Synthesis and Biological Evaluation of Some Pyrrolidine-2-one Derivatives

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ABSTRACT
In this research a number of pyrrolidine-2-one derivatives were prepared by lactamization of γ – butyrolactone (GBL) with hydrazine hydrate (80%) to produce (1-aminopyrrolidine-2-one) that undergoes several reactions to afford these derivatives that diagnosed by infrared, nuclear magnetic resonance and mass spectroscopy. Antibacterial activity has also been studied using some types of bacteria, some were found to have good antibacterial activity.

KEYWORDS: Pyrrolidine – 2- one; Biological activity; Lactamization.

INTRODUCTION
Pyrrolidine-2-one is so important heterocyclic compound which is found in natural and unnatural products. This fascinating compound has diverse pharmacological activities such as antibacterial, antifungal, anticancer and anticonvulsant [1]. Pyrrolidine-2-one is 5-membered lactam ring which has been of great interest in the curing of epilepsy, HIV, neurodegenerative disease and depression [2]. Pyrrolidine-2-one is colorless liquid that miscible with common organic solvents besides water [3]. Pyrrolidine-2-one can be synthesized by the reaction of ammonia (NH₃) with γ-butyrolactone (GBL) and also by partial hydrogenation of succinamide [4]. N-substituted pyrrolidine-2-one can be prepared by the condensation of primary amines and (GBL) (scheme 1). As long as the primary amine will stand up to the (200-300°C) temperatures necessary to dehydrate and cyclize the hydroxyl butyl amide intermediate, a wide variety of amines can be employed [5].Pyrrolidine-2-one wide solvent ability has found application in the pharmaceutical industry as a processing aid (Takayama et al., 1977) [6].

A new series of helicid–pyrrolidine 2-one analogues (Figure 1) were synthesized and examined for their anticancer effect against human skov3 cell. The results showed that these analogues exhibited high anticancer effect against this cell line (Jiang et al., 2015) [7].

The copolymer which consists of N-vinyl pyrrolidine-2-one (NVP) and acrylic acid (AA) was grafted with N-diethyl amino ethanol through acrylic acid group to form an ester (Figure 2). The antibacterial effect of this grafted copolymer was studied against Klebsiella aerogenes, Pseudomonas desmolyticum, Escherichia coli and staphylococcus aureus. The results showed...
considerable antibacterial effect against all bacteria used (Hemalatha et al., 2014) [8].

Mizushina et al. synthesized chemically epolactaene that is neurogenic substance in human neuroblastoma cells and studied the biological activity belonging to it in vitro. Epolactaene and its derivatives (Figure 3) selectively inhibited the activities of mammalian DNA polymerase (alpha and beta) and human DNA topoisomerase, with IC (50) values of 25, 94, and 10 µM, respectively [9].

Zhuang et al. prepared highly potent pyrrolidine-2-one derivatives with improved P53−MDM2 inhibitory activity and in vitro anti-proliferative potency [10]. Yang et al. investigated antimicrobial activity of 2-pyrrolidone-5-carboxylic acid (PCA) and found that this compound inhibited many spoilage bacteria, particularly Enterobacter cloacae and Pseudomonas fluorescens [11]. Sangnoi et al. prepared novel amino phenyl pyrrolidine-2-one and found that this compound exhibited selective inhibition against vancomycin-resistant Enterococcus faecalis (VRE) with the MIC of 5.97 m M. [12]. N-substituted pyrrolidine-2-one such as piracetam [13] or oxiracetam [14] is known as nootropic drug (Figure 4).

MATERIALS & METHODOLOGIES
The melting points were recorded in open capillary tubes using a Gallenkamp melting point apparatus and were left uncorrected. The FT-IR Spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer, utilizing KBr discs. The 1H-NMR Spectra of some prepared derivatives were recorded in DMSO or CDCL3 with TMS as internal standard on a Varian-Mercury 300 MHZ. Mass spectra recorded using (SHIMADZU model QP 1000EX using (SCI) mode.

