 2.25–2.34 m (2H, 2CH), 3.45 d (4H, $2CH_2$), 4.27–4.37 m (2H, 2CH), 4.67–4.77 m (2H, 2CH), 6.97–7.51 m (10H, 2Ph-H), 8.10 d, 8.78 d (8H, Pyr-H), 8.43 s, 9.05 s (3H, pyr-H-4), 8.65 s, 8.89 s, 9.24 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.32, 17.38, 18.67 (6C, $6CH_3$), 23.82 (2C, 2CH), 40.34 (2C, $2CH_2$), 42.45 (2C, CH_2), 52.50, 53.25 (4C, 4CH), 124.25, 128.26, 129.38, 138.66 (12C, 2Ph-C), 167.98 (2C, 2C=N), 131.65, 140.20, 152.18, 123.90, 138.02, 148.94 (15C, 3pyr-C), 163.94, 169.30 (4C, 4 CO-amide), 177.98 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 922 (14) $[M]^+$. Found, %: C 66.32; H 6.36; N 16.61. $C_{51}H_{59}N_{11}O_6$. Calculated, %: C 66.43; H 6.45; N 16.71.

Synthesis of cyclic pyridine derivative VIII. A mixture of compound **IV** (1 mmol) and 2,6-diacetylpyridine (0.163 g, 1 mmol) [15] in absolute ethanol (100 mL) was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure, the solid formed was collected by filtration, washed with ether and recrystallized from ethanol to give the corresponding product **VIII**. Yield 74%, mp 254–256°C. $[\alpha]_D^{25}$ = –118 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3435–3380 (NH), 3092 (CH-Ar), 2985 (CH-aliph.), 1656, 1538, 1253 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.92–0.98 m (18H, $6CH_3$), 1.65–1.75 m (4H, $2CH_2$), 2.25–2.35 m (2H, 2CH), 3.45 d (4H, $2CH_2$), 4.25–4.35 m (2H, 2CH), 4.66–4.77 m (2H, 2CH), 6.91–7.54 m (10H, 2Ph-H), 8.22–8.26 m (3H, pyr-H), 8.45 s, 9.18 s (3H, pyr-H), 8.74 s, 8.87 s, 9.17 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 13.48, 17.37, 18.67 (6C, $6CH_3$), 23.77 (2C, 2CH), 40.27 (2C, $2CH_2$), 42.34 (2C, CH_2), 52.56, 53.19 (4C, 4CH), 124.27, 128.28, 129.42, 138.78 (12C, 2Ph-C), 155.24 (2C, 2C=N), 126.05, 131.68, 135.82, 140.48, 152.42, 154.56 (10C, 2 pyr-C), 163.86, 169.39 (4C, 4CO-amide), 178.59 (2C, 2CO-hydrazone). MS (EI, 70 eV): *m/z* (%) = 843 (42) $[M]^+$. Found, %: C 65.43; H 6.40; N 16.51. $C_{46}H_{54}N_{10}O_6$. Calculated, %: C 65.54; H 6.46; N 16.62.

Synthesis of N^{α}-dinicotinoyl-bis[L-leucyl-L-phenylalaninyl aromatic imide] derivatives IXa, IXb, and X. A mixture of compound **IV** (1 mmol) and dicarboxylic acid anhydride derivatives, namely, phthalic anhydride, tetrachlorophthalic anhydride or 2,3-pyridinedicarboxylic acid anhydride (2 mmol) was refluxed in glacial acetic acid (50 mL) for 6 h. The reaction mixture was poured into ice-water, thus obtained precipitate was filtered off, washed with water, dried, and crystallized from DMF/EtOH to isolate the corresponding bisimide hexacarboxamide derivatives **IXa, IXb**, and **X**, respectively.

