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# Synthesis of Some New Derivatives of Pyrrolidine-2-one and Studying Their Antibacterial Potentials

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K E Y W O R D S

Pyrrolidine-2-one,
Lactamization,
Biological activity.

A B S T R A C T

*New derivatives of pyrrolidine-2-one have been synthesized through lactamization of γ –butyrolactone (GBL) by hydrazine hydrate (80%), ethylene diamine and ethanol amine to afford compounds (1-aminopyrrolidin-2-one), (1-(2-aminoethyl)pyrrolidine-2-one) and (1-(2-hydroxyethyl)pyrrolidine-2-one), respectively. Compound (1-aminopyrrolidin-2-one) underwent several reactions to synthesize the rest of these derivatives. All synthesized compounds were approved by their FT-IR, 1H-NMR and some by Mass spectra. The biological activities of these derivatives were evaluated against Escherichia coli and Staphylococcus aureus. Many of these derivatives showed moderate biological activity against one or both kind of bacteria in comparison to amoxicillin and some showed no biological activity at all.*

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## 1. INTRODUCTION

Pyrrolidine-2-one nucleus is one of the most important heterocyclic compounds indicating notable pharmaceutical effects and considered to be a versatile lead compound for designing powerful bioactive agents. This fascinating group of compounds has diverse pharmacological activities such as antibacterial, antifungal, anticancer and anticonvulsant [1]. Pyrrolidine-2-one is a five membered lactam ring (Figure 1) which is a colorless liquid that miscible with water and most organic solvents [2].

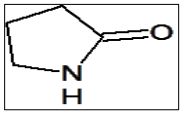
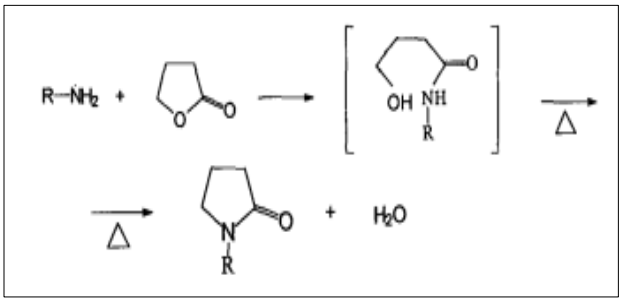



**Figure 1: Structure of pyrrolidine-2-one**

In this regard, the existence of (5-lactams or - Lactams) in medications and natural products has gained considerable attention for the expansion of novel methodologies of their synthesis. The various reactions of pyrrolidine-2-one offer great scope in the field of medicinal chemistry. Pyrrolidine-2-one can be synthesized by the reaction of ammonia ($NH_3$) with γ-butyrolactone (GBL) and by partial hydrogenation of succinamide [3]. 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 [4].




**Scheme 1: Preparation of N-substituted pyrrolidine-2-one**

Yang *et al* synthesized a series of novel 2-pyrrolidone-fused (2-oxoindolin-3-ylidene) methyl pyrrole derivatives as potential multi-target tyrosine kinase receptor inhibitors. The target compounds were obtained by condensation of 5-substituted oxindoles with N-substituted 2-pyrrolidone aldehyde in satisfactory yields [5]. N-vinyl pyrrolidine-2-one (NVP) has been extensively studied for usages in different fields as a surfactant, reducing agent, shape controlling agent and dispersant in nanoparticle synthesis and their self-assembly [6]. In recent years, poly vinyl pyrrolidine-2-one (PVP) has received special attention because of its high chemical stability, non-toxicity, and excellent solubility in many polar solvents. Metals stabilized by PVP not only exhibit a high degree of dispersibility against agglomeration, but the modification by this polymer reduces the toxicity of magnetic nano-materials, which are suitable for application in the biomedical field [7]. N-substituted-5-methyl pyrrolidine-2-one (Figure 2) were synthesized in one pot process starting from ethyl levulinate and nitro compounds in the presence of nano-sized platinum based catalyst [8].