Procedure for the Synthesis of 1-aminopyrrolidine-2-one (N1) [15]: Hydrazine hydrate ((80%) NH2NH2) (3.92 ml, 3.99 g., 10 mmol.) was added to (10.3 ml, 12.3 g., 10 mmol.) of GBL and the mixture refluxed for (24 hrs.) at 2200C. After which time, the mixture was cooled to room temperature. The white precipitate that observed upon cooling...
washed with petroleum ether and acetone then recrystallized from absolute C2H5OH. White solid (68%, 8.5 g.); m. p. (85-87°C); FT-IR ν (cm^-1): (3294 and 3203) (-NH2), (2964 and 2877) (C-H aliphatic), 1703 (C=O) lactam, 1635 (-NH) bending, 1H-NMR (CDCl3, 300 MHz) δ (ppm): 1.3(m, 2H, -CH2 aliphatic), 1.7(t, J = 6.5 Hz, 2H,-CH2 aliphatic), 2.1(t, J = 1.8 Hz, 2H,-CH2 aliphatic), 2.7(s,2H,-NH2). Mass, the molecular ion peak (M+, m/z) =100 and the base peak = 41.

General procedure for the synthesis of (N2-N4) [16]: Compound (N1) (1 g., 10 mmol.) was dissolved in an absolute C2H5OH (30 ml). Then, aromatic aldehyde (2-carboxaldehyde –thiophene) (1.12 g., 10 mmol.) or (N, N-dimethyl benzaldehyde) (1.49 g., 10 mmol.) or (p-chloro benzaldehyde) (1.40 g., 10 mmol.) was added in presence of (4 drops) of glacial CH3COOH and the mixture was refluxed for (4-7 hrs.). Afterwards; the mixture was cooled and filtered. The obtained solid was then recrystallized from absolute C2H5OH to produce the desired compound.

N2:1-[(E)-tiophene-2-ylmethylidine] amino) pyrrolidine-2-one: Yellow solid (52%, 1 g.); m. p. (145-147°C); FT-IR ν (cm^-1): (3055 and 3032) (C-H aromatic), 1678(C=O) lactam ring, 1600(C=N). Mass, the molecular ion peak (M+, m/z) =194 and the base peak = 137.

N3:1-[(E)-(4-chlorophenyl) methylidene] amino) pyrrolidine-2-one: Yellow solid (63%,1.39 g.); m. p. (158-160°C); FT-IR ν(cm^-1): 3018(C-H aromatic), 1678(C=O) lactam ring,1612(C=N),740(C-Cl), 1H-NMR(CDCl3, 300 MHz) δ (ppm):1.2(m,2H,-CH2 aliphatic), 1.8(t, J = 3.3 Hz, 4H,2(-CH2) aliphatic),6.9(d, J = 9.3 Hz, 2H,aromatic protons of benzene ring ),7.7(d, J = 9.9 Hz, 2H,aromatic protons of benzene ring), 8.5(s,1H,CH=N).

N4:1-[(E)-[4-dimethylamino] phenyl] methylidene) pyrrolidine-2-one: Orange solid (81%, 1.87 g.); m. p. (194-196°C); FT-IR ν (cm^-1): 3006(C-H aromatic),1686(C=O) lactam ring,1594(C=N), 1H-NMR(CDCl3, 300 MHz) δ (ppm): 0.9(m,2H,-CH2 aliphatic),1.5(t, J = 5.2 Hz,4H,2(-CH2) aliphatic),3.3(s,6H, -N(CH3)2),6.8(d, J = 11.2 Hz, 2H,aromatic protons of benzene ring). 7.9(d, J = 10.2 Hz, 2H,aromatic protons of benzene ring), 8.7(s,1H,CH=N).

General Procedure for the synthesis of (N5 and N6) [17]: Compound (N2) (1.94 g., 10 mmol.) or (N3) (2.22 g., 10 mmol.) was dissolved in dry C6H6 (20 ml). Then, phthalic anhydride (1.48 g., 10 mmol.) or maleic anhydride (0.98 g., 10 mmol.) was added to the reaction mixture and the mixture was refluxed on water bath for about (4-5 hrs.). At the end of the reaction, the mixture was cooled and filtered. The obtained solid was then recrystallized from absolute C2H5OH to afford the desired compound.

