ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 8, pp. 1952–1958. © Pleiades Publishing, Ltd., 2015.

Synthesis of Chiral Macrocyclic Candidates: IV.[1] Synthesis and Antimicrobial Activity of Some Tricyclooctacosa(triaconta)hexaene Bis-Schiff Base Derivatives[2]

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Received April 28, 2015

Abstract—A series of macrocyclic tricyclooctacosa- and -triacontahexaene Schiff base derivatives were synthesized by reacting pyridine-3,5-dicabonyl dichloride with dibasic amino acids esters, followed by hydrazinolysis and treatment of the resulting tricyclic bis-hydrazides with aromatic aldehydes. The newly synthesized compounds were characterized by IR, NMR, and MS spectra and screened for antimicrobial activity. Some compounds exhibited antimicrobial activity comparable to that of reference controls.

Keywords: synthesis, tricyclooctacosahexaene candidates, bis-Schiff bases, antimicrobial activity

DOI: 10.1134/S1070363215080253

Development of antibiotic-resistant bacterial and fungal strains over recent decades resulted in substantial need of new classes of antimicrobial agents. Heterocyclic compounds are important as biologically and pharmacologically active candidates, in particulr antimicrobial [1–5], antihypertensive [6], anti-inflammatory [7], anti-HIV [8], anticancer [9], anticonvulsant [10], and antidepressant [11]. In continuation of our previous work on the synthesis of new amino acids and peptides, new macrocyclic peptide candidates have been prepared from pyridinedicarboxylic acids and some amino acids and screened for biological activity [12–18]. In this context, in the present article we report some new macrocyclic tricyclooctacosa(triaconta)hexaene Schiff base derivatives containing amino acid and pyridine moieties.

Treatment of pyridine-3,5-dicarboxylic acid (**I**) or pyridine-3,5-dicarbonyl dichloride (**II**) with dibasic L-amino acid esters in the presence of ethyl chloroformate (mixed anhydride method, *a*) [19] or triethylamine (acid chloride method, *b*) [19] afforded the corresponding tricyclic diesters **IIIa** and **IIIb**. Compounds **IIIa** and **IIIb** reacted with excess hydrazine hydrate in boiling methanol to give hydrazides **IVa** and **IVb**, and condensation of the latter with aromatic aldehydes produced hydrazones (Schiff bases) **Va**–**Vl** (Scheme 1).

Compounds **III**–**V** were tested for antimicrobial activity at a concentration of 50 μg/mL against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*) and fungi (*Candida albicans*), using the bioassay technique for antibiotics [20] specified in the US pharmacopeia. Streptomycin and fusidic acid were used as standards. The results are summarized in table.

