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Synthesis of Novel Azapseudopeptide Derivatives and Their Antimicrobial Activities

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ABSTRACT

The synthesis of β-lactams as azapseudopeptides was carried out in three stages affording reasonable yields. The Schiff base [ethyl 2-{2-(benzylidene)hydrazinyl}acetate] (**2**) has been prepared from ethyl hydrazinylacetate and benzaldehydes derivatives. Schiff bases led to novel azapseudopeptide derivatives **3** on treatment with chloro acetyl chloride in the presence of triethylamine. Identification of final compounds were confirmed by FT-IR, ^{1}H NMR and ^{13}C NMR data.

KEYWORDS

Hydrazinoester, Peptidomimitics, Pseudopeptides, Schiff base, Antibacterial activity.

INTRODUCTION

Peptidomimetics are considered mimics of natural peptides, retaining the main biological effect of the latter, while improving their established many poor therapeutic profiles such as poor bioavailability, poor metabolic stability and receptor selectivity. For this reason, numerous structural modifications, involving both the peptide backbone and the amino acid side chains, have been considered and proved to be promising for future development [1-7].

Among interesting modifications of the backbone of peptides included the synthesis of aza-peptides, involving the replacement of α-C or β-C of amino acid residues with a nitrogen atom. Therefore, aza-amino acids impart a unique conformational feature to peptidic structures because of the loss of chirality and reduction of flexibility of the parent linear peptide [8]. Hess *et al.* [9] replaced an amino acid residue in a natural peptide with an azaamino acid. Their work consisted in incorporating an aza-valine (aza-val) residue in position three in the analog of the angiotensin bovine II (Fig. 1). The biological activity assessment of the novel compound showed a major vasoconstriction entailing an increase of blood pressure.

Besides aza-amino acids form an important class of compounds because of their interesting diversified biological and pharmacokinetic properties such as a good ovulation-inducing property of luliberin [11,12], together with inhibitory activities

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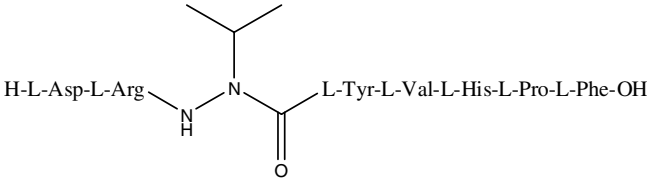


Fig. 1. Analog pseudopeptide of angiotensin bovine II [Ref. 10]

such as serine proteases [13-18], potent HIV-1 proteases with high antiviral activity [19-24], β-lactamases [25] and both anticoagulant [26,27] and anticonvulsant activities [28].

We report herein the synthesis of novel azapseudopeptides derivatives belonging to β-lactams family. As literature set forth the azetidinone ring system is a common structural moiety in number of broad spectrum β-lactam antibiotics like penicillins and cephalosporins behaving as chemotherapeutic agents to treat bacterial infections and diseases [29-32]. In the light of these observations, we planned to prepare a series of azapseudopeptides derivatives by incorporating the azetidinone moiety from hydrazinoesters with an aim to improve antibacterial as well as antifungal activities.

EXPERIMENTAL

All the reactions with dry solvents were carried out under dry nitrogen. Infrared spectra were collected from a Mattson Genesis II FTIR instrument. NMR spectra were recorded in $CDCl_3$/DMSO-d_6 as solvent on a Bruker 300 MHz instrument using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) and coupling constants (*J*) values in Hertz (Hz). Melting points were determined on an Electrothermal T1A F3.15A apparatus. Column chromatography was achieved on silica gel 230-270 mesh (Merck) using appropriate solvent or mixture of solvents (dichloromethane, methanol or ether).

Synthesis of hydrazinoethylacetic ester (1): Hydrazinoethylacetic ester (**1**) was prepared by literature procedure [33]. The chloroacetic acid (0.1 mol) was mixed with anhydrous hydrazine (0.1 mol) in absolute ethanol. The mixture was refluxed for 6 h. At the end of reaction, the reaction mixture was concentrated. The residue was dissolved in an aqueous sodium carbonate solution (20 mL) and extracted with dichloromethane (3 × 15 mL) and the combined organic fractions were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to provide compound **1** as yellow oil in good yield (92 %). It was sufficiently pure to be used in the following step without further purification.

General procedure for the synthesis of ethyl 2-(2-benzylidenehydrazinyl)acetate derivatives (2): A mixture of **1** (0.01 mol) and benzaldehyde derivatives (0.01 mol) were stirred at room temperature for 18 h in ethanol (20 mL). The solid mass thus obtained was recrystallized from water to obtain compounds **2a-j**.