N5:4-(2-oxopyrrolidin-1-yl)-3-(thiophene-2-yl)-3,4-dihydro-2,4-benzoxazepin-1,5-dione: Light brown solid (67%,2.29 g.); m. p. (108-110°C); FT-IR ν (cm^-1): 3016(C-H aromatic),(1731 and 1680) (C=O) ester and amide group of oxazepine ring respectively,1692(C=O) lactam ring, 1H-NMR (CDCl3, 300 MHz) δ (ppm): 1.3(m, 2H, -CH2 aliphatic),5.4(s,4H,2(-CH2 aliphatic),5.5(s,1H,C-H aliphatic of oxazepine ring),7.4(t, J = 6.2 Hz, 1H, aromatic proton of thiophene ring),7.8(d, J = 7.5 Hz, 2H,aromatic protons of thiophene), 8.2( m,4H, aromatic protons of benzene ring).

N6:2-(4 -chlorophenyl)-3-( 2-oxopyrrolidin-1-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione: Creamy solid (67%, 2.14 g.):m. p. (178-180°C); FT-IR ν(cm^-1):3095(C-H aromatic), (1714 and 1670) (C=O) ester and amide group of oxazepine ring respectively, 1681(C=O) lactam ring, 1H-NMR (DMSO, 300 MHz) δ (ppm): 0.9(m, 2H, -CH2 aliphatic),1.3(m,4H,2(-CH2 aliphatic),6.2(s,1H,C-H aliphatic of oxazepine ring), 6.6(m,4H,aromatic protons interacted with vinyl protons of oxazepine ring ),7.0(d, J = 6.5 Hz, 2H,aromatic protons).

Procedure for the Synthesis of (N7) [18]: Compound (N4) (2.3 g., 10 mmol.) was dissolved in dry dioxane (30 ml). Then, thioglycolic acid (2.31 g., 10 mmol.) was added to the reaction mixture in presence of anhydrous ZnCl2 and the mixture was refluxed for (10 hrs.). At the end of the reaction, excess of solvent was removed by vaporization and the residue was poured onto crushed ice and then filtered. The sticky solid was recrystallized from absolute C2H5OH to afford the desired compound.

N7:2-[4 – (dimethylamino) phenyl]-3-(2-oxopyrrolidin-1-yl)-1, 3-thiazolidin-4-one: Yellow solid (63%, 1.9 g.); m. p. (240-242°C);
FT-IR ν (cm⁻¹): 3074(C-H aromatic), 1703(C=O lactam), 1680(C=O) thizolidin-4-one ring, ¹H-NMR (DMSO, 300 MHz) δ (ppm): 1.5(m,2H,-CH₂ aliphatic), 1.8(t, J = 4.3 Hz, 4H,-CH₂ aliphatic), 2.1(s,3H,C-H aliphatic of (thizolidin-4-one ring ), 3.3(s,6H, N(CH₂)₃), 7.6(d, J = 6.1 Hz, 2H, aromatic protons of benzene ring), 8.5(d, J = 6.3 Hz, 2H, aromatic protons of benzene ring).

Procedure for the Synthesis of (N8) [19]: Compound (N1) (1 g., 10 mmol.) was dissolved in DMF (20 ml). Then, ethyl acetocetate (1.3 g, 10 mmol.) was added to the reaction mixture and refluxed for (10 hrs.). Afterwards; the mixture was cooled to room temperature and filtered. The solid was recrystallized from absolute C₂H₅OH to afford the desired compound.

N8:3-oxo-N-(2-oxopyrrolidin-1-yl) butanamide: Light brown solid (81%, 1.49 g.); m. p. (119-121°C); FT-IR ν (cm⁻¹): 3255 (-NH), 1721(C=O) lactam ring, 1662(C=O) amide group, ¹H-NMR (DMSO, 300 MHz) δ (ppm): 1.4(m, 2H, -CH₂ aliphatic), 1.7(t, J = 5.4 Hz, 2H, -CH₂ aliphatic), 2.2(t, J = 5.1 Hz, 2H, -CH₂ aliphatic), 2.8(s,3H, -CH₃ aliphatic), 3.2(s,2H, -CH₂ aliphatic)5.6(s, 1H, -NHCO). Mass, the molecular ion peak (M+, m/z) = 184 and the base peak = 49.

Procedure for the Synthesis of (N9) [20]: Compound (N8) (1.84 g, 10 mmol.) was dissolved in an absolute C₂H₅OH (20 ml). Then, anhydrous CH₂COONH₄ (0.77 g, 10 mmol.), p-chloro benzaldehyde (1.4 g, 10 mmol.) and ethyl cyanoacetate (1.13 g, 10 mmol.) were added to the reaction mixture and mixture refluxed for (5 hrs.). Afterwards; the reaction mixture was cooled to room temperature and filtered. The formed solid which obtained on cooling was recrystallized from absolute C₂H₅OH to afford the desired compound.

