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Analgesic and Anti-Inflammatory Activities of Some Newly Synthesized 3,5-Bis-[(peptidohydrazinyl) Pyridine Schiff Bases

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ABSTRACT

A series of bis-schiff base candidates 5a-l, 6a-c and 7a-c were synthesized by using N^2, $N^{2'}$-(pyridine-3,5-dicarbonyl)-di-L-lucylhydrazide (4) as starting material which was synthesized from 3,5-pyridinedicarboxylic acid (1) and screening for their analgesic and anti-inflammatory. Bis-ester 3 was prepared from 3,5-pyridinedi-carboxylic acid 1 and L-lucine methyl ester, which was hydrazonolysis with hydrazine hydrate afforded compounds 4. Treatment of acid hydrazide 4 with aromatic aldehydes afforded the corresponding bis-dipeptide Schiff bases 5a-l, respectively. Compounds 6a-c and 7a-c were synthesized by reacting of hydrazide 4 with cycloalkanone and acetyl pyridine derivatives. Some of the newly synthesized compounds exhibited better analgesic and anti-inflammatory activities than the reference controls. The structures of newly synthesized compounds were confirmed by IR, NMR, MS spectral data and elemental analysis. The detailed synthesis, spectroscopic data, pharmacological activities of the synthesized compounds was reported.

Key words: 3,5-Pyridinedicarboxylic acid, peptide coupling methods, bis-schiff bases, pharmacological activities

INTRODUCTION

In a previous study some newly substituted heterocyclic compounds exhibited antiparkinsonian (Amr *et al*., 2003b), antitumor (Abou-Ghalia and Amr, 2004), antimicrobial (Amr *et al*., 1999, 2003a) and anti-inflammatory (Amr *et al*., 2005; Abou-Ghalia *et al*., 2003) activities. On the other hand, Schiff base and other heterocyclic derivatives were reported to possess diverse biological activities, such as antibacterial (Bayrak *et al*., 2009; Ashok *et al*., 2007; Karthikeyan *et al*., 2006; Tozkoparan *et al*., 2007) and anti-inflammatory (Labanauskas *et al*., 2004; Navidapour *et al*., 2006; Maxwell *et al*., 1984) properties. In addition, the heterocyclic nitrogen derivatives exhibited a general ionophoric potency for divalent cations (Hassan *et al*., 2003a) and used a novel thiocyanate-selective membrane sensor (Hassan *et al*., 2003b). Also, pharmacological and biological screening for some of synthesized heterocyclic compounds was reported (Amr and Abdulla, 2006; Amr *et al*., 2006, 2009a, b, 2007; Fakhr *et al*., 2008). Recently some newly substituted heterocyclic compounds and their Schiff base derivatives have been synthesized (Khalifa *et al*., 2014a, b) and tested as antimicrobial (Al-Salahi *et al*., 2010; Al-Omar and Amr, 2010; Ghozlan *et al*., 2011; Abd El-Salam *et al*., 2012a, b), Anti-HSV-1 (Mohamed *et al*., 2010) antimicrobial, anti-inflammatory and anticancer activities (Khayyat and Amr, 2014) activities. In view of these observations and as a further continuation of previous work in heterocyclic chemistry, some new linear Schiff base peptides containing amino acid and

pyridine moieties were synthesized and screened for their analgesic and anti-inflammatory activities compared to the reference drugs.

MATERIALS AND METHODS

Chemistry: Melting points were determined in open glass capillary tubes with an Electro Thermal Digital melting point apparatus IA9100 (Shimadzu, Tokyo, Japan) and are uncorrected. Elemental microanalysis for carbon, hydrogen and nitrogen (Microanalytical Unit, NRC) was found within the acceptable limits of the calculated values (±0.1%). Infrared spectra (KBr) were recorded on a Nexus 670 FTIR Fourier Transform infrared spectrometer (Nicolet, Norwalk, CT, USA). Proton and carbon nuclear magnetic resonance (^{1}H-NMR-500 MHz and ^{13}C-NMR-125 MHz) spectra were run in DMSO-d_6 on a JEOL 500 MHz instrument (Tokyo, Japan). Mass spectra were run on a MAT Finnigan SSQ 7000 spectrometer (Madison, WI, USA), using the electron impact technique (EI). Analytical Thin Layer Chromatography (TLC) was performed on silica gel aluminum sheets, $60F_{254}$ (E. Merck, Darmstadt, Germany). Specific optical rotations were measured with an Optronic, P8000 polarimeter (A. Krauss, Hamburg, Germany) in a 1 dm length observation tube, at the indicated conditions and according to the equation:

$$[a]\frac{T}{D} = 100\ \alpha/(c\times l)$$

where, α = Observed rotation angle, D = Sodium line (λ = 589 nm), c = Concentration (g/100 mL), l = Path length in dm and T = Experimental temperature (°C).

Synthesis of 3,5-bis{N-[1-{2-[1-(substituted phenyl)ethylidene]hydrazinyl}-4-methyl-1-oxopentane]-3-carbox-amido} pyridines 5a-l: A mixture of 3,5-bis peptidohydrazide 4 (1 mmol) and substituted aromatic aldehydes, namely, 2-methoxy-, 2-chloro-, 2-nitro-, 4-flouro-, 4-bromo-, 4-hydroxy-, 4-isopropyl-, 4-dimethylamino-, 3, 4, 5-trimethoxy-, 2, 6-dichloro-, 3, 4-dichloro- or 2-chloro-6-flouro-benzaldehydes (2 mmol) in acetic acid (30 mL) was refluxed for 3-5 h. The reaction mixture was concentrated under reduced pressure, the obtained solid product was filtered off, dried and recrystallized from the proper solvents to give the corresponding Schiff base derivatives 5a-l, respectively.