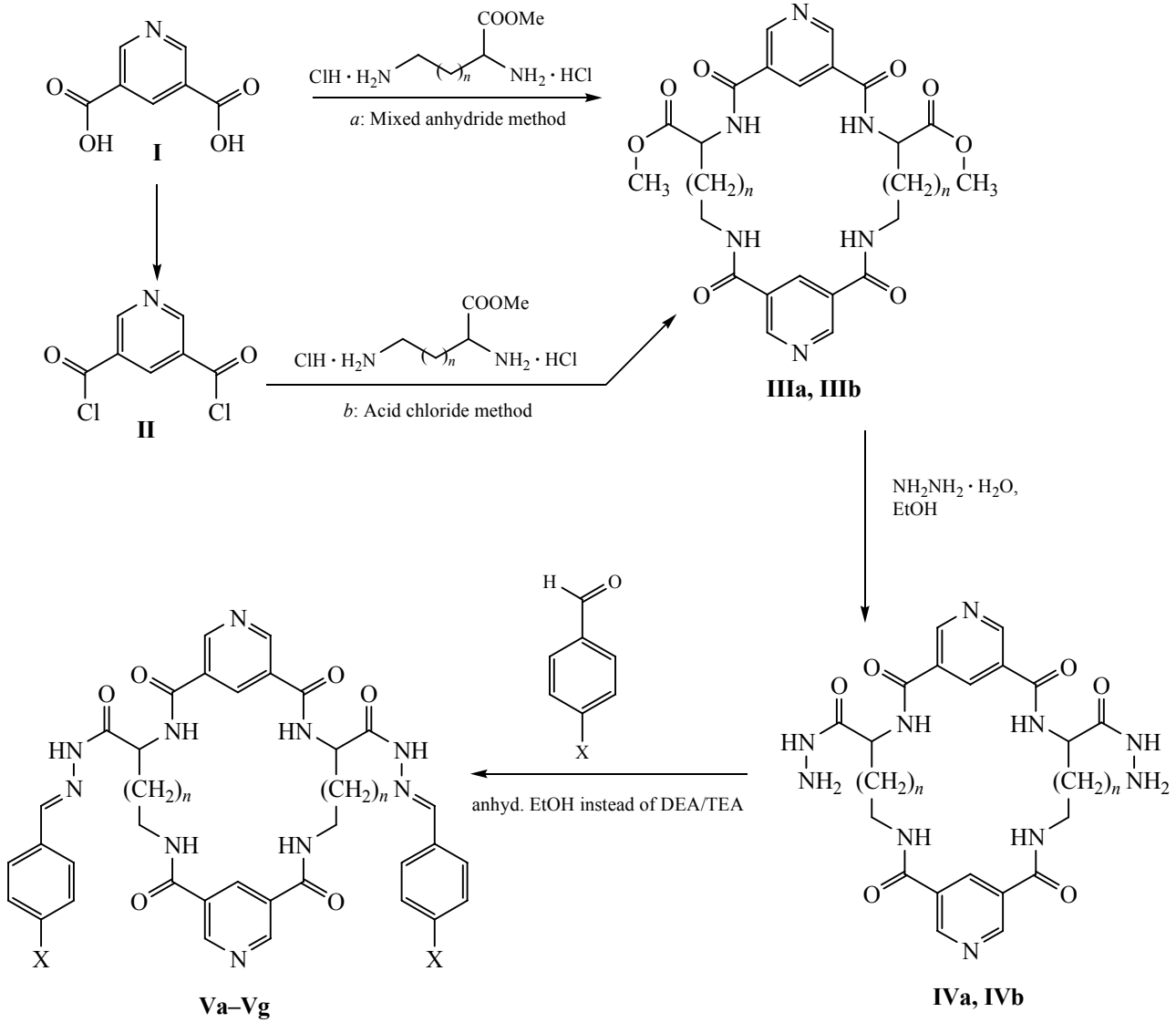
EXPERIMENTAL

The melting points were determined in capillaries using an Electro Thermal IA9100 digital melting point apparatus and are uncorrected. The elemental microanalyses (Microanalytical Unit, NRC) were within the acceptable limits of the calculated values. The IR spectra (KBr) were recorded on a Nicolet Nexus 670 FTIR spectrometer with Fourier transform.

[1] For communication III, see [1].

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

Scheme 1.



III, **IV**, n = 2 (**a**), 3 (**b**); **V**, n = 2 (**a**–**f**), 3 (**g**–**l**); X = H (**a**, **g**), Me (**b**, **h**), MeO (**c**, **i**), Cl (**d**, **j**), Br (**e**, **k**), F (**f**, **l**).

The ^{1}H and ^{13}C NMR spectra were run in DMSO-d_6 on a Jeol instrument (500 MHz). The mass spectra (electron impact, 70 eV)) were obtained on a Finnigan MAT SSQ 7000 spectrometer. Antimicrobial tests were carried out by El-Sayed E. Mostafa (Department of Microbial Chemistry, National Research Center, Cairo, Egypt).

Dimethyl 2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),·23,25-hexaene-4,20-dicarboxylate (IIIa) and dimethyl 2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,13,·15(30),25,27-hexaene-4,22-dicarboxylate (IIIb) *(general procedures). a. Mixed anhydride method.* A cold (–30°C) mixture of 1 mmol of 3,5-pyridinedicarboxylic acid (**I**) in 50 mL of anhydrous methylene chloride, 2 mmol of ethyl chloroformate, and 2 mmol of triethylamine was stirred for 10 min, and a solution of 1 mmol of L-ornithine or L-lysine methyl ester in 25 mL of anhydrous methylene chloride was added dropwise. The mixture was stirred for 3 h at –30°C and for 12 h at room temperature, washed with water, 1 N hydrochloric acid, 1 N aqueous sodium hydrogen carbonate, and water again, and dried over anhydrous calcium chloride. The

Antimicrobial activity of compounds **IIIa**, **IIIb**, **IVa**, **IVb**, and **Va–Vl**