N9:2-[4-(4-chlorophenyl)5-cyano-6-oxo-1,6-dihydropyridin-2-yl]-N-(2-oxopyrrolidin-1-yl)acetamide: Light brown solid (63%, 2.3 g.); m. p. (200-202°C); FT-IR ν (cm⁻¹): 3321(-NH), 2214(CN),1716(C=O) lactam, 1695(C=O) 2-pyridone ring, 1654(C=O) amide, 831 (Para sub. benzene), 756 (C-Cl). Mass, the molecular ion peak (M+, m/z) = 370 and the base peak = 115.

Procedure for the Synthesis of (N10) [21]: Compound (N1) (1 g., 10 mmol.) was dissolved in benzene (30ml). Then, chloro acetyl chloride (0.78ml, 10 mmol.) was added drop wise to the reaction mixture and the mixture was refluxed for (5 hrs.). Afterwards; the reaction mixture was cooled to room temperature and excess of the solvent was evaporated under reduced pressure. The obtained precipitate was filtered off and recrystallized from absolute C₂H₅OH to give the desired compound.

N10:2-chloro-N (2-oxopyrrolidene-1-yl): Creamy white solid (73%, 1.2 g.); m. p. (128-130°C); FT-IR ν (cm⁻¹): 3352(-NH), 1691(C=O) lactam, 1674(C=O) amide, 812(C-Cl), ¹H-NMR (DMSO, 300 MHz) δ (ppm): 1.6(m, 2H, -CH₂ aliphatic), 3.2(t, J = 3.1 Hz, 2H, -CH₂ aliphatic), 4.4(s, 2H, C=O-CH₂-Cl), 5.8(s, 1H, -NHCO).

General procedure for the Synthesis of (N11 and N12) [22]: Compound (N10) (1.76 g., 10 mmol.) was dissolved in an absolute C₂H₅OH (20ml). Then, thiourea (0.76 g., 10 mmol.) or thiosemicarbazide (0.91 g., 10 mmole,) was added to the reaction mixture and the mixture refluxed for (12hrs). Afterwards; the mixture was poured onto ice water and filtered. The obtained solid was washed with 2% NaHCO₃ solution and then recrystallized from absolute C₂H₅OH to afford the desired compound.

N11:1-[{(2-amino, 3-thiazol-4-yl) amino}pyrroloidine-2-one: Yellowish white solid (63%, 1.24 g.); m. p. (194-196°C); FT-IR ν (cm⁻¹): 3311 and 3212 (−NH₂), 3210(−NH), 1698 (C=O) lactam ring. Mass, the molecular ion peak (M+, m/z) = 198 and the base peak = 156.

N12:1-{(2-hydrasynyl-1,3-thiazol-4-yl)amino}pyrroloidine-2-one: Yellowish white solid (81%, 1.72 g.); m. p. (245-247°C); FT-IR ν (cm⁻¹): (3328 and 3267) (−NH₂), 3209(−NH), 1693 (C=O) lactam, ¹H-NMR(CDCl₃, 300 MHz) δ (ppm): 1.0 (m, 2H, -CH₂ aliphatic ), 1.3 (m, 2H, -CH₂ aliphatic), 1.8 (t, J = 4.3 Hz, 2H, -CH₂ aliphatic), 6.60 (s,3H, -NNH₂), 7.0 (s,2H, (-NH and proton of thiophene ring)). Mass, The molecular ion peak (M+, m/z) = 213 and the base peak = 48.

Procedure for the Synthesis of (N13) [23]: Compound (N11) (1.98 g, 10 mmol.) was dissolved in an absolute C₂H₅OH (20 ml). Then, diethyl oxalate (1.46 g, 10 mmol.) was added to the reaction mixture in presence of a few drops of CH₃COOH acid and the mixture was refluxed for (9 hrs.). Afterwards; the reaction mixture was...
cooled to room temperature and filtered. The solid obtained was recrystallized from absolute C₂H₅OH to afford the desired compound.