Ethyl 2-(2,4,6-trimethylbenzylidene)hydrazinecarboxylate (2a): Yield 60 %; m.p. 268-270 °C; $C_{14}H_{20}N_2O_2$; IR (KBr, ν_{max}, cm^{-1}): 3178.99, 3072, 2913, 2874, 1671, 1135, 1019, ^{1}H NMR (DMSO-d_6) δ: 1.32 (m, 3H, CH_3), 2.47 (s, 9H, CH_3-Ar), 2.55 (s, 2H, CH_2), 4.23 (q, 2H, CH_2), 7.28 and 8.23 (s, 2H, H-Ar), 9.03 (s, 1H, -HC=N-), 10.38 (s, 1H, -NH-) ppm, ^{13}C NMR (DMSO-d_6) δ: 20.6, 21.1, 21.8, 56.7, 68.6, 127.7, 128.4, 129.6, 137.7, 138.6, 139.6, 143.7, 161.7, 174.2 ppm.

Ethyl 2-[2-(3-chlorobenzylidene)hydrazinyl]acetate (2b): Yield 60 %; m.p. 176-178 °C; $C_{11}H_{15}N_2O_2Cl$, IR (KBr, ν_{max}, cm^{-1}): 3169, 3097, 2970, 2851, 1686, 1133, 910, ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, *J* = 7Hz, -CH_3), 3.34 (s, 2H, -CH_2-), 3.83 (q, 2H, *J* = 1.7 Hz, -O-CH_2-), 7.35 (m, 4H, H-Ar), 9.67 (s, 1H, -HC=N-), 11.13 (s, 1H, -NH-) ppm, ^{13}C NMR (DMSO-d_6) δ: 20.7, 55.8, 72.5, 121.3, 122, 127.1, 143, 165.7, 172.1 ppm.

Ethyl 2-[2-(2,6-dichlorobenzylidene)hydrazinyl]-acetate (2c): Yield 62 %; m.p. 53-55 °C; $C_{11}H_{14}N_2O_2Cl_2$; IR (KBr, ν_{max}, cm^{-1}): 3171, 3090, 2891, 1667, 1206, 1093, 814, 776, ^{1}H NMR (DMSO-d_6) δ: 1.08 (t, 3H, *J* = 7 Hz, -CH_3), 3.35 (s, 2H, -CH_2-), 4.27 (q, 2H, *J* = 5.7 Hz, -O-CH_2-), 7.83 (m, 3H, H-Ar), 9.64 (s, 1H, -HC=N-), 11.17 (s, 1H, -NH-) ppm, ^{13}C NMR (DMSO-d_6) δ: 20.6, 22, 53.8, 68.6, 113, 130.5, 145.2, 166, 174.1 ppm.

Ethyl 2-[2-(benzo[1,3]dioxol-5-ylmethylene)hydrazinyl]-acetate (2d): Yield 60 %; m.p. 268-270 °C; $C_{12}H_{14}N_2O_3$; IR (KBr, ν_{max}, cm^{-1}): 3183, 3069, 2967, 2915, 1679, 1196, 1100, 1035, ^{1}H NMR (DMSO-d_6) δ: 1.08 (t, 3H, *J* = 7 Hz, -CH_3), 3.17 (s, 2H, -CH_2-), 3.35 (m, 2H, -OCH_2-), 6.0.6 (s, -OCH_2O-), 7.23 (m, 2H, H-Ar), 8.56 (s, 1H, -HC=N-), 10.9 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ: 12.2, 20.5, 56.4, 68, 102.1, 105.5, 106.6, 108.9, 122.9, 125.2, 129.4, 142.8, 148.4, 150.4, 161.5, 168.7 ppm.