Compound no.	Inhibition zone, mm			
	gram-positive		gram-negative	fungi
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Candida albicans*
IIIa	1.86	1.75	0.86	1.12
IIIb	1.92	1.82	0.95	1.15
IVa	1.78	1.85	0.78	0.94
IVb	1.69	1.76	0.64	0.96
Va	1.56	1.58	0.67	0.94
Vb	1.95	1.94	0.93	1.18
Vc	1.50	1.84	0.62	1.00
Vd	1.92	1.85	0.83	0.98
Ve	1.68	1.78	0.62	–
Vf	1.73	1.68	0.65	1.00
Vg	1.82	1.76	0.78	0.95
Vh	1.74	1.59	0.66	1.05
Vi	1.95	1.85	0.74	0.95
Vj	1.72	1.75	0.76	1.00
Vk	1.78	1.75	0.68	0.86
Vl	1.88	1.88	0.64	0.65
Streptomycin	2.00	2.00	0.95	–
Fusidic acid	–	–	–	1.90

solvent was evaporated under reduced pressure, and the crude product was purified by preparative chromatography (silica gel, $CHCl_3$–MeOH, 9 : 1, v/v).

b. Acid chloride method. A solution of 0.204 g (1 mmol) of pyridine-3,5-dicarbonyl dichloride (**II**) in 10 mL of anhydrous tetrahydrofuran (THF) was added at –15°C to a solution of 1 mmol of L-ornithine or L-lysine methyl ester in 20 mL of anhydrous THF containing triethylamine (pH ≈ 8). The mixture was stirred for 3 h at –15°C and ethyl acetate, and the solution was washed with water, 1 N hydrochloric acid, 1 N aqueous sodium hydrogen carbonate, and water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to dryness, the residue was treated with diethyl ether, and the product was purified by preparative TLC (silica gel, $CHCl_3$–MeOH, 9 : 1, v/v).

Compound **IIIa**. Yield 65 (*a*), 82% (*b*); mp 126–128°C, $[\alpha]_D^{25}$ = –76° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3432–3324 (N–H), 3088 ($C–H_{arom}$), 2993 ($C–H_{aliph}$), 1743 (C=O, ester), 1668 (C=O, amide), 1530 ($\delta_{N–H}$), 1315 (C–N). ^1H NMR spectrum, δ, ppm: 1.45–1.55 m (4H, CH_2), 1.86–1.95 m (4H, CH_2), 2.94–2.98 m (4H, CH_2), 3.62 s (6H, OCH_3), 4.30–4.42 m (2H, CH), 8.58 s and 9.15 s (6H, pyridine), 8.78 s and 9.40 s (4H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.32, 28.48, 41.16 (6C, CH_2); 51.32 (2C, OCH_3), 58.24 (2C, CH); 131.78, 140.28, 151.86 (10C, pyridine); 167.15 and 167.65 (4C, C=O, amide), 171.78 (2C, C=O, ester). Mass spectrum: *m*/*z* 554 (I_{rel} = 45%) $[M]^+$. Found, %: C 56.22; H 5.40; N 15.10. $C_{26}H_{30}N_6O_8$. Calculated, %: C 56.31; H 5.45; N 15.15.

Compound **IIIb**. Yield 82%, mp 148–150°C, $[\alpha]_D^{25}$ = –108° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3415–3313 (N–H), 3092 ($C–H_{arom}$), 2990 ($C–H_{aliph}$), 1746 (C=O, ester), 1665 (C=O, amide), 1535 ($\delta_{N–H}$), 1318 (C–N). ^1H NMR spectrum, δ, ppm: 1.28–1.15 m

(4H, CH_2), 1.46–1.50 m (4H, CH_2), 1.85–1.96 m (4H, CH_2), 2.88–2.93 m (4H, CH_2), 3.56 s (6H, OCH_3), 4.36–4.40 m (2H, CH), 8.55 s and 9.10 s (6H, pyridine), 8.74 s and 9.32 s (4H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.32, 29.08, 30.65, 46.78 (8C, CH_2); 51.42 (2C, OCH_3), 58.98 (2C, CH); 131.86, 140.35, 151.80 (10C, pyridine); 167.42 and 167.58 (4C, C=O, amide), 171.98 (2C, C=O, ester). Mass spectrum: *m*/*z* 582 (I_{rel} = 12%) $[M]^+$. Found, %: C 57.60; H 5.80; N 14.34. $C_{28}H_{34}N_6O_8$. Calculated, %: C 57.72; H 5.88; N 14.42.