**N13:3-[(2-oxopyrrolidin-1-yl) amino] imidazole [2, 1-b] [1, 3] thiazole-5, 6-dione:** White solid (78%, 1.87 g.); m. p. (232-234°C); FT-IR ν (cm⁻¹): 3282(-NH), 1695(C=O) lactam ring, (1690 and 1680) (C=O) imidazole -4, 5-dione) ring, 1H-NMR (CDCl₃, 300 MHz) δ (ppm):1.2(m,2H, -CH₂ aliphatic), 2.3(t, J = 7.1 Hz, 2H, -CH₂ aliphatic), 2.8(t, J = 6.4 Hz, 2H, -CH₂ aliphatic), 7.3(s,1H, aromatic proton of thiophene ring), 7.8(s,2H, -NH₂). Mass, the molecular ion peak (M+, m/z) =240 and the base peak = 239.

**Procedure for the Synthesis of (N14) [24]:** Compound N1 (1 g., 10 mmol.) was dissolved in dry pyridine (25 ml). Then, p- nitro benzoyl chloride (1.85 g, 10 mmol.) was added to the reaction mixture and the mixture refluxed for (4 hrs.). Afterwards; the reaction mixture was cooled to room temperature and filtered. The obtained solid was washed with petroleum ether and recrystallized from (C₂H₅OH: water 10:1) mixture to afford the desired compound.

**N14:4-nitro-N-(2-oxopyrrolidin-1-yl) benzamide:** Light orange solid (63%, 1.56 g.); m. p. (220-222°C); FT-IR ν (cm⁻¹): 3111(-NH), 1693 (C=O) lactam ring, 1653 (C=O) amide, (1510 and 1348) (-NO₂), 871 (Para sub. benzene). Mass, the molecular ion peak (M+, m/z) =249 and the base peak = 164.

**ANTIBACTERIAL ACTIVITIES**

Derivatives of pyrrolidine-2-one were estimated against four bacteria (Escherichia coli, Staphylococcus aureus, Staphylococcus epidermis and Klebsiella sp.) using in vitro antibacterial testing. Agar well diffusion was the method used to determine the antibacterial activity. Dimethyl sulfoxide (DMSO) utilized as a control and the tests were performed at concentrations of (500 and 1000 µg /ml) using (DMSO) as solvent. Amoxicillin was the antibacterial agent for comparison. The bacteria were sub cultured in agar. The plates were incubated at 37 °C and checked after (24 hrs.).

**RESULTS AND DISCUSSION**

The preparation of (N1) through lactamization of GBL with hydrazine hydrate (80%) was approved by FT-IR, ¹H-NMR and Mass spectroscopy. The FT-IR (cm⁻¹) spectra of compound (N1) showed disappearance of stretching vibration band at 1760 which was belong to (C=O) of GBL (Figure 5) and appearance of new band at 1703 due to stretching vibration of (C=O) of lactam ring beside appearance of new bands at 3294 and 3203 that belong to symmetric and asymmetric stretching vibrations of (-NH₂) (Figure 6).
Table 1. Antibacterial activities for compounds N1- N14 against (E.coli)and (St.aur.)

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<th>Escherichia coli</th>
<th>Staphylococcus aureus</th>
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<td></td>
<td>Conc. (µg /ml)</td>
<td>Inhibition zone diameter (mm)</td>
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<tr>
<td>Comp. no.</td>
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<td>N1</td>
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<tr>
<td>Amoxicillin</td>
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Table 2. Antibacterial activities for compounds N1- N14 against (st. epi.) and (kleb. Sp.)

<table>
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<th>Staphylococcus epidermis</th>
<th>Klebsiella sp.</th>
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<td>Conc. (µg /ml)</td>
<td>Conc. (µg /ml)</td>
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<td>Inhibition zone diameter (mm)</td>
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<td>Comp. no.</td>
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<td>N2</td>
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<td>N3</td>
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<td>N4</td>
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</table>

Scheme 2. Synthesis routes for compounds N1 - N7.

The molecular ion peak in Mass spectra of compound (N1) showed (M+, m/z) =100 which was corresponded to its molecular weight, while the base peak = 41. Schiff bases (N2-N4) were synthesized by the reaction of compound (N1) with some aromatic aldehydes in absolute C2H5OH. The formation of Schiff bases has been proved by their FT-IR and some by 1H-NMR or Mass spectroscopy. The FT-IR (cm⁻¹) spectra of all synthesized Schiff bases showed presence of stretching vibration bands of imine groups (N=CH) at the range (1594-1612) besides disappearance of stretching vibration bands of (-NH2) that belonged to compound (N1). The FT-IR (cm⁻¹) spectra of compound (N2) is shown in (Figure 8). The molecular ion peak in Mass
spectra of compound (N2) showed (M+, m/z) = 194 which was corresponded to its molecular weight, while base peak = 137. The \( ^1H\)-NMR (ppm) spectra of compound (N3) showed multiplet and triplet at 1.2 and 1.8 respectively due to aliphatic protons of lactam ring and also showed two doublet peaks at (6.9 and 7.7) due to aromatic protons (Para sub. benzene) and singlet at 8.5 due to the proton of imine group (-CH=N).