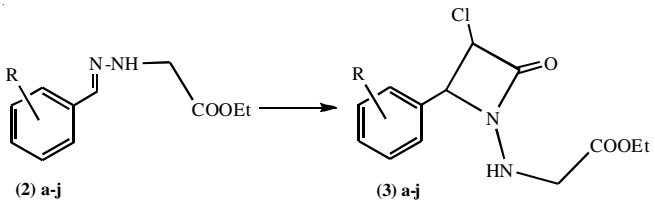
Ethyl 2-[2-(3,4-dimethoxybenzylidene)hydrazinyl]-acetate (2e): Yield 60 %; m.p. 128-130 °C; $C_{13}H_{18}N_2O_4$; IR (KBr, cm^{-1}): 3194, 3003, 2954, 2840, 1657, 1140, 1017, ^{1}H NMR (DMSO-d_6) δ: 1.08 (t, 3H, *J* = 7 Hz, -CH_3), 3.35 (s, 2H, -CH_2-), 3.81 (s, 6H, -OCH_3), 4.06 (m, 2H, -O-CH_2-), 7.5 (m, 3H, H-Ar), 9.67 (s, 1H, -HC=N-), 11.13 (s, 1H, -NH-) ppm, ^{13}C NMR (DMSO-d_6) δ: 20.8, 22, 56.1, 72.1, 109.5, 112, 121.3, 122, 127.3, 143, 149.4, 152, 161.2, 172.1 ppm.

Ethyl 2-[2-(3,4-dichlorobenzylidene)hydrazinyl]-acetate (2f): Yield 74 %; m.p. 68-70 °C; $C_{11}H_{14}N_2O_2Cl_2$; IR (KBr, ν_{max}, cm^{-1}): 3182, 3067, 2948, 2855, 1662, 1129, 1030, 872, 816, ^{1}H NMR (DMSO-d_6) δ: 1.20 (m, 3H, -CH_3), 3.33 (s, 2H, -CH_2-), 4.11 (m, 2H, -O-CH_2-), 7.83 (m, 3H, H-Ar), 8.72 (s, 1H, -HC=N-), 11.41 (s, 1H, -NH-) ppm, ^{13}C NMR (DMSO-d_6) δ: 15.8, 51.5, 67.2, 126, 128.5, 130.5, 131.2, 134.7, 144.8, 160.3, 171.1 ppm.

Ethyl 2-[2-(2,5-dimethylbenzylidene)hydrazinyl]-acetate (2j): Yield 60 %; m.p. 128-132 °C; $C_{13}H_{18}N_2O_2$; IR (KBr, ν_{max}, cm^{-1}): 3181, 3090, 2974, 2872, 1679, 1149, 1035, ^{1}H NMR (DMSO-d_6) δ: 1.31 (m, 3H, -CH_3), 2.15 (s, 6H, CH_3-Ar), 2.53 (s, 2H, -CH_2-), 4.26 (m, 2H, -O-CH_2-), 7.5 (m, 3H, H-Ar), 9.03 (s, 1H, -HC=N-), 10.3 (s, 1H, -NH-) ppm, ^{13}C NMR (DMSO-d_6) δ: 16.6, 19, 19.6, 20.5, 20.9, 53.4, 57.5, 62.3, 127.4, 127.7, 128.8, 130.6, 131, 131.7, 132, 135.6, 135.8, 139, 143.4, 160.8, 172.7 ppm.

General procedure for the synthesis of ethyl 2-(3-chloro-2-oxo-4-phenylazetidin-1-ylamino) acetate derivatives (3): To a stirred solution of **2** (0.1 mol) in dioxane (20 mL), chloro acetylchloride (0.1 mol) was added dropwise at 0-5 °C in the presence of triethylamine (TEA). The mixture was stirred for 24 h and the hydro-chloride was filtered off and excess of dioxane was distilled off. The mass thus obtained was cooled,

poured in ice-cold water, filtered, washed, dried and recrystallized from ethanol/water (3:2) to furnish compounds **3a-j (Scheme-I)**.



Scheme-I: Synthetic route of compounds **3a-j**

Ethyl 2-[3-chloro-2-mesityl-4-oxoazetidin-1-ylamino]-acetate (3a): Yield 55 %; m.p. 165-166 °C; $C_{16}H_{21}N_2O_3Cl$; IR (KBr, ν_{max}, cm^{-1}): 3176, 3067, 2966, 2914, 2873, 2737, 2676, 1670, 1134, 1019, 849, 784, ^{1}H NMR ($CDCl_3$) δ: 1.27 (dt, 3H, *J* = 8.4, 5.5 Hz, -CH_3), 2.47 (s, 9H, Ar-CH_3), 2.68 (s, 2H, -CH_2-), 3.75 (d, 1H, *J* = 7.2 Hz, -CH-), 4.10 (m, 2H, -O-CH_2-), 4.61 (d, 1H, *J* = 16.4 Hz, -CHCl-), 7.58 (s, 3H, H-Ar), 10.81 (s, 1H, -NH-) ppm, ^{13}C NMR ($CDCl_3$) δ: 11.73, 15.02, 20.6, 21, 21.5, 35.5, 41.6, 64.8, 127.7, 129.7, 137.7, 139, 143.6, 173, 174.4 ppm.