2,9,15,22-Tetraoxo-3,8,12,16,21,25-hexaazatricyclo[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (IVa) and 2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (IVb) *(general procedure)*. A mixture of 1 mmol of diester **IIIa** or **IIIb** and 0.4 mL (8 mmol) of hydrazine hydrate in 50 mL of anhydrous methanol was heated for 6 h under reflux. The solvent was removed under reduced pressure, the residue was treated and washed with hexane, and the solid product was recrystallized from ethanol.

Compound **IVa**. Yield 65%, mp 214–216°C, $[\alpha]_D^{25}$ = –86° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3476–3318 (N–H), 3083 (C–H_{arom}), 2991 (C–H_{aliph}), 1665 (C=O), 1533 (δ_{N-H}), 1312 (C–N). ^1H NMR spectrum, δ, ppm: 1.53–1.43 m (4H, CH_2), 1.85–1.94 m (4H, CH_2), 2.92–2.96 m (4H, CH_2), 4.32–4.40 m (2H, CH), 4.56 br.s (4H, NH_2, exchangeable with D_2O), 8.55 s and 9.17 s (6H, pyridine); 8,65 s, 8.75 s, and 9.36 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.36, 28.52, 41.26 (6C, CH_2); 54.28 (2C, CH); 131.72, 140.23, 151.84 (10C, pyridine); 167.24 and 167.42 (4C, C=O, amide), 170.45 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 554 (I_{rel} = 24%) $[M]^+$. Found, %: C 51.90; H 5.40; N 25.20. $C_{24}H_{30}N_{10}O_6$. Calculated, %: C 51.98; H 5.45; N 25.26.

Compound **IVb**. Yield 75%, mp 238–240°C, $[\alpha]_D^{25}$ = –87° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3488–3322 (N–H), 3080 (C–H_{arom}), 2985 (C–H_{aliph}), 1664 (C=O), 1534 (δ_{N-H}), 1314 (C–N). ^1H NMR spectrum, δ, ppm: 1.32–1.22 m (4H, CH_2), 1.44–1.56 m (4H, CH_2), 1.84–1.96 m (4H, CH_2), 2.85–2.96 m (4H, CH_2), 4.35–4.43 m (2H, CH), 4.50 br.s (4H, NH_2, exchangeable with D_2O), 8.54 s and 9.12 s (6H, pyridine); 8,62 s, 8.74 s, and 9.32 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.30, 29.16, 30.68, 46.74 (8C, CH_2); 58.92 (2C, CH); 131.85, 140.38, 151.87 (10C, pyridine); 167.55 and 167.64 (4C, C=O, amide), 170.94 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 582 (I_{rel} = 16%) $[M]^+$. Found, %: C 53.48; H 5.80; N 23.88. $C_{26}H_{34}N_{10}O_6$. Calculated, %: C 53.60; H 5.88; N 24.04.

***N′*^{4},*N′*^{20}-Bis(benzylidene)-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo[21.3.1.1^{10,14}]-octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazides Va–Vf and *N′*^{4},*N′*^{22}-bis-(benzylidene)-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo[23.3.1.1^{11,15}]triaconta-1(29),11,·13,15(30),25,27-hexaene-4,22-dicarbohydrazides Vg–Vl** *(general procedure)*. A mixture of 1 mmol of bis-hydrazide **IVa** or **Vb** and 2 mmol of the corresponding substituted benzaldehyde in 50 mL of anhydrous ethanol was heated for 4–6 h under reflux. The mixture was concentrated under reduced pressure and poured into ice water, and the precipitate was filtered off, washed with water, dried, and recrystallized from appropriate solvent.