The \( ^1H\)-NMR (ppm) spectra of compound (N4) showed multiplet and triplet at 0.9 and 1.5 respectively due to aliphatic protons of lactam ring and also showed singlet at 3.3 due to (6H, -N(CH\(_3\))\(_2\)), two doublet peaks at (6.8 and 7.9) due to aromatic protons (Para sub. benzene) and singlet at 8.7 due to the proton of imine group (-CH=N) (Figure 9).

Cyclization of Schiff bases (N2 and N3) with some anhydrides in benzene as solvent afforded oxazepines (N5 and N6), the structures of these compounds were approved by FT-IR and \( ^1H\)-NMR. The FT-IR (cm\(^{-1}\)) spectra of compounds (N5 and N6) showed appearance of carbonyl stretching vibration bands at the range (1714-1731) and (1670-1680) due to ester and amide carbonyl groups of oxazepine rings, respectively besides the stretching vibration bands of carbonyl groups of lactam rings that appeared at the range (1681-1692). The \( ^1H\)-NMR (ppm) spectra of compound (N5) showed two multiplet peaks at 1.3 and 2.8 due to aliphatic protons of lactam ring and also showed singlet at 5.5 due to aliphatic proton of oxazepine ring (1H, CH), triplet at 7.4 due to one proton of thiophene ring, doublet at 7.8 due to the other two protons of thiophene ring and multiplet at 8.2 due to aromatic protons of benzene ring. The \( ^1H\)-NMR (ppm) spectra of compound (N6) showed two multiplet peaks at 0.9 and 1.3 due to aliphatic protons of lactam ring and also showed singlet at 6.2 due to aliphatic proton of oxazepine ring (1H, CH), multiplet at 6.6 due to (two aromatic protons of benzene ring...
interacted with two vinylic protons of oxazipine ring) and doublet at 7.0 due to other two aromatic protons of benzene ring. Cyclization of Schiff base (N4) with thioglycolic acid in dry dioxan afforded compound (N7) which was confirmed by its FT-IR and \(^1\)H-NMR spectroscopy. The FT-IR (cm\(^{-1}\)) spectra of compound (N7) showed presence of carbonyl stretching vibration bands at 1703 and 1680 due to carbonyl groups of lactam and (thizolidin-4-one) ring, respectively. The \(^1\)H-NMR (ppm) spectra of compound (N7) showed multiplet and triplet at 1.5 and 1.8 respectively due to aliphatic protons of lactam ring and also showed two singlet peaks at 2.1 and 3.3 due to aliphatic protons of ((-CH\(_2\)) and (–CH) of (thizolidin-4-one) ring) and aliphatic protons of (-N (CH\(_3\))\(_2\)), respectively and also showed two doublet peaks at 7.6 and 8.5 due to aromatic protons of Para substituted benzene. The formation of compound (N8) approved by FT-IR, \(^1\)H-NMR and Mass spectroscopy. The FT-IR (cm\(^{-1}\)) spectra of compound (N8) showed new bands at 1721 and 1662 due to (C=O) of ketone and amide groups, respectively and disappearance of stretching vibration bands of (-NH\(_2\)) that belonged to lactam ring of compound (N1),while the \(^1\)H-NMR (ppm) spectra of this compound showed multiplet, triplet and another triplet at 1.4,1.7 and 2.2 respectively due to aliphatic protons of lactam ring and also showed singlet peaks at 2.8,3.2 and 5.6 due to aliphatic protons of (-CH\(_3\)),((-CH\(_2\)) between two carbonyl groups of amide and ketone) and (1H,-NHCO), respectively.