Ethyl 2-[3-chloro-2-(3-chlorophenyl)-4-oxoazetidin-1-ylamino]acetate (3b): Yield 48 %, m.p 160-163 °C; $C_{13}H_{14}Cl_2N_2O_3$; IR (KBr, ν_{max}, cm^{-1}): 3312 (NH), 3078 (CH aromatic), 1760, 1728 (C=O), 1622 (C=N), 744 (C–Cl); ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H, *J* = 5.2 Hz, -CH_3), 2.14 (d, 1H, *J* = 18.7 Hz, -CH-), 2.39 (s, 2H, -CH_2-), 3.7 (d, 1H, *J* = 6.7 Hz, -CHCl-), 4.23 (m, 2H, -O-CH_2-), 7.49 (m, 4H, H-Ar), 10.97 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 20.41, 56.1, 64.8, 66.5, 125.5, 126.5, 127, 128.1, 130, 131.32, 134.8, 135.7, 142.3, 161.1, 169.1, 174.5 ppm.

Ethyl 2-[3-chloro-2-(2,6-dichlorophenyl)-4-oxoazetidin-1-ylamino]acetate (3c): Yield 60 %; m.p. 133-135 °C; $C_{13}H_{13}N_2O_3Cl_3$; IR (KBr, ν_{max}, cm^{-1}): 3181, 3091, 2925, 1667, 1206, 1093, 864, 841, 776, ^{1}H NMR ($CDCl_3$) δ: 1.25 (dt, 3H, *J* = 7, 4.8 Hz, -CH_3), 1.84 (s, 2H, CH_2), 2.5 (m, 1H, -CH-), 3.67 (d, 1H, *J* = 14 Hz, -CHCl-), 4.17 (m, 2H, CH_2), 7.43 (m, 4H, HAr), 10.45 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 20.2, 24.9, 47.4, 53.3, 57.3, 59, 129, 130.2, 132.5, 133.6, 136.7, 152, 157.4, 168.1, 188.7 ppm.

Ethyl 2-[2-(benzo[1,3]dioxol-5-yl)-3-chloro-4-oxoazetidin-1-ylamino]acetate (3d): Yield 60 %; m.p. 168-170 °C; $C_{14}H_{15}N_2O_5Cl$; IR (KBr, ν_{max}, m^{-1}): 3184, 3071, 2965, 2916, 1683, 1263, 1115, 1036, 931, 805, ^{1}H NMR ($CDCl_3$) δ: 1.10 (t, 3H, CH_3), 2.18 (s, 2H, CH_2), 2.5 (q, 2H, CH_2), 3.16 (s, 2H, CH_2), 6.9 (d, 1H, Ar-CH), 7.1 (d, 1H, CH-Cl), 7.23 (d, 2H, H-Ar), 8.5 (s, 1H, H-Ar), 10.9 (s, 1H, NH) ppm, 20.5, 39, 40, 41, 60.2, 101.8, 104.7, 122.9, 129.4, 132.3, 142.7, 148.4, 151.8, 172.1 ppm.

Ethyl 2-[3-chloro-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-1-ylamino]acetate (3e): Yield 51 %; m.p. 178-181 °C; $C_{15}H_{19}N_2O_5Cl$; IR (KBr, ν_{max}, cm^{-1}): 3186, 3063, 2964, 2840, 1710, 1122, 1032, 784, 745, ^{1}H NMR ($CDCl_3$) δ: 1.28-1.38 (m, 3H, CH_3), 3.96 (s, 6H, O-CH_3), 4.20- 4.25 (m, 2H, O-CH_2), 6.92- 6.95 (d, 1H, CH), 7.25- 8.62 (m, 3H, H-Ar), 9.98 (s, 1H,-NH); ^{13}C NMR ($CDCl_3$) δ: 14.02, 23.76, 28.92, 30.37, 38.75, 55.96, 68.16, 108.83, 110.71, 123.93, 128.798, 138.66, 151.84, 161.17, 182.17 ppm.