***N′*^{4},*N′*^{20}-Dibenzylidene-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo[21.3.1.1^{10,14}] octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (Va).** Yield 55%, mp 256–258°C (from EtOH), $[\alpha]_D^{25}$ = –102° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3413–3357 (N–H), 3090 (C–H_{arom}), 2985 (C–H_{aliph}), 1662 (C=O), 1535 (δ_{N-H}), 1315 (C–N). ^1H NMR spectrum, δ, ppm: 1.32–1.24 m (4H, CH_2), 1.85–1.92 m (4H, CH_2), 2.90–2.94 m (4H, CH_2), 4.34–4.42 m (2H, CH), 7.05–7.65 m (12H, H_{arom}, CH=N), 8.57 s and 9.10 s (6H, pyridine); 8.68 s, 8.76 s, and 9.34 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.36, 28.52, 41.26 (6C, CH_2); 58.53 (2C, CH); 128.53, 129.05, 131.00, 133.65 (12C, C_{arom}); 131.44, 140.35, 152.33 (10C, pyridine); 142.68 (2C, CH=N), 167.35 and 167.75 (4C, C=O, amide), 177.45 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 731 (I_{rel} = 8%) $[M]^+$. Found, %: C 62.34; H 5.20; N 19.10. $C_{38}H_{38}N_{10}O_6$. Calculated, %: C 62.46; H 5.24; N 19.17.

***N′*^{4},*N′*^{20}-Bis(4-methylbenzylidene)-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo-[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (Vb).** Yield 55%, mp 247–249°C (from EtOH), $[\alpha]_D^{25}$ = –111° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3422–3345 (N–H), 3088 (C–H_{arom}), 2984 (C–H_{aliph}), 1663 (C=O), 1536 (δ_{N-H}), 1312 (C–N). ^1H NMR spectrum, δ, ppm: 1.38–1.32 m

(4H, CH_2), 1.80–1.90 m (4H, CH_2), 2.24 s (6H, CH_3), 2.88–2.96 m (4H, CH_2), 4.42–4.46 m (2H, CH), 7.00–7.62 m (10H, H_{arom}, CH=N), 8.52 s and 9.15 s (6H, pyridine); 8.67 s, 8.74 s, and 9.30 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 23.85 (2C, CH_3); 24.33, 28.50, 41.28 (6C, CH_2); 58.50 (2C, CH); 128.78, 129.05, 130.48, 140.52 (12C, C_{arom}); 131.35, 140.42, 152.36 (10C, pyridine); 142.72 (2C, CH=N), 167.24 and 167.65 (4C, C=O, amide), 177.62 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 759 (I_{rel} = 6%) $[M]^+$. Found, %: C 63.20; H 5.50; N 18.40. $C_{40}H_{42}N_{10}O_6$. Calculated, %: C 63.31; H 5.58; N 18.46.

***N′*⁴,*N′*²⁰-Bis(4-methoxybenzylidene)-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo-[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (Vc).** Yield 62%, mp 262–264°C (from AcOH–H_2O), $[\alpha]_D^{25}$ = –118° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3418–3328 (N–H), 3097 (C–H_{arom}), 2989 (C–H_{aliph}), 1663 (C=O), 1533 (δ_{N-H}), 1313 (C–N). ^1H NMR spectrum, δ, ppm: 1.36–1.27 m (4H, CH_2), 1.85–1.93 m (4H, CH_2), 2.90–2.96 m (4H, CH_2), 3.64 s (6H, OCH_3), 4.36–4.47 m (2H, CH), 6.92–7.54 m (10H, H_{arom}, CH=N), 8.51 s and 9.08 s (6H, pyridine); 8.67 s, 8.70 s, and 9.32 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.42, 28.68, 41.16 (6C, CH_2); 55.43 (2C, OCH_3), 58.46 (2C, CH); 114.65, 126.76, 130.12, 162.80 (12C, C_{arom}); 131.52, 140.48, 152.24 (10C, pyridine); 142.73 (2C, CH=N), 167.42 and 167.86 (4C, C=O, amide), 177.65 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 791 (I_{rel} = 12%) $[M]^+$. Found, %: C 60.66; H 5.30; N 17.62. $C_{40}H_{42}N_{10}O_8$. Calculated, %: C 60.75; H 5.35; N 17.71.