3,5-Bis{N-[1-{2-[1-(2-methoxyphenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5a: Yield: 68%, m.p. 145-147°C (DMF/EtOH), $[a]^{25}_D$ = -101.5 (c = 0.5, DMF). IR (KBr): ν = 3528-3410 (NH), 3065 (CH-Ar), 2972 (CH-aliph.), 1662, 1523, 1315 C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.92-0.98 (m, 12H, 4 CH_3), 1.72-1.80 (m, 6H, 2 CH_2+2CH), 3.62 (s. 6H, 2 OCH_3), 4.60 (t, 2H, 2CH), 7.00-7.62 (m, 10H, Ar-H+2CH = N), 7.80, 8.36 (2s, 4H, 4NH, exchangeable with D_2O), 8.56, 9.12 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.54 (4C, 4CH_3), 23.16 (2C, 2CH), 41.38 (2C, 2CH_2), 52.85 (2C, 2CH), 55.78 (2C, 2OCH_3), 131.56, 140.08, 152.18 (5C, Pyr-C), 167.18 (2C, 2C = O), 172.90 (2C, 2C = O), 143.16 (2C, C = N), 114.00, 116.08, 120.65, 129.56, 131.94, 159.48 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 658 [M^+, 18], $C_{35}H_{43}N_7O_6$ (657.76): calcd. C, 63.91; H, 6.59; N, 14.91; found C, 63.82; H, 6.50; N, 14.83.

3,5-Bis{N-[1-{2-[1-(2-chlorophenyl)ethylidene]hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5b: Yield: 83%, m.p. 242-245°C (AcOH/H_2O), $[a]^{25}_D$ = -96.2 (c = 0.5, DMF). IR (KBr): ν = 3512-3405 (NH), 3078 (CH-Ar), 2989 (CH-aliph.), 1664, 1525, 1318 C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.02 (m, 12H, 4 CH_3), 1.70-1.84 (m, 6H, 2 CH_2+2CH), 4.62 (t, 2H, 2CH), 6.95-7.56 (m, 10H, Ar-H+2CH = N), 7.85, 8.35 (2s, 4H, 4NH, exchangeable with D_2O), 8.50, 9.15 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 23.04 (4C, 4CH_3), 23.38 (2C, 2CH), 41.44 (2C, 2CH_2), 52.84 (2C, 2CH), 131.52, 140.02, 152.15 (5C, Pyr-C), 166.98 (2C, 2C = O), 173.12 (2C, 2C = O), 143.46 (2C, C = N), 126.65, 129.10, 130.02, 132.06, 133.12, 134.00 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 666 [M^+, 12]. $C_{33}H_{37}Cl_2N_7O_4$ (666.60): calcd. C, 59.46; H, 5.59; Cl, 10.64; N, 14.71; found C, 59.37; H, 5.50; Cl, 10.56; N, 14.60.

3,5-Bis{N-[1-{2-[1-(2-nitrophenyl)ethylidene]hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5c: Yield: 72%, m.p. 232-234°C (AcOH/H_2O), $[a]^{25}_D$ = -98.15 (c = 0.5, DMF). IR (KBr): ν = 3535-3412 (NH), 3072 (CH-Ar), 2980 (CH-aliph.), 1662, 1523, 1315 C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.95-1.00 (m, 12H, 4 CH_3), 1.74-1.82 (m, 6H, 2 CH_2+2CH), 4.65 (t, 2H, 2CH), 7.15 (s, 2H, 2CH = N), 7.45-7.90 (m, 8H, Ar-H), 7.95, 8.36 (2s, 4H, 4NH, exchangeable with D_2O), 8.54, 9.18 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.78 (4C, 4CH_3), 23.45 (2C, 2CH), 42.08 (2C, 2CH_2), 53.24 (2C, 2CH), 131.55, 140.08, 152.12 (5C, Pyr-C), 166.96 (2C, 2C = O), 172.92 (2C, 2C = O), 144.15 (2C, C = N), 121.62, 126.10, 130.10, 132.18, 135.10, 148.85 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 688 [M^+, 24]. $C_{33}H_{37}N_9O_8$ (687.70): calcd. C, 57.63; H, 5.42; N, 18.33; found C, 57.54; H, 5.31; N, 18.22.

3,5-Bis{N-[1-{2-[1-(4-flourophenyl)ethylidene]hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5d: Yield: 86%, m.p. 224-226°C (dioxane), $[a]^{25}_D$ = -118.5 (c = 0.5, DMF). IR (KBr): ν = 3520-3414 (NH), 3074 (CH-Ar), 2968 (CH-aliph.), 1663, 1522, 1314 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.95-1.02 (m, 12H, 4 CH_3), 1.74-1.86 (m, 6H, 2CH_2+2CH), 4.65 (t, 2H, 2CH), 6.88-7.54 (m, 10H, Ar-H+2CH = N), 7.82, 8.32 (2s, 4H, 4NH, exchangeable with D_2O), 8.60, 9.14 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.58 (4C, 4CH_3), 23.22 (2C, 2CH), 41.46 (2C, 2CH_2), 52.88 (2C, 2CH), 131.48, 140.16, 152.32

(5C, Pyr-C), 167.44 (2C, 2C = O), 172.95 (2C, 2C = O), 143.78 (2C, C = N), 115.13, 129.66, 130.12, 164.88 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 634 [M^+, 25]. $C_{33}H_{37}F_2N_7O_4$ (633.69): calcd. C, 62.55; H, 5.89; N, 15.47; found C, 62.43; H, 5.80; N, 15.40.