Ethyl 2-[3-chloro-2-(3,4-dichlorophenyl)-4-oxo-azetidin-1-ylamino]acetate (3f): Yield 80 %; m.p. 155-158 °C; $C_{13}H_{13}N_2O_3Cl_3$; IR (KBr, ν_{max}, cm^{-1}): 3182, 3067, 2948, 2855, 1662, 1129, 1030, 872, 816, 745, ^{1}H NMR ($CDCl_3$) δ: 1.18-132 (t, 3H, CH_3), 4.15 (s, 2H, CH_2), 7.19-6.85 (d, 1H, Ar-CH), 7.45-7.47 (d, 1H, CH), 7.75-7.92 (m, 3H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$) δ: 14.03, 22.98, 29.71, 38.75, 104.67, 127.69, 128.8, 130.9, 133.34, 135.55, 150.95, 153.99, 160.26 ppm.

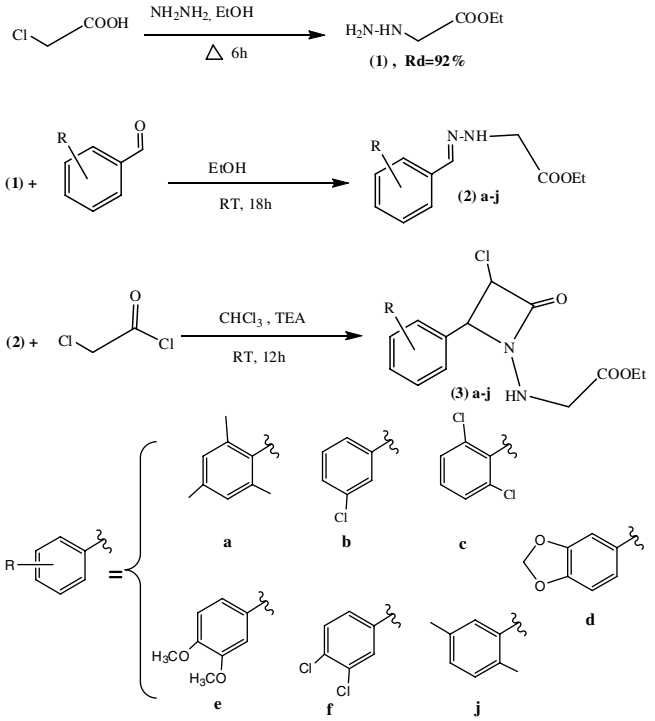
Ethyl 2-[3-chloro-2-(2,5-dimethylphenyl)-4-oxoazetidin-1-ylamino]acetate (3j): Yield 72 %; m.p. 124-126 °C; $C_{15}H_{19}Cl_1N_2O_3$; IR (KBr, ν_{max}, cm^{-1}): 3177, 3070, 2964, 2852, 1686, 1143, 1023, 872, 816, 745,^{1}H NMR ($CDCl_3$) δ: 1.27-139 (t, 3H, CH_3), 2.14-2.43 (m, 2H,OCH_2), 2.53 (s, 9H, CH_3-Ar), 4.64 (s, 2H, CH_2), 6.83-6.85 (d, 1H, Ar-CH), 7.16-7.18 (d, 1H, CH-Cl), 7.75-7.92 (d, 1H, Ar–H), 8.15-8.39 (d, 1H, Ar–H), 9.03 (s, 1H, Ar–H), 10.81 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 15.16, 18.66, 19.71, 20.57, 20.7, 20.95, 127.47, 130.56, 131, 131.7, 134.12, 135.6, 143.75, 16.79, 174.75 ppm.

Antimicrobial activity: The *in vitro* anti-microbial activity was carried out against 24 h-old cultures of two bacteria and two fungi by cup-plate method. Compounds **2a-j** and **3a-j** have been tested for their antibac-terial activity against *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis* and *Staphylococcus aureus.* Nutrient agar and potato dextrose agars were used to grow bacteria and fungi, respectively. The compounds were tested at a concentration of 200 µg/mL in DMSO solution using test discs of amoxicillin (25 µg/disc), ciprofloxacin (5 µg/disc) and gentamycin (10 µg/disc) as references. Inhibition was recorded by measuring the diameter of inhibition zone (Ø) 24 h for bacteria. Each experiment was repeated thrice and the average of three independent determinations was recorded.

RESULTS AND DISCUSSION

Scheme-II describes the whole process from chloroacetic acid to targets. Thus ethyl hydrazinylacetate (**1**) was prepared from anhydrous hydrazine on reacting with chloroacetic acid in absolute ethanol at reflux for 6 h [34] and its spectral analysis gave satisfactorily results. Thus IR spectrum showed a sharp and strong absorption band in the region of 3418-3198 cm^{-1} due to NH–NH_2 group and another one above 1728 cm^{-1} due to the presence of the ester function in the structure. ^{1}H NMR spectra substantiated the results of the IR analysis. The characteristic signals of an ester moiety confirmed the presence of an ethyl ester group as a quartet and a triplet for CH_2 and CH_3 at δ 4.22 ppm (*J* = 14 Hz) and δ 1.27 ppm (*J* = 2.7 Hz), respectively and δ 4.62 ppm for –NH and –NH_2 [35].