***N′*⁴,*N′*²⁰-Bis(4-chlorobenzylidene)-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo-[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (Vd).** Yield 68%, mp 276–278°C (from dioxane), $[\alpha]_D^{25}$ = –105° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3432–3340 (N–H), 3085 (C–H_{arom}), 2976 (C–H_{aliph}), 1665 (C=O), 1534 (δ_{N-H}), 1316 (C–N). ^1H NMR spectrum, δ, ppm: 1.35–1.22 m (4H, CH_2), 1.87–1.95 m (4H, CH_2), 2.91–2.95 m (4H, CH_2), 4.37–4.45 m (2H, CH), 7.02–7.58 m (10H, H_{arom}, CH=N), 8.54 s and 9.12 s (6H, pyridine); 8.68 s, 8.72 s, and 9.35 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.31, 28.56, 41.35 (6C, CH_2); 58.55 (2C, CH); 128.60, 130.70, 131.72, 136.12 (12C, C_{arom}); 131.65, 140.54, 152.32 (10C, pyridine); 142.83 (2C, CH=N), 167.45 and 167.85 (4C, C-O, amide), 177.78 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 800 (I_{rel} = 4%) $[M]^+$. Found, %: C 56.95; H 4.50; Cl 8.78; N 17.45. $C_{38}H_{36}Cl_2N_{10}O_6$. Calculated, %: C 57.07; H 4.54; Cl 8.87; N 17.52.

***N′*⁴,*N′*²⁰-Bis(4-bromobenzylidene)-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo-[21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (Ve).** Yield 60%, mp 254–256°C (from DMF–H_2O), $[\alpha]_D^{25}$ = –98° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3445–3334 (N–H), 3088 (C–H_{arom}), 2978 (C–H_{aliph}), 1662 (C=O), 1531 (δ_{N-H}), 1314 (C–N). ^1H NMR spectrum, δ, ppm: 1.37–1.26 m (4H, CH_2), 1.89–1.94 m (4H, CH_2), 2.88–2.92 m (4H, CH_2), 4.36–4.44 m (2H, CH), 7.15–7.62 m (10H, H_{arom}, CH=N), 8.54 s and 9.10 s (6H, pyridine); 8.65 s, 8.79 s, and 9.30 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.37, 28.57, 41.40 (6C, CH_2); 58.66 (2C, CH); 125.30, 130.98, 131.54, 132.78 (12C, C_{arom}); 131.67, 140.57, 152.38 (10C, pyridine); 142.76 (2C, CH=N), 167.52 and 167.80 (4C, C=O, amide), 177.46 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 889 (I_{rel} = 12%) $[M]^+$. Found, %: C 51.25; H 4.00; N 15.70. $C_{38}H_{36}Br_2N_{10}O_6$. Calculated, %: C 51.36; H 4.08; N 15.76.

***N′*⁴,*N′*²⁰-Bis(4-fluorobenzylidene)-2,9,15,22-tetraoxo-3,8,12,16,21,25-hexaazatricyclo [21.3.1.1^{10,14}]octacosa-1(27),10,12,14(28),23,25-hexaene-4,20-dicarbohydrazide (Vf).** Yield 72%, mp 212–214°C (from AcOH), $[\alpha]_D^{25}$ = –116° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3435–3322 (N–H), 3082 (C–H_{arom}), 2987 (C–H_{aliph}), 1663 (C=O), 1534 (δ_{N-H}), 1316 (C–N). ^1H NMR spectrum, δ, ppm: 1.36–1.28 m (4H, CH_2), 1.88–1.95 m (4H, CH_2), 2.85–2.94 m (4H, CH_2), 4.35–4.46 m (2H, CH), 6.95–7.64 m (10H, H_{arom}, CH=N), 8.52 s and 9.11 s (6H, pyridine); 8.67 s, 8.75 s, and 9.34 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.32, 28.54, 41.35 (6C, CH_2); 58.70 (2C, CH); 115.30, 128.96, 130.30, 164.82 (12C, C_{arom}); 131.62, 140.53, 152.45 (10C, pyridine); 142.66 (2C, CH=N), 167.48 and 167.65 (4C, C=O, amide), 176.98 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 767 (I_{rel} = 34) $[M]^+$. Found, %: C 59.40; H 4.65; N 18.20. $C_{38}H_{36}F_2N_{10}O_6$. Calculated, %: C 59.52; H 4.73; N 18.27.