3, 5-Bis{N-[1-{2-[1-(4-bromophenyl)ethylidene]hydrazinyl} -4-methyl-1-oxopentane]-3-carboxamido} pyridine 5e: Yield: 78%, m.p. 196-198°C (EtOH), $[a]^{25}_D$ = -132.12 (c = 0.5, DMF). IR (KBr): n = 3536-3432 (NH), 3078 (CH-Ar), 2970 (CH-aliph.), 1664, 1523, 1315 C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.00 (m, 12H, 4 CH_3), 1.73-1.85 (m, 6H, 2 CH_2+2CH), 4.68 (t, 2H, 2CH), 7.15-7.58 (m, 10H, Ar-H+2CH = N), 7.86, 8.42 (2s, 4H, 4NH, exchangeable with D_2O), 8.65, 9.18 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.62 (4C, 4CH_3), 23.44 (2C, 2CH), 41.55 (2C, 2CH_2), 52.86 (2C, 2CH), 131.56, 140.24, 152.36 (5C, Pyr-C), 167.42 (2C, 2C = O), 172.93 (2C, 2C = O), 143.74 (2C, C = N), 125.18, 130.84, 131.76, 132.92 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 755 [M^+, 34]. $C_{33}H_{37}Br_2N_7O_4$ (755.50): calcd. C, 52.46; H, 4.94; N, 12.98; found C, 52.35; H, 4.84; N, 12.90.

3,5-Bis{N-[1-{2-[1-(4-hydroxyphenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5f: Yield: 65%, m.p. 232-234°C (DMF/EtOH), $[a]^{25}_D$ = -124.6 (c = 0.5, DMF). IR (KBr): ν = 3576-3456 (OH, NH), 3076 (CH-Ar), 2965 (CH-aliph.), 1663, 1522, 1316 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.95-1.01 (m, 12H, 4 CH_3), 1.74-1.88 (m, 6H, 2 CH_2+2CH), 4.70 (t, 2H, 2CH), 4.98 (bs, 2H, 2OH), 6.98-7.52 (m, 10H, Ar-H+2CH = N), 7.92, 8.62 (2s, 4H, 4NH, exchangeable with D_2O), 8.70, 9.12 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.56 (4C, 4CH_3), 23.32 (2C, 2CH), 41.38 (2C, 2CH_2), 53.02 (2C, 2CH), 131.50, 141.00, 152.24 (5C, Pyr-C), 167.40 (2C, 2C = O), 172.90 (2C, 2C = O), 143.82 (2C, C = N), 116.05, 126.32, 130.14, 160.45 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 630 [M^+, 16]. $C_{33}H_{39}N_7O_6$ (629.71): calcd. C, 62.94; H, 6.24; N, 15.57; found C, 62.82; H, 6.15; N, 15.50.

3,5-Bis{N-[1-{2-[1-(4-isopropylphenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carbox-amido} pyridine 5g: Yield: 66%, m.p. 252-254°C (dioxane), $[a]^{25}_D$ = -136.5 (c = 0.5, DMF). IR (KBr): ν = 3518-3432 (NH), 3088 (CH-Ar), 2972 (CH-aliph.), 1664, 1522, 1313 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.94-1.00 (m, 12H, 4 CH_3), 1.24 (d, 12H, 4CH_3), 1.72-1.86 (m, 6H, 2 CH_2+2CH), 3.12 (m, 2H, 2CH), 4.68 (t, 2H, 2CH), 7.05-7.52 (m, 10H, Ar-H+2CH = N), 7.80, 8.30 (2s, 4H, 4NH, exchangeable with D_2O), 8.62, 9.10 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.62 (4C, 4CH_3), 23.18 (2C, 2CH), 23.46 (4C, 4CH_3), 36.15 (2C, CH), 41.42 (2C, 2CH_2), 52.85 (2C, 2CH), 131.46, 140.12, 152.34 (5C, Pyr-C), 167.45 (2C, 2C = O), 172.94 (2C, 2C = O), 143.75 (2C, C = N), 125.98, 128.78, 130.95, 150.76 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 682 [M^+, 8]. $C_{39}H_{51}N_7O_4$ (681.87): calcd. C, 68.70; H, 7.54; N, 14.38; found C, 68.59; H, 7.42; N, 14.30.

3,5-Bis{N-[1-{2-[1-(4-(dimethylaminophenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carbox-amido} pyridine 5h: Yield: 62%, m.p. 204-206°C (EtOH), $[a]^{25}_D$ = -115.6 (c = 0.5, DMF). IR (KBr): ν = 3535-3425 (NH), 3077 (CH-Ar), 2971 (CH-aliph.), 1662, 1518, 1316 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.00 (m, 12H, 4 CH_3), 1.76-1.84 (m, 6H, 2 CH_2+2CH), 2.78 (s, 12H, 4CH_3), 4.65 (t, 2H, 2CH), 7.04-7.52 (m, 10H, Ar-H+2CH = N), 7.84, 8.43 (2s, 4H, 4NH, exchangeable with D_2O), 8.62, 9.17 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.54 (4C, 4CH_3), 23.46 (2C, 2CH), 40.15 (4C, 4CH_3), 41.56 (2C, 2CH_2), 52.85 (2C, 2CH), 131.54, 140.24, 152.48 (5C, Pyr-C), 167.40 (2C, 2C = O), 172.95 (2C, 2C = O), 143.76 (2C, C = N), 114.05, 123.08, 129.85, 151.60 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 684 [M^+, 26]. $C_{37}H_{49}N_9O_4$ (683.84): calcd. C, 64.99; H, 7.22; N, 18.43; found C, 64.90; H, 7.09; N, 18.32.

3,5-Bis{N-[1-{2-[1-(3,4,5-trimethoxyphenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5i: Yield: 82%, m.p. 242-244°C (AcOH/H_2O), $[a]^{25}_D$ = -108.5 (c = 0.5, DMF). IR (KBr): ν = 3521-3418 (NH), 3075 (CH-Ar), 2964 (CH-aliph.), 1662, 1522, 1316 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.95-1.02 (m, 12H, 4 CH_3), 1.74-1.85 (m, 6H, 2 CH_2+2CH), 3.68 (s, 18H, 6OCH_3), 4.68 (t, 2H, 2CH), 6.78 (s, 2H, 2CH = N), 7.15 (s, 4H, Ar-H), 7.82, 8.36 (2s, 4H, 4NH, exchangeable with D_2O), 8.60, 9.14 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.60 (4C, 4CH_3), 23.28 (2C, 2CH), 41.45 (2C, 2CH_2), 52.88 (2C, 2CH), 56.18 (6C, 6OCH_3), 131.46, 140.15, 152.32 (5C, Pyr-C), 167.46 (2C, 2C = O), 172.92 (2C, 2C = O), 143.75 (2C, C = N), 105.13, 128.66, 141.12, 150.56 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 778 [M^+, 12]. $C_{39}H_{51}N_7O_{10}$ (777.86): calcd. C, 60.22; H, 6.61; N, 12.60; found. C, 60.10; H, 6.50; N, 12.51.