Mass spectra of compound (N10) showed the molecular ion peak (M+, m/z) = 184 which was corresponded to its molecular weight, while the base peak = 49, see (Figure 10). The FT-IR (cm\(^{-1}\)) spectra of compound (N9) approved its formation by the presence of very distinctive sharp band at 2214 due to (-CN) besides presence of new bands at 1695 due to (2-pyridone ring), 1654 due to (C=O) of amide group, 1716 due to (C=O) lactam, 831 due to (Para sub. benzene) and 756 due to (C-Cl), see (Figure 11). Mass spectra of compound (N11) showed molecular ion peak (M+, m/z) =370 which was corresponded to its molecular weight, while base peak = 115.

The formation of compound (N10) was confirmed by FT-IR and \(^1\)H-NMR spectroscopy. The FT-IR (cm\(^{-1}\)) spectra of compound (N10) showed disappearance of stretching vibration bands of (-NH\(_2\)) that belonged to lactam ring of compound (N1) and appearance of new bands at 3352 due to (-NH) of amide group, (1691 and 1674) due to (C=O) of lactam and amide groups, respectively and 812 due to (C-Cl). The \(^1\)H-NMR (ppm) spectra of compound (N10) showed multiple, triplet and another triplet at 1.6, 2.2 and 2.8 respectively due to aliphatic protons of lactam ring and also showed two singlet peaks at 4.4 and 5.8 due to (2H,C=O-CH\(_2\)-Cl) and (1H,-NHCO), respectively. Compounds (N11 and N12) were confirmed by their FT-IR, \(^1\)H-NMR and Mass spectroscopy. The FT-IR(cm\(^{-1}\)) spectra of compounds (N11 and N12) showed new bands at the ranges (3209-3210) and (3311-3328) due to stretching vibration bands of (-NH) and (-NHNH\(_2\)), respectively. Mass spectra of compound (N11) showed molecular ion peak (M+, m/z) =198 which was corresponded to its molecular weight, while base peak = 156. The \(^1\)H-NMR (ppm) spectra of compound (N12) showed multiplet, multiplet and triplet at 1.0,1.3 and 1.8.
respectively due to aliphatic protons of lactam ring and also showed two singlet peaks at 6.60 and 7.0 due to (3H of -NHNH₂) and (2H, -NH and proton of thiophene ring), respectively (Figure 12). The Mass spectra of compound (N12) showed molecular ion peak (M+, m/z) =213 which was corresponded to its molecular weight, while the base peak = 48.

Figure 12. ¹H-NMR of compound N12.

Compound (N13) was confirmed by FT-IR, ¹H-NMR and Mass spectroscopy. The FT-IR (cm⁻¹) spectra of compound (N13) showed bands at 3282 due to stretching vibration of (-NH) and (1695, 1690 and 1680) due to stretching vibration bands of carbonyl groups of lactam ring and for the two carbonyl groups of (imidazole-4, 5-dione) ring, respectively. The ¹H-NMR(ppm) spectra showed multiplate, triplet and another triplet at 1.2, 2.3 and 2.8 respectively due to aliphatic protons of lactam ring and also showed two singlet peaks at 7.3 and 7.8 due to (1H, aromatic proton of thiophene ring) and (2H,-NH₂), respectively. The Mass spectra of compound (N13) showed molecular ion peak (M+, m/z) =240 which was corresponded to its molecular weight, while the base peak = 239, see (Figure 13).

Figure 13. Mass spectra of compound N13.

ANTIBACTERIAL ACTIVITIES

We see from Table 1 and 2 that all prepared compounds have good inhibition against all or some bacterial species, except (N2, N6 and N10) that show no inhibition at all. Compounds N5, N7, N9, N11, N12, N13 and N14 showed good inhibition against (E. coli). Compounds N1, N4, N7, N8, N9, N11, N12 and N13 showed good inhibition against (St. aur.). Compounds N1, N7, N9, and N11 and N13 showed good inhibition against (St. epi.). Compounds N3, N4, N5, N7, N9, N11, N13 and N14 showed good inhibition against Kleb. sp., while compounds N7, N9, N11 and N13 have good inhibition against all selected bacteria.

CONCLUSIONS

Pyrrolidine–2–one derivatives were synthesized and characterized by spectral data. Their antibacterial activities tested against four types of bacteria namely: S. epi, S. aur. as (G+), E. coli and Kleb. sp. as (G-). Many of these derivatives have good inhibition against some or all selected bacteria. Some of these derivatives show no inhibition at all.
REFERENCES