***N′*⁴,*N′*²²-Dibenzylidene-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo[23.3.1.1^{11,15}]-triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (Vg).** Yield 60%, mp 204–206°C (from EtOH–Et_2O), $[\alpha]_D^{25}$ = –124° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3442–3352 (N–H), 3085 (C–H_{arom}), 2992 (C–H_{aliph}), 1665 (C=O), 1534 (δ_{N-H}), 1313

(C–N). ^{1}H NMR spectrum, δ, ppm: 1.45–1.24 m (8H, CH_2), 1.75–1.90 m (4H, CH_2), 2.92–2.95 m (4H, CH_2), 4.25–4.40 m (2H, CH), 7.02–7.64 m (12H, H_{arom}, CH=N), 8.53 s and 9.13 s (6H, pyridine); 8.65 s, 8.77 s, and 9.32 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.65, 29.34, 31.75, 46.76 (8C, CH_2); 57.40 (2C, CH); 128.66, 129.12, 130.86, 133.68 (12C, C_{arom}); 131.32, 140.34, 152.34 (10C, pyridine); 142.54 (2C, CH=N), 167.32 and 167.72 (4C, C=O, amide), 177.34 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 759 (I_{rel} = 14%) $[M]^+$. Found, %: C 63.20; H 5.50; N 18.40. $C_{40}H_{42}N_{10}O_6$. Calculated, %: C 63.31; H 5.58; N 18.46.

***N′*^{4},*N′*^{22}-Bis(4-methylbenzylidene)-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo-[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (Vh).** Yield 70%, mp 225–227°C (from AcOH–H_2O), $[\alpha]_D^{25}$ = –86°C (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3456–3352 (N–H), 3085 (C–H_{arom}), 2991 (C–H_{aliph}), 1665 (C=O), 1534 (δ_{N-H}), 1315 (C–N). ^{1}H NMR spectrum, δ, ppm: 1.26–1.44 m (8H, CH_2), 1.72–1.91 m (4H, CH_2), 2.28 s (6H, CH_3), 2.94–2.96 m (4H, CH_2), 4.34–4.42 m (2H, CH), 6.95–7.55 m (10H, H_{arom}, CH=N), 8.50 s and 9.16 s (6H, pyridine); 8.69 s, 8.76 s, and 9.34 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 24.05 (2C, CH_3); 20.62, 29.42, 31.70, 46.71 (8C, CH_2); 57.50 (2C, CH); 128.75, 129.00, 130.40, 140.62 (12C, C_{arom}); 131.30, 140.40, 152.30 (10C, pyridine); 142.65 (2C, CH=N), 167.45 and 167.62 (4C, C=O, amide), 176.98 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 787 (I_{rel} = 22%) $[M]^+$. Found, %: C 64.00; H 5.80; N 17.70. $C_{42}H_{46}N_{10}O_6$. Calculated, %: C 64.11; H 5.89; N 17.80.

***N′*^{4},*N′*^{22}-Bis(4-methoxybenzylidene)-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo-[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (Vi).** Yield 60%, mp 215–217°C (from dioxane), $[\alpha]_D^{25}$ = –108° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3415–3322 (N–H), 3095 (C–H_{arom}), 2986 (C–H_{aliph}); 1665 (C=O), 1535 (δ_{N-H}), 1315 (C–N). ^{1}H NMR spectrum, δ, ppm: 1.42–1.27 m (8H, CH_2), 1.82–1.93 m (4H, CH_2), 2.90–2.96 m (4H, CH_2), 3.60 s (6H, OCH_3), 4.32–4.45 m (2H, CH), 6.96–7.56 m (10H, H_{arom}, CH=N), 8.56 s and 9.14 s (6H, pyridine); 8.70 s, 8.76 s, and 9.35 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.68, 29.47, 31.71, 46.76 (8C, CH_2); 55.48 (2C, OCH_3), 57.34 (2C, CH); 114.22, 125.76, 129.84, 162.82 (12C, C_{arom}); 131.46, 140.44, 152.25 (10C, pyridine); 142.66 (2C, CH=N), 167.41 and 167.56 (4C, C=O, amide), 177.60 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 819 (I_{rel} = 18%) $[M]^+$. Found, %: C 61.50; H 5.60; N 17.00. $C_{42}H_{46}N_{10}O_8$. Calculated, %: C 61.60; H 5.66; N 17.10.