3,5-Bis{N-[1-{2-[1-(2,6-dichlorophenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carbox-amido} pyridine 5j: Yield: 72 %, m.p. 252-255°C (AcOH/H_2O), $[a]^{25}_D$ = -98.6 (c = 0.5, DMF). IR (KBr): ν = 3522-3405 (NH), 3078 (CH-Ar), 2982 (CH-aliph.), 1664, 1525, 1318 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.00 (m, 12H, 4 CH_3), 1.72-1.84 (m, 6H, 2 CH_2+2CH), 4.64 (t, 2H, 2CH), 6.95-7.56 (m, 8H, 6 Ar-H+2CH = N), 7.85, 8.35 (2s, 4H, 4NH, exchangeable with D_2O), 8.50, 9.15 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.96 (4C, 4CH_3), 23.40 (2C, 2CH), 41.42 (2C, 2CH_2), 52.86 (2C, 2CH), 131.55, 140.12, 152.18 (5C, Pyr-C), 166.95 (2C, 2C = O), 173.18 (2C, 2C = O), 143.45 (2C, C = N), 127.65, 131.12, 133.10, 135.18 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 735 [M^+, 16]. $C_{33}H_{35}Cl_4N_7O_4$ (735.49): calcd. C, 53.89; H, 4.80; Cl, 19.28; N, 13.33; found C, 53.78; H, 4.68; Cl, 19.19; N, 13.20.

3,5-Bis{N-[1-{2-[1-(3,4-dichlorophenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carbox-amido} pyridine 5k: Yield: 68%, m.p. 196-198°C (AcOH),

$[a]^{25}_D$ = -105.4 (c = 0.5, DMF). IR (KBr): ν = 3525-3418 (NH), 3075 (CH-Ar), 2980 (CH-aliph.), 1662, 1523, 1317 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.98-1.10 (m, 12H, 4 CH_3), 1.69-1.86 (m, 6H, 2 CH_2+2CH), 4.65 (t, 2H, 2CH), 6.95-7.48 (m, 6H, 4 Ar-H+2CH = N), 7.60 (s, 2H, Ar-H), 7.83, 8.42 (2s, 4H, 4NH, exchangeable with D_2O), 8.56, 9.24 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.95 (4C, 4CH_3), 23.55 (2C, 2CH), 41.48 (2C, 2CH_2), 52.85 (2C, 2CH), 131.38, 140.21, 152.27 (5C, Pyr-C), 166.94 (2C, 2C = O), 173.32 (2C, 2C = O), 143.56 (2C, C = N), 128.45, 129.84, 130.32, 132.75, 133.10, 135.65 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 735 [M^+, 32]. $C_{33}H_{35}Cl_4N_7O_4$ (735.49): calcd. C, 53.89; H, 4.80; Cl, 19.28; N, 13.33; found C, 53.79; H, 4.69; Cl, 19.21; N, 13.18.

3,5-Bis{N-[1-{2-[1-(2-chloro-6-flourophenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridine 5l: Yield: 58%, m.p. 218-220°C (DMF/EtOH), $[a]^{25}_D$ = -108.6 (c = 0.5, DMF). IR (KBr): ν = 3542-3435 (NH), 3065 (CH-Ar), 2980 (CH-aliph.), 1661, 1523, 1316 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.00 (m, 12H, 4 CH_3), 1.74-1.84 (m, 6H, 2 CH_2+2CH), 4.65 (t, 2H, 2CH), 6.98-7.42 (m, 8H, 6 Ar-H+2CH = N), 7.83, 8.33 (2s, 4H, 4NH, exchangeable with D_2O), 8.53, 9.13 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.96 (4C, 4CH_3), 23.40 (2C, 2CH), 41.42 (2C, 2CH_2), 52.86 (2C, 2CH), 131.55, 140.12, 152.13 (5C, Pyr-C), 166.97 (2C, 2C = O), 173.17 (2C, 2C = O), 143.47 (2C, C = N), 113.08, 117.86, 124.65, 133.98, 135.16, 160.75 (12C, Ar-C). MS (EI, 70 eV): m/z (%) = 702 [M^+, 8]. $C_{33}H_{35}Cl_2F_2N_7O_4$ (702.58): calcd. C, 56.41; H, 5.02; Cl, 10.09; N, 13.96; found C, 56.30; H, 4.89; Cl, 10.00; N, 13.88.

Synthesis of 3, 5-bis {N-[1-(cycloalkanonylidenehydrazinyl) -4-methyl-1-oxopentane-2-yl]-3-carbo-xamide}pyridine 6a-c: A mixture of 3, 5-bis(peptidohydrazide)pyridine 4 (1 mmol) and cycloalkanone, namely, cyclopentanone, cyclohexanone or cycloheptanone (2 mmol) in acetic acid (30 mL) was refluxed for 6 h. The reaction mixture was poured onto ice water, the obtained precipitate was filtered off, washed with water, dried and crystallized from the proper solvents to give the corresponding compounds 6a-c, respectively.