Compound IXa. Yield 65%, mp 252–254°C. $[\alpha]_D^{25}$ = –126 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3460–3350 (NH), 3076 (CH-Ar), 2985 (CH-aliph.), 1654, 1532, 1255 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.89–0.96 m (12H, $4CH_3$), 1.67–1.74 m (4H, $2CH_2$), 2.25–2.32 m (2H, 2CH), 3.40 d (4H, $2CH_2$), 4.24–4.32 m (2H, 2CH), 4.54–4.68 m (2H, 2CH), 7.08–7.98 m (18H, 4Ph-H), 8.36, 9.05 m (3H, pyr-H), 8.65 s, 8.78 s, 9.18 s (6H, 6NH), exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 17.35, 18.56 (4C, $4CH_3$), 23.74 (2C, 2CH), 40.05 (2C, $2CH_2$), 42.25 (2C, CH_2), 52.43, 53.03 (4C, 4CH), 124.13, 127.20, 128.21, 129.37, 131.85, 132.15, 138.67 (24C, 4Ph-C), 131.58, 140.10, 152.10 (5C, pyr-C), 164.65 (4C, 4CO-Imide), 163.86, 169.39, 170.02 (6C, 6CO-amide). MS (EI, 70 eV): *m/z* (%) = 976 (6) $[M]^+$. Found, %: C 65.10; H 5.40; N 12.84. $C_{53}H_{53}N_9O_{10}$. Calculated, %: C 65.22; H 5.47; N 12.92.

Compound IXb. Yield 58%, mp 274–276°C. $[\alpha]_D^{25}$ = –132 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3455–3313 (NH), 3088 (CH-Ar), 2989 (CH-aliph.), 1653, 1534, 1253 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.92–0.98 m (12H, $4CH_3$), 1.64–1.77 m (4H, $2CH_2$), 2.21–2.36 m (2H, 2CH), 3.43 d (4H, $2CH_2$), 4.23–4.36 m (2H, 2CH), 4.56–4.65 m (2H, 2CH), 6.98–7.51 m (10H, 2Ph-H), 8.42, 9.10 m (3H, pyr-H), 8.62 s, 8.74 s, 9.22 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 17.38, 18.52 (4C, $4CH_3$), 23.78 (2C, 2CH), 40.14 (2C, $2CH_2$), 42.36 (2C, CH_2), 52.48, 53.12 (4C, 4CH), 124.25, 127.96, 128.32, 129.38, 132.76, 138.10, 138.66 (24C, 4Ph-C), 131.52, 140.18, 152.34 (5C, pyr-C), 164.72 (4C, 4 CO-Imide), 163.92, 169.45, 170.12 (6C, 6CO-amide). MS (EI, 70 eV): *m/z* (%) = 1252 (10) $[M]^+$. Found, %: C 50.76; H 3.54; Cl 22.60; N 10.00. $C_{53}H_{45}Cl_8N_9O_{10}$. Calculated, %: C 50.86; H 3.62; Cl 22.66; N 10.07.

Compound X. Yield 64%, mp 224–226°C. $[\alpha]_D^{25}$ = –104 (*c* = 0.5, DMF). FT-IR, ν, cm^{-1}: 3444–3318 (NH), 3086 (CH-Ar), 2990 (CH-aliph.), 1652, 1538, 1257 (C=O, amide I, II, and III). ^1H NMR spectrum, δ_H, ppm: 0.86–0.97 m (12H, $4CH_3$), 1.65–1.75 m (4H, $2CH_2$), 2.26–2.36 m (2H, 2CH), 3.41 d (4H, $2CH_2$), 4.25–4.35 m (2H, 2CH), 4.52–4.63 m (2H, 2CH), 6.98–7.50 m (10H, 2Ph-H), 8.42, 9.12 m (3H, pyr-H), 7.98 t (2H, pyr-H), 8.54 d, 9.00 d (4H, pyr-H), 8.68 s, 8.74 s, 9.15 s (6H, 6NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 17.26, 18.67 (4C, $4CH_3$), 23.70 (2C, 2CH), 39.88 (2C, $2CH_2$), 42.28 (2C, CH_2), 52.45, 53.08 (4C, 4CH), 124.26, 128.23, 129.35, 138.65 (12C, 2Ph-C), 127.12, 128.00, 131.60, 137.98, 140.16, 145.08, 152.12, 152.52 (15C, pyr-C), 164.60, 164.98 (4C, 4CO-Imide), 163.80, 169.46, 170.15 (6C, 6CO-amide). MS (EI, 70 eV): *m/z* (%) = 978 (24) $[M]^+$. Found, %: C 62.52; H 5.20; N 15.68. $C_{51}H_{51}N_{11}O_{10}$. Calculated, %: C 62.63; H 5.26; N 15.75.

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