***N′*^{4},*N′*^{22}-Bis(4-chlorobenzylidene)-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo-[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (Vj).** Yield 58%, mp 236–238°C from (MeOH–H_2O), $[\alpha]_D^{25}$ = –114° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3435–3342 (N–H), 3088 (C–H_{arom}), 2992 (C–H_{aliph}), 1664 (C=O), 1534 (δ_{N-H}), 1316 (C–N). ^{1}H NMR spectrum, δ, ppm: 1.24–1.45 m (8H, CH_2), 1.80–1.92 m (4H, CH_2), 2.88–2.94 m (4H, CH_2), 4.30–4.40 m (2H, CH), 7.10–7.62 m (10H, H_{arom}, CH=N), 8.55 s and 9.08 s (6H, pyridine); 8.68 s, 8.73 s, and 9.32 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.42, 29.65, 31.76, 46.78 (8C, CH_2); 57.56 (2C, CH); 128.42, 130.55, 131.65, 136.16 (12C, C_{arom}); 131.64, 140.56, 152.38 (10C, pyridine); 142.80 (2C, CH=N), 167.42 and 167.54 (4C, C=O, amide), 177.55 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 828 (I_{rel} = 16%) $[M]^+$. Found, %: C 57.88; H 4.80; Cl 8.50; N 16.84. $C_{40}H_{40}Cl_2N_{10}O_6$. Calculated, %: C 58.04; H 4.87; Cl 8.57; N 16.92.

***N′*^{4},*N′*^{22}-Bis(4-bromobenzylidene)-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo-[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (Vk).** Yield 64%, mp 242–244°C (from DMF–EtOH), $[\alpha]_D^{25}$ = –96° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3448–3345 (N–H), 3085 (C–H_{arom}), 2975 (C–H_{aliph}), 1664 (C=O), 1533 (δ_{N-H}), 1313 (C–N). ^{1}H NMR spectrum, δ, ppm: 1.32–1.48 m (8H, CH_2), 1.82–1.91 m (4H, CH_2), 2.89–2.93 m (4H, CH_2), 4.34–4.43 m (2H, CH), 7.18–7.68 m (10H, H_{arom}, CH=N), 8.62 s and 9.10 s (6H, pyridine); 8.72 s, 8.82 s, and 9.31 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.35, 29.60, 31.70, 46.68 (8C, CH_2); 57.32 (2C, CH); 124.98, 130.92, 131.24, 132.74 (12C, C_{arom}); 131.65, 140.56, 152.35 (10C, pyridine); 142.72 (2C, CH=N), 167.67 and 167.72 (4C, C=O, amide), 177.33 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 917 (I_{rel} = 15%) $[M]^+$. Found, %: C 52.30; H 4.32; N 15.20. $C_{40}H_{40}Br_2N_{10}O_6$. Calculated, %: C 52.41; H 4.40; N 15.28.

***N′*^{4},*N′*^{22}-Bis(4-fluorobenzylidene)-2,10,16,24-tetraoxo-3,9,13,17,24,27-hexaazatricyclo-[23.3.1.1^{11,15}]triaconta-1(29),11,13,15(30),25,27-hexaene-4,22-dicarbohydrazide (Vl).** Yield 75%, mp

234–236°C (from AcOH), $[\alpha]_D^{25}$ = –105° (*c* = 0.5, DMF). IR spectrum, ν, cm^{-1}: 3430–3320 (N–H), 3085 (C–H_{arom}), 2984 (C–H_{aliph}), 1664 (C=O), 1535 (δ_{N-H}), 1315 (C–N). ^1H NMR spectrum, δ, ppm: 1.45–1.28 m (8H, CH_2), 1.80–1.90 m (4H, CH_2), 2.90–2.95 m (4H, CH_2), 4.38–4.43 m (2H, CH), 6.98–7.65 m (10H, H_{arom}, CH=N), 8.62 s and 9.12 s (6H, pyridine), 8.69 s, 8.74 s, and 9.32 s (6H, NH, exchangeable with D_2O). ^{13}C NMR spectrum, δ_C, ppm: 20.45, 29.55, 31.81, 46.65 (8C, CH_2); 57.62 (2C, CH); 115.08, 128.95, 130.65, 164.90 (12C, C_{arom}); 131.69, 140.56, 152.48 (10C, pyridine); 142.62 (2C, CH=N), 167.58 and 167.66 (4C, C=O, amide), 177.35 (2C, C=O, hydrazide). Mass spectrum: *m*/*z* 795 (I_{rel} = 8%) $[M]^+$. Found, %: C 60.36; H 5.00; N 17.55. $C_{40}H_{40}F_2N_{10}O_6$. Calculated, %: C 60.45; H 5.07; N 17.62.

ACKNOWLEDGMENTS

The authors thank the Deanship of Scientific Research at the King Saud University for funding this research through the Research Group project no. RGP-172.

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