3, 5-Bis {N-[1-(2-cyclopentylidenehydrazinyl)-4-methyl-1-oxopentane-2-yl]-3-carboxamide}pyridine 6a: Yield: 74 %, m.p. 212-214°C (DMF/EtOH), $[a]^{25}_D$ = -104.6 (c = 0.5, DMF). IR (KBr): ν = 3546-3424 (NH), 3080 (CH-Ar), 2978 (CH-aliph.), 1661, 1521, 1314 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.00 (m, 12H, 4 CH_3), 1.24-1.32 (m, 16H, 2 cyclopentyl), 1.73-1.85 (m, 6H, 2 CH_2+2CH), 4.72 (t, 2H, 2CH), 7.90, 8.64 (2s, 4H, 4NH, exchangeable with D_2O), 8.71, 9.14 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.55 (4C, 4CH_3), 23.36 (2C, 2CH), 41.35 (2C, 2CH_2), 53.02 (2C, 2CH), 131.51, 141.03, 152.30 (5C, Pyr-C), 167.43 (2C, 2C = O), 172.93 (2C, 2C = O), 26.08, 37.86, 186.56 (10C, cyclopentyl). MS (EI, 70 eV): m/z (%) = 554 [M^+, 24]. $C_{29}H_{43}N_7O_4$ (553.70): calcd. C, 62.91; H, 7.83; N, 17.71; found C, 62.80; H, 7.72; N, 17.60.

3,5-Bis {N-[1-(2-cyclohexylidenehydrazinyl)-4-methyl-1-oxopentane-2-yl]-3-carboxamide}pyridine 6b: Yield: 52%, m.p. 188-190°C (AcOH/H_2O), $[a]^{25}_D$ = -99.5 (c = 0.5, DMF). IR (KBr): ν = 3565-3432 (NH), 3085 (CH-Ar), 2972 (CH-aliph.), 1663, 1521, 1315 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.94-0.99 (m, 12H, 4 CH_3), 1.26-1.35 (m, 20H, 2 cyclohexyl), 1.75-1.84 (m, 6H, 2 CH_2+2CH), 4.76 (t, 2H, 2CH), 7.91, 8.68 (2s, 4H, 4NH, exchangeable with D_2O), 8.77, 9.16 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.48 (4C, 4CH_3), 23.35 (2C, 2CH), 41.42 (2C, 2CH_2), 53.08 (2C, 2CH), 131.53, 141.06, 152.32 (5C, Pyr-C), 167.45 (2C, 2C = O), 172.95 (2C, 2C = O), 24.18, 26.85, 28.12, 161.30 (12C, cyclohexyl). MS (EI, 70 eV): m/z (%) = 582 [M^+, 14]. $C_{31}H_{47}N_7O_4$ (581.75): calcd. C, 64.00; H, 8.14; N, 16.85; found C, 63.88; H, 8.04; N, 16.75.

3,5-Bis{N-[1-(2-heptylidenehydrazinyl)-4-methyl-1-oxopentane-2-yl]-3-carboxamide}pyridine 6c: Yield: 68%, m.p. 204-208°C (EtOH), $[a]^{25}_D$ = -116.2 (c = 0.5, DMF). IR (KBr): ν = 3554-3428 (NH), 3090 (CH-Ar), 2978 (CH-aliph.), 1661, 1523, 1316 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.98-1.12 (m, 12H, 4 CH_3), 1.22-1.32 (m, 24H, 2 cycloheptyl), 1.72-1.85 (m, 6H, 2 CH_2+2CH), 4.75 (t, 2H, 2CH), 7.88, 8.62 (2s, 4H, 4NH, exchangeable with D_2O), 8.79, 9.18 (2s, 3H, Pyr-H). ^{13}C-NMR: δ = 22.52 (4C, 4CH_3), 23.41 (2C, 2CH), 41.45 (2C, 2CH_2), 53.10 (2C, 2CH), 132.02, 141.15, 152.36 (5C, Pyr-C), 167.48 (2C, 2C = O), 172.98 (2C, 2C = O), 24.06, 29.12, 32.70, 183.84 (14C, cycloheptyl). MS (EI, 70 eV): m/z (%) = 610 [M^+, 35]. $C_{33}H_{51}N_7O_4$ (609.80): calcd. C, 65.00; H, 8.43; N, 16.08; found C, 64.88; H, 8.35; N, 16.00.

Synthesis of 3,5-Bis{N-(4-methyl-1-oxo-1-{2-[1-(pyridinyl)ethylidene]hydrazinyl}pentane-2-yl)-3-carboxamide} pyridine 7a-c: A mixture of 4 (1 mmol) and acetylpyridine, namely, 2-acetylpyridine, 3-acetylpyridine or 4-acetylpyridine (2 mmol) in ethanol (30 mL), in the presence of sodium hydroxide (2 mL, 5%) was refluxed for 3-6 h. The reaction mixture was poured onto water, neutralized with diluted hydrochloric acid to ~ pH 7, the obtained precipitate was filtered off, washed with water, dried and crystallized from the proper solvents to give compounds 7a-c, respectively.

3,5-Bis{N-(4-methyl-1-oxo-1-{2-[1-(pyridin-2-yl)ethylidene]hydrazinyl}pentane-2-yl)-3-carboxamide} pyridine 7a: Yield: 58%, m.p. 236-238°C (DMF/H_2O), $[a]^{25}_D$ = -108.5 (c = 0.5, DMF). IR (KBr): ν = 3520-3414 (NH), 3074 (CH-Ar), 2968 (CH-aliph.), 1663, 1522, 1314 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.96-1.15 (m, 18H, 6 CH_3), 1.74-1.86 (m, 6H, 2 CH_2+2CH), 4.65 (t, 2H, 2CH), 7.82, 8.32 (2s, 4H, 4NH, exchangeable with D_2O), 7.86-9.36 (m, 11H, Pyr-H). ^{13}C-NMR: δ = 14.05 (2C, 2CH_3), 22.58 (4C, 4CH_3), 23.22 (2C, 2CH), 41.46 (2C, 2CH_2), 52.88 (2C, 2CH), 131.48, 140.16, 152.32 (5C, Pyr-C), 167.44 (2C, 2C = O), 172.95 (2C, 2C = O), 145.78 (2C, C = N), 123.13, 126.60, 136.12, 149.88, 154.72 (10C, Pyr-C). MS

(EI, 70 eV): m/z (%) = 628 [M^+, 18]. $C_{33}H_{41}N_9O_4$ (627.74): calcd. C, 63.14; H, 6.58; N, 20.08; found C, 63.02; H, 6.50; N, 20.00.