Schiff bases **2** were obtained through treatment of compound **1** with various aromatic aldehydes in absolute ethanol in moderate yields. Identification was performed by IR and ^{1}H NMR spectral analysis. The IR spectrum of **2** showed no absorption band of esters stretching frequency; but instead it showed an absorption band at 1679 cm^{-1} for carbonyl group, showing two sharp bands in the region of 3181 cm^{-1} for –NH and at 3090 cm^{-1} for H-Ar frequencies. ^{1}H NMR spectrum of **2** exhibited multiplets at δ 7.11-8.39 ppm for aromatic protons.



Scheme-II: General procedure for the synthesis of ethyl 2-(3-chloro-2-oxo-4-phenylazetidin-1-ylamino)acetate derivatives

Quartet, triplet and singlet for CH_2, CH_3 and N-CH_2-C=O at δ 4.29 ppm (J = 5.7 Hz), δ 1.2 ppm (J = 7 Hz) and 3.35 ppm, respectively were observed. In the meantime imine protons were found at δ 9.03 ppm and –NH protons appeared at δ 10.34 ppm. Finally the title compounds **3** were obtained from compounds **2** that were reacted with chloroacetyl chloride and triethylamine in chloroform [33,36-41]. The structural analyses of the new compounds were confirmed by IR and ^{1}H NMR spectral analysis. Thus IR spectra of **3** showed two sharp strong absorption bands at 1670 cm^{-1} for carbonyl amide group. Further, ^{1}H NMR spectrum exhibited multiplets in the region at δ 7.60-8.90 ppm for aromatic protons. Quartet and triplet or multiplets for CH_2 and CH_3 at δ 4.22 ppm (J = 14 Hz) and δ 1.27 ppm (J = 5.5 Hz), respectively and δ 10.97 ppm for –NH were observed. Protons present on the azetidinone ring, *i.e.* N-CH-C and C-CH-Cl were observed as doublets at δ 2.11 ppm and δ 2.6 ppm, respectively. All these compounds were purified by recrystallization in ethanol and water with appropriate proportions and characterized on the basis of spectral analysis.

Biological activity: We used test disc of amoxicillin (25 µg/disc), ciprofloxacin (5 µg/disc) and gentamycin (10 µg/disc) as references. The compounds were tested at a 200 µg/mL concentration in dimethyl sulfoxide as a solvent. Inhibition was recorded by measuring the diameter (Ø) of the inhibition zone at the end of 24 h growing for bacteria. Each experiment was repeated thrice and the average of the three independent determinations was recorded. The results are summarized in Tables 1 and 2.

Compounds **2a, 2e** and **2j** showed promising activity against *Escherichia coli,* whereas **2b, 2d** and **2e** were interesting against *P. aeruginosa*. In the meanwhile compounds **2a** and **2j** showed good activity against *P. mirabilis* and **2e** was active against *S. aureus.* The introduction of the β-lactam moiety into **3a-j**, led to good antimicrobial activity against *P. aeruginosa* and *S. aureus.*

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **2a-j**

Compd.	Antibacterial activity zone of inhibition (mm)			
	E. coli	*P. aeruginosa*	*P. mirabilis*	*S. aureus*
2a	**22**	10	**16**	6
2b	10	**20**	10	–
2c	–	–	–	–
2d	10	15	10	11
2e	14	**20**	10	**16**
2f	–	–	–	–
2j	15	13	**17**	6
2h	–	9	–	–
DMSO	–	–	–	–
Amoxicillin	16	12	–	10
Ciprofloxacin	24	23	–	–
Gentamycin	–	16	–	21

TABLE-2
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **3a-j**

Compd.	Antibacterial activity zone of inhibition (mm)	
	P. aeruginosa	*S. aureus*
3a	15	**17**
3b	14	9
3c	12	14
3d	**16**	**15**
3f	**19**	8
3j	**18**	9
3h	**16**	**15**
DMSO	–	–
Amoxicillin	12	10
Ciprofloxacin	23	–
Gentamycin	16	21

The inhibition activity values represent the average of triplicate readings and are labeled in the following manner*: Highly active = Inhibition Ø: > 12 mm; Moderately active = Inhibition Ø: 9-12 mm; Slightly active = Inhibition Ø: 6-9 mm; Not sensitive (Inactive) = Inhibition Ø: < 6 mm; –: No inhibition

Conclusion

Since chemotherapy by means of antibiotics is almost into a bottleneck, it interesting to explore different synthetic approaches that could enable to improve the fight against bacteria. New hydrazinoesters **2a-j** (Schiff bases) and pseudoazapeptides **3a-j**, were synthesized and were identified by different spectral studies and their antibacterial activities showed interesting initial activities and some among them showed good antibacterial behaviour.