3,5-Bis{N-(4-methyl-1-oxo-1-{2-[1-(pyridin-3-yl)ethylidene]hydrazinyl}pentane-2-yl)-3-carboxamide} pyridine 7b: Yield: 72%, m.p. 252-254°C (AcOH/H_2O), $[a]^{25}_D$ = -112.4 (c = 0.5, DMF). IR (KBr): ν = 3534-3422 (NH), 3075 (CH-Ar), 2974 (CH-aliph.), 1662, 1523, 1318 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.98-1.16 (m, 18H, 6 CH_3), 1.75-1.85 (m, 6H, 2 CH_2+2CH), 4.68 (t, 2H, 2CH), 7.80, 8.44 (2s, 4H, 4NH, exchangeable with D_2O), 7.88-9.32 (m, 11H, Pyr-H). ^{13}C-NMR: δ = 13.86 (2C, 2CH_3), 23.05 (4C, 4CH_3), 23.28 (2C, 2CH), 41.45 (2C, 2CH_2), 52.90 (2C, 2CH), 131.52, 140.14, 152.30 (5C, Pyr-C), 167.46 (2C, 2C = O), 172.90 (2C, 2C = O), 145.77 (2C, C = N), 123.63, 126.12, 137.16, 151.30, 151.95 (10C, Pyr-C). MS (EI, 70 eV): m/z (%) = 628 [M^+, 32]. $C_{33}H_{41}N_9O_4$ (627.74): calcd. C, 63.14; H, 6.58; N, 20.08; found C, 63.00; H, 6.48; N, 20.01.

3,5-Bis{N-(4-methyl-1-oxo-1-{2-[1-(pyridine-4-yl)ethylidene]hydrazinyl}pentane-2-yl)-3-carboxamide} pyridine 7c: Yield: 64%, m.p. 210-212°C (AcOH/H_2O), $[a]^{25}_D$ = -102.8 (c = 0.5, DMF). IR (KBr): ν = 3535-3424 (NH), 3077 (CH-Ar), 2978 (CH-aliph.), 1663, 1524, 1318 (C = O, amide I, II and III) cm^{-1}. ^{1}H-NMR: δ = 0.98-1.18 (m, 18H, 6 CH_3), 1.73-1.86 (m, 6H, 2 CH_2+2CH), 4.70 (t, 2H, 2CH), 7.81, 8.43 (2s, 4H, 4NH, exchangeable with D_2O), 7.95-9.36 (m, 11H, Pyr-H). ^{13}C-NMR: δ = 13.92 (2C, 2CH_3), 23.10 (4C, 4CH_3), 23.35 (2C, 2CH), 41.52 (2C, 2CH_2), 52.91 (2C, 2CH), 131.53, 140.24, 152.34 (5C, Pyr-C), 167.52 (2C, 2C = O), 172.86 (2C, 2C = O), 145.75 (2C, C = N), 124.63, 138.14, 149.56 (10C, Pyr-C). MS (EI, 70 eV): m/z (%) = 628 [M^+, 15]. $C_{33}H_{41}N_9O_4$ (627.74): calcd. C, 63.14; H, 6.58; N, 20.08; found C, 63.01; H, 6.47; N, 19.98.

Experimental animals: Animals were obtained from Theodor Bilharz Research Institute (TBRI), Egypt and approval of the institutional animal ethical committee for the animals' studies was obtained from the Office of Environmental Health and Radiation Safety, ACUC Protocol 1096-5. The animals were maintained according to accepted standards of animal care. The acute toxicity (LD_{50}) has been performed following current OECD guideline according to Austen and Brocklehurst (1961).

Analgesic activity: One hundred and fourteen Webster mice of both sexes weighting from 20-25 g were divided into 19 groups. One group was kept as control (received saline), the second group received vehicle (Gum acacia) and the third one received Valdecoxib as a reference drug, whereas the other groups received tested compounds (SC administration). Mice were dropped gently in a dry glass beaker of 1 L capacity maintained at 55-55.5°C. Normal reaction time in seconds for all animals was determined at time intervals of 10, 20, 30, 45, 60, 90 and 120 min. This is the interval extending from the instant the mouse reaches the hot beaker till the animals licks its feet or jump out of the beaker (dose 5 mg kg^{-1}) (Tjolsen *et al*., 1991), relative potencies to that of Valdecoxib were determined. Lower doses than 5 mg kg^{-1} give flactuated lower non significant responsive analgesia activities.

Anti-inflammatory activity: Some of newly synthesized candidate derivatives were dissolved in 0.5% Carboxymethyl Cellulose (CMC) as a homogeneous solution and administered intraperitoneally (i.p.). One hundred and eight rats were divided into eighteen groups, each group consisting of six animals. Anti-inflammatory activity of the compounds was studied in rats using carrageenan. A suspension of the tested compound and the reference drug, Indomethacin® in aqueous solution was administered orally at a dose 5 mg kg^{-1}. Control animals were treated with 0.5% CMC only. After 30 min, 0.1 mL of freshly prepared 1.0% carrageenan (Type IV Sigma) solution (in formol saline) was injected into the sub-plantar region of the right hind paw according to Hernandez-Perez *et al.* (1995). The right paw volume was measured using a digital plethysmometer (Model 7150), directly before and after 1, 2 and 3 h, intervals after administration of the tested compounds. Lower doses than 5 mg kg^{-1} give flactuated lower non significant responsive anti-inflammatory activities.

RESULTS AND DISCUSSION

Chemistry: A series of bis-schiff base candidates 5a-l, 6a-c and 7a-c were synthesized by using N^2, $N^{2'}$-(pyridine-3, 5-dicarbonyl)-di-L-lucylhydrazide (4) as starting material which was prepared according to reported procedure (Khayyat and Amr, 2014). Reaction of 3,5-pyridinedicarboxylic acid 1 or 3,5-pyridinedicarbonyl dichloride 2 with L-lucine methyl ester to give N^{α}-dinicotinoyl-bis-(amino acid) methyl ester 3 which was treated with hydrazine hydrate to give N^{α}-dinicotinoyl-bis-amino acid hydrazide 4 (Fig. 1).

Treatment of 3, 5-bis-hydrazide pyridine 4 with aromatic aldehyde derivatives in refluxing glacial acetic acid afforded the corresponding 3,5-bis-hydrazone dipeptide pyridine derivatives 5a-l, respectively. Additionally, condensation of bis-hydrazide 4 with cyclic alkanone and acetylpyridine derivatives in refluxing glacial acetic acid gave the corresponding 3,5-bis-Schiff base pyridine derivatives 6a-c and 7a-c, respectively (Fig. 2).

Pharmacological screening

Acute toxicity: Initially the acute toxicity of the compounds was assayed determining their LD_{50}. Interestingly, all the synthesized compounds were less toxic than the reference drug (Table 1).

Analgesic activity: All tested compounds exhibited analgesic activities in a hot plate assay (Table 2). Compounds (7c and 6b), 7b, 5i and 5h show higher analgesic activities than valdecoxib after 1 h and they arranged in descending order of potency.

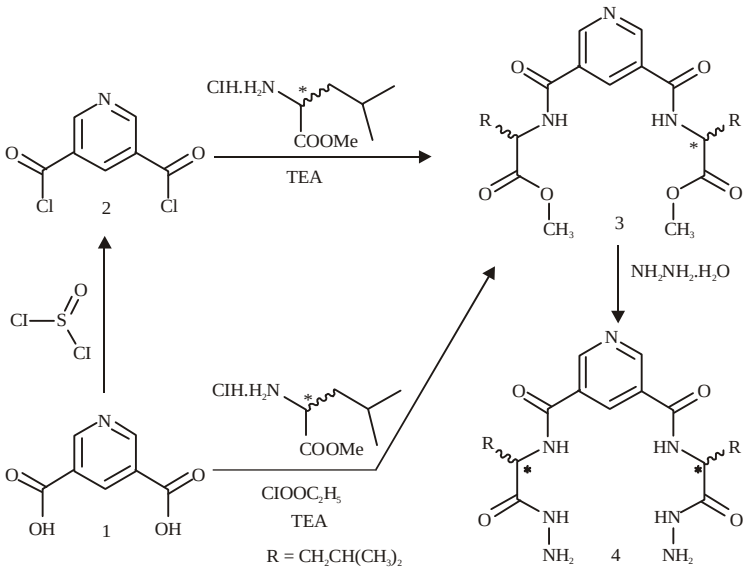

Fig. 1: Synthetic route for starting material 4 (Khayyat and Amr, 2014)

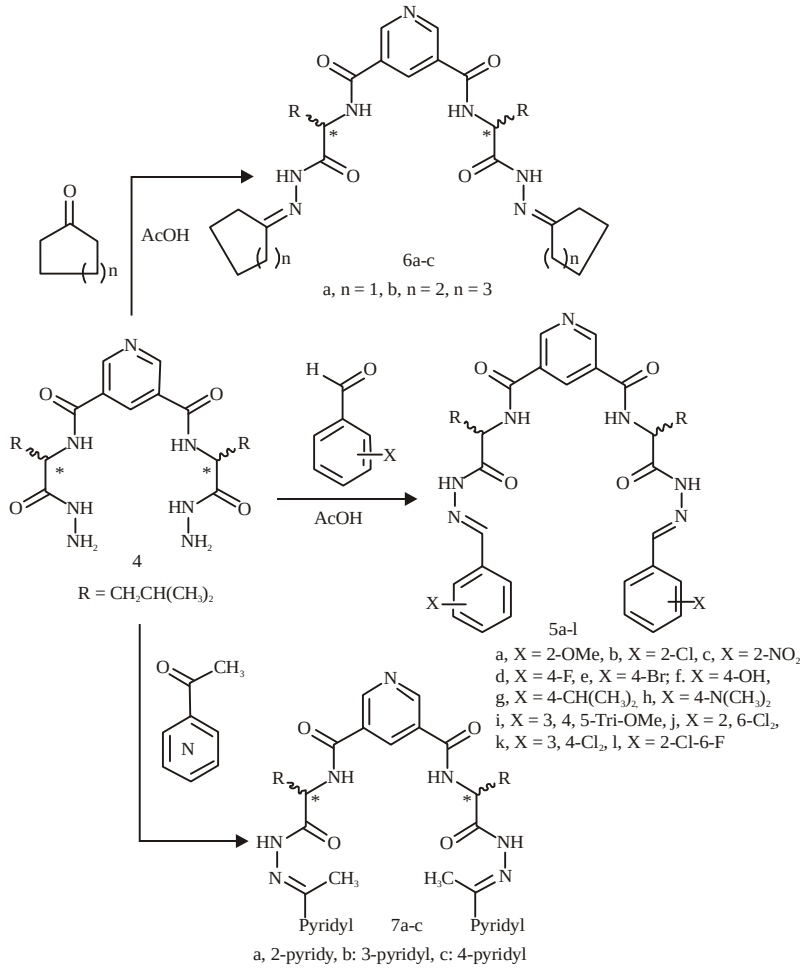

Fig. 2: Synthetic route for compounds 5-7

Table 1: Acute toxicity LD_{50} of the synthesized compounds 5-7

Compound No.	LD_{50} (mg kg^{-1})
Prednisolone®	1618±12.18
5a	1856±12.12
5b	1730±10.11
5c	1856±8.99
5d	1972±7.89
5e	1690±21.20
5f	1805±8.81
5g	1875±7.29
5h	1878±11.23
5i	1776±13.23
5j	1780±21.23
5k	1753±12.12
5l	1924±21.25
6a	1981±8.39
6b	1678±8.34
6c	1718±5.94
7a	1792±6.49
7b	1810±7.65
7c	1881±8.77