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REFERENCES

1. A.F. Spatola, Peptide Backbone Modifications: A Structure-Activity Analysis of Peptides Containing Amide Bond Surrogates, Conformational Constraints and Related Backbone Replacements, Marcel Dekker, Inc.: New York and Basel (1983).
2. J. Gante, *Angew. Chem. Int. Ed. Engl.*, **33**, 1699 (1994); http://dx.doi.org/10.1002/anie.199416991.
3. M. Goodman and S. Roin eds. M.E. Wolff, Principles and Practice, Wiley: New York, edn 5, vol. 1, pp. 803-861 (1995).
4. W.-J. Zhang, A. Berglund, J.L.-F. Kao, J.-P. Couty, M.C. Gershengorn and G.R. Marshall, *J. Am. Chem. Soc.*, **125**, 1221 (2003); http://dx.doi.org/10.1021/ja020994o.
5. A. Zega and U. Urleb, *Acta Chim. Slov.*, **49**, 649 (2002).
6. K. Bouget, S. Aubin, J.-G. Delcros, Y. Arlot-Bonnemains and M. Baudy-Floc'h, *Bioorg. Med. Chem.*, **11**, 4881 (2003); http://dx.doi.org/10.1016/j.bmc.2003.09.018.
7. S. Aubin, B. Martin, J.-G. Delcros, Y. Arlot-Bonnemains and M. Baudy-Floc'h, *J. Med. Chem.*, **48**, 330 (2005); http://dx.doi.org/10.1021/jm049455f.
8. J. Gante, *Synthesis*, 405 (1989); http://dx.doi.org/10.1055/s-1989-27269.
9. H.-J. Hess, W.T. Moreland and G.D. Laubach, *J. Am. Chem. Soc.*, **85**, 4040 (1963); http://dx.doi.org/10.1021/ja00907a036.
10. C. Abbas, G. Pickaert, C. Didierjean, B.J. Grégoire and R. Vanderesse, *Tetrahedron Lett.*, **50**, 4158 (2009); http://dx.doi.org/10.1016/j.tetlet.2009.04.131.
11. R. Xing and R.P. Hanzlik, *J. Med. Chem.*, **41**, 1344 (1998); http://dx.doi.org/10.1021/jm970802d.
12. F.G. Hutchinson and B.J.A. Furr, *Trends Biotechnol.*, **5**, 102 (1987); http://dx.doi.org/10.1016/0167-7799(87)90028-X.
13. J.C. Powers, R. Boone, D.L. Carroll, B.F. Gupton, C.M. Kam, N. Nishino, M. Sakamoto and P.M. Tuhy, *J. Biol. Chem.*, **259**, 4288 (1984).
14. J.C. Powers and B. Frank Gupton, *Methods Enzymol.*, **46**, 208 (1977); http://dx.doi.org/10.1016/S0076-6879(77)46021-X.
15. B.F. Gupton, D.L. Carroll, P.M. Tuhy and C.M. Kam, *J. Biol. Chem.*, **259**, 4279 (1984).
16. M. Nardini, M. Pesce, M. Rizzi, E. Casale, R. Ferraccioli, G. Balliano, P. Milla, P. Ascenzi and M. Bolognesi, *J. Mol. Biol.*, **258**, 851 (1996); http://dx.doi.org/10.1006/jmbi.1996.0292.
17. J.E. Semple, D.C. Rowley, T.K. Brunck and W.C. Ripka, *Bioorg. Med. Chem. Lett.*, **7**, 315 (1997); http://dx.doi.org/10.1016/S0960-894X(97)00005-X.
18. T.L. Graybill, M.J. Ross, B.R. Gauvin, J.S. Gregory, A.L. Harris, M.A. Ator, J.M. Rinker and R.E. Dolle, *Bioorg. Med. Chem. Lett.*, **2**, 1375 (1992); http://dx.doi.org/10.1016/S0960-894X(00)80516-8.
19. Y. Mehellou and E. De Clercq, *J. Med. Chem.*, **53**, 521 (2010); http://dx.doi.org/10.1021/jm900492g.
20. A.F. Santos and M.A. Soares, *Viruses*, **2**, 503 (2010); http://dx.doi.org/10.3390/v2020503.