Values were calculated from the mean values of data from three separate experiments. All results are significantly different from control values at $p \leq 0.005$, All results are significantly different from reference standard values at $p \leq 0.005$

Table 2: Analgesic activities of synthesized compounds 5a-l, 6a-c and 7a-c in a hot plate assay

	Analgesic activity related to valdecoxib after (min±SE)						
Compound No.	10	20	30	45	60	90	120
5a	0.66±0.014	0.61±0.011	0.85±0.011	0.85±0.015	0.85±0.020	0.85±0.016	0.88±0.016
5b	0.88±0.010	0.88±0.009	0.87±0.010	0.91±0.018	0.90±0.014	0.92±0.015	0.90±0.017
5c	0.84±0.012	0.90±0.014	0.88±0.016	0.92±0.021	0.93±0.028	0.92±0.018	0.92±0.024
5d	0.85±0.010	0.86±0.011	0.90±0.011	0.90±0.016	0.94±0.015	0.92±0.013	0.91±0.015
5e	0.62±0.015	0.62±0.010	0.72±0.010	0.74±0.018	0.76±0.011	0.76±0.011	0.76±0.013
5f	0.75±0.010	0.83±0.013	0.83±0.012	0.85±0.014	0.86±0.016	0.83±0.012	0.84±0.019
5g	0.66±0.012	0.60±0.014	0.84±0.011	0.84±0.015	0.86±0.018	0.85±0.016	0.86±0.014
5h	1.31±0.18	1.36±0.12	1.41±0.26	1.40±0.30	1.40±0.19	1.38±0.11	1.40±0.28
5i	1.29±0.16	1.40±0.14	1.39±0.26	1.39±0.32	1.41±0.17	1.40±0.11	1.37±0.28
5j	0.86±0.010	0.91±0.010	0.92±0.015	0.88±0.019	0.82±0.019	0.80±0.013	0.66±0.010
5k	0.60±0.011	0.62±0.015	0.74±0.012	0.72±0.018	0.73±0.018	0.76±0.015	0.76±0.010
5l	1.29±0.17	1.39±0.12	1.39±0.26	1.38±0.31	1.38±0.15	1.37±0.11	1.38±0.28
6a	0.85±0.012	0.88±0.010	0.92±0.015	0.87±0.019	0.85±0.019	0.78±0.014	0.65±0.012
6b	0.96±0.015	0.96±0.013	1.40±0.140	1.46±0.180	1.50±0.320	1.45±0.300	1.40±0.420
6c	0.60±0.011	0.65±0.015	0.74±0.012	0.72±0.017	0.74±0.015	0.75±0.015	0.76±0.011
7a	0.62±0.014	0.64±0.011	0.72±0.011	0.74±0.016	0.76±0.011	0.76±0.010	0.74±0.013
7b	1.31±0.18	1.40±0.15	1.40±0.28	1.36±0.32	1.42±0.17	1.40±0.10	1.38±0.26
7c	0.98±0.014	0.98±0.013	1.38±0.138	1.48±0.180	1.50±0.320	1.46±0.301	1.40±0.420
Gum acacia	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Valdecoxib	1.00±0.01	1.00±0.01	1.00±0.01	1.00±0.01	1.00±0.01	1.00±0.01	1.00±0.01

Values were calculated from the mean values of data from three separate experiments. All results are significantly different from control values at $p \leq 0.005$, All results are significantly different from reference standard values at $p \leq 0.005$

Anti-inflammatory activity: Compounds 5l, 5i, 5h, 6b, 7b, 7d, 5d, 5c, 5f, 15b and 6a showed moderate anti-inflammatory activities after one hour but less than that of indomethacin (Table 3). They are arranged in descending order of activities.

Careful examination of the relation between the structure of the tested compounds and their analgesic properties had culminated on the following structural activities relationships:

- 3,5-Bis{N-(4-methyl-1-oxo-1-{2-[1-(pyridinyl) ethylidene]hydrazinyl}pentane-2-yl)-3-carbox-amide} pyridine essential for higher analgesic activities after 1 h from starting the assay
- 3,5-Bis{N-[1-(cycloalkanonylidenehydrazinyl)-4-methyl-1-oxopentane-2-yl]-3-carbo-xamide}-pyridine less active than the former ones
- 3,5-Bis{N-[1-{2-[1-(substituted phenyl)ethylidene] hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido} pyridines less active than the former ones

Careful examination of the relation between the structure of the tested compounds and their anti-inflammatory properties had culminated on that the 3,5-bis{N-[1-{2-[1-(substituted phenyl) ethylidene]hydrazinyl}-4-methyl-1-oxopentane]-3-carboxamido}pyridines essential for higher anti-inflammatory activities after 1 h from starting the assay.

Table 3: Anti-inflammatory activity of some newly synthesized compounds

	Edema inhibition (Means±E.M)[a,b] (%)		
Compound No.	1 h	2 h	3 h
5b	15.4±1.2	14.9±1.1	11.1±1.3
5c	19.5±1.2	15.2±1.3	18.3±1.5
5d	21.8±1.3	21.3±1.3	24.1±1.2
5f	19.3±1.5	22.3±1.3	23.9±1.3
5h	37.2±1.3	46.3±1.5	40.2±1.6
5i	39.1±1.5	42.1±1.3	48.2±1.2
5l	44.3±1.1	48.2±1.2	56.1±1.4
6a	13.7±1.2	15.2±1.5	14.2±1.3
6b	34.5±1.2	48.4±1.2	55.6±1.1
7b	31.2±1.2	35.1±1.5	54.4±1.1
7d	22.3±1.2	23.6±1.1	25.5±1.2
CMC 0.5%	0.0±0.0	0.0±0.0	0.0±0.0
Indomethacin	44.7±1.2	52.4±1.2	61.2±1.3

[a]Dose 5 mg kg^{-1} b.m (p.o.). [b]n = 6. Values were calculated from the mean values of data from three separate experiments. All results are significant different from control values at $p \leq 0.005$. All results are significant different from reference standard values at $p \leq 0.005$

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