21. D. Kato, S.H.L. Verhelst, K.B. Sexton and M. Bogyo, *Org. Lett.*, **7**, 5649 (2005); http://dx.doi.org/10.1021/ol052275v.
22. A. Fässler, G. Bold, H.-G. Capraro, R. Cozens, J. Mestan, B. Poncioni, J. Rösel, M. Tintelnot-Blomley and M. Lang, *J. Med. Chem.*, **39**, 3203 (1996); http://dx.doi.org/10.1021/jm960022p.
23. F. Lebon and M. Ledecq, *Curr. Med. Chem.*, **7**, 455 (2000); http://dx.doi.org/10.2174/0929867003375146.
24. A. Mastrolorenzo, S. Rusconi, A. Scozzafava, G. Barbaro and C.T. Supuran, *Curr. Med. Chem.*, **14**, 2734 (2007); http://dx.doi.org/10.2174/092986707782360141.
25. J. Marchandbrynaert, P. Mougenot, Y. Combret, D. Belotti, N. Guillot and L. Ghosez, *Farmaco*, **50**, 455 (1995).
26. A. Zega, G. Mlinsek, P. Sepic, S. Golie-Grdadolnik, T. Solmajer, T.B. Tschopp, B. Steiner, D. Kikelj and U. Urleb, *Bioorg. Med. Chem.*, **9**, 2745 (2001); http://dx.doi.org/10.1016/S0968-0896(01)00202-4.
27. A. Zega, A. Trampus-Bakija, M. Fortuna, M. Stegnar, T.B. Tschopp, B. Steiner and U. Urleb, *Pharmazie*, **56**, 683 (2001).
28. S.V. Andurkar, C. Béguin, J.P. Stables and H. Kohn, *J. Med. Chem.*, **44**, 1475 (2001); http://dx.doi.org/10.1021/jm0005171.
29. S.G. Shingade, S.B. Bari and U.B. Waghmare, *Med. Chem. Res.*, **21**, 1302 (2012); http://dx.doi.org/10.1007/s00044-011-9644-y.
30. S. Rollas and S.G. Kücükgüzel, *Molecules*, **12**, 1910 (2007); http://dx.doi.org/10.3390/12081910.
31. M. Noolvi, S. Agrawal, H. Patel, A. Badiger, M. Gaba and A. Zambre, *Arabian J. Chem.*, **7**, 219 (2014); http://dx.doi.org/10.1016/j.arabjc.2011.02.011.
32. G.S. Singh, M. Elbert and P. Tshepo, *ARKIVOC*, 80 (2007). http://dx.doi.org/10.3998/ark.5550190.0008.910.
33. R. Ahmad, M. Zia-ul-Haq and R. Jabeen, *Turk. J. Chem.*, **20**, 186 (1996).
34. S. Jubie, B. Gowramma and K. Nitin, *Int. J. ChemTech Res.*, **1**, 153 (2009).
35. K.S. Gawande and E.R. Khadsan, *Der Pharma Chemica*, **6**, 70 (2014).
36. T.M. Patel and A.M. Patel, *Der Pharm. Lett.*, **4**, 579 (2012).
37. A. Bhalla, S.S. Bari, S. Berry, J. Bhalla, S. Vats, S. Mandal and S. Khullar, *ARKIVOC*, 10 (2015). http://dx.doi.org/10.3998/ark.5550190.p009.172.
38. M. Gopal, B. Padmashali, Y.N. Manohara and B.M. Gurupadayya, *Indian J. Pharm. Sci.*, **70**, 572 (2008); http://dx.doi.org/10.4103/0250-474X.45393.
39. 40 E.J. Kantorowski and M.J. Kurth, *Tetrahedron*, **56**, 4317 (2000); http://dx.doi.org/10.1016/S0040-4020(00)00218-0.
40. F. Abdulaziz Al-Omary, Ph.D. Thesis: Studies on Monocyclic β-Lactams, College of Pharmacy, King Saud University, p. 32 (2000).
41. C. Palomo, J.M. Aizpurua, I. Ganboa and M. Oiarbide, *Eur. J. Org. Chem.*, 3223 (1999); http://dx.doi.org/10.1002/(SICI)1099-0690(199912)1999:12<3223::AID-EJOC3223>3.0.CO;2-1.