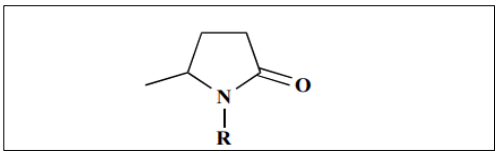
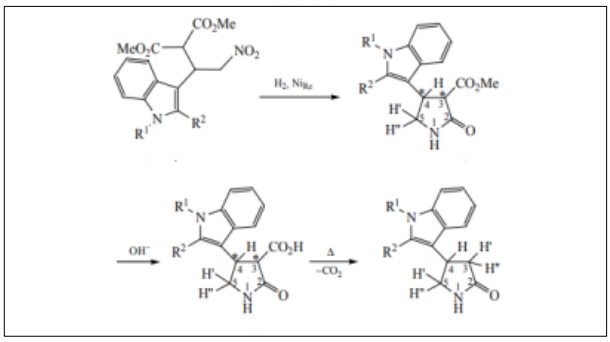


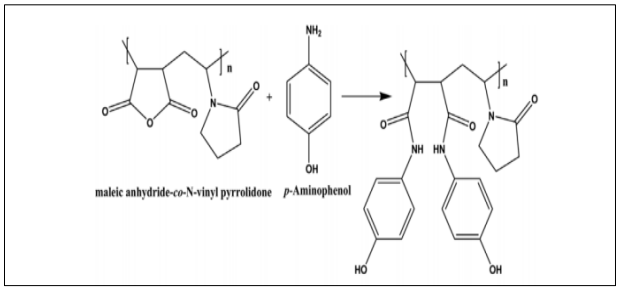

**Figure 2: N-substituted-5-methyl- pyrrolidine-2-one**
**Where R =4CN-Ph-NO2, 4CHO-Ph-NO2, 4MeO-Ph-NO2, 4Cl-Ph-NO2**

Ostroglyadov *et al* synthesized 4-(Indol-3-yl) - pyrrolidine-2-one derivatives via sequential hydrogenation of indole-containing esters of 4-nitrobutanoic acid, alkaline hydrolysis of the resulting 3-methoxycarbonyl- pyrrolidine-2-one, and decarboxylation of the isolated 2-pyrrolidone-3-carboxylic acids (scheme 2) [9].



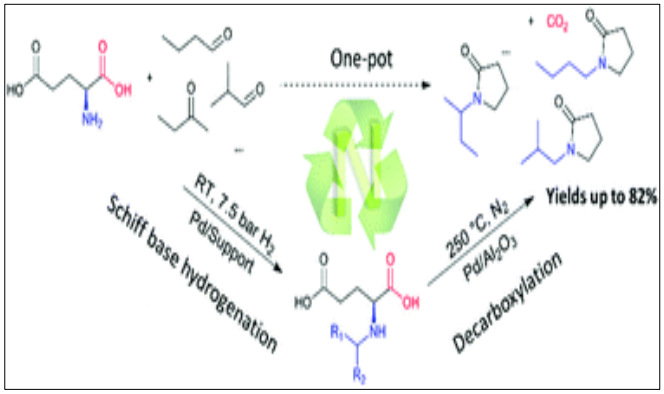

**Scheme 2: Indole-containing derivatives of pyrrolidine-2-one**

A. Nagaraja *et al* reported synthesis and characterization of antimicrobial functionalized poly (Maleic anhydride-co-N-vinyl pyrrolidine-2- one -g-aminophenol) with efficient microbial growth inhibiting property (scheme 3). By understanding the thermal stability and degradation, the polymer can be listed in the class of high-performance polymers. Even though the polymer showed comparatively less activity towards *E. coli* and *C. albicans*, it showed better activity towards *S. aureus* and *M. smegmatis*. Additionally, the polymer showed excellent film forming property. By considering these properties, the polymer can be exploited in paint, food packaging industries etc. [10].




**Scheme 3: Maleic anhydride-co-N-vinyl pyrrolidine-2-one -g-aminophenol (MA-co-NVP-g-AP)**

Schouwer *et al* reported less toxic bio-based two-step chemo-catalytic system for the synthesis of a broad range of N-alkyl- pyrrolidine-2-one starting from glutamic acid and C3–C5 carbonyl compounds. In the first step N-mono-alkylated derivatives of glutamic acid were synthesized in high yields (>85%) by a mild and efficient Pd-catalyzed reductive N-alkylation. Subsequently, thermally induced lactamization to the corresponding N-alkyl pyroglutamic acid followed by Pd-catalyzed decarboxylation at 250 °C under inert atmosphere resulted in N-alkyl- pyrrolidine-2-one (scheme 4) [11].




**Scheme 4: Bio-based two-step chemo-catalytic system for the synthesis of a broad range of N-alkyl-pyrrolidine-2-one**

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 3).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 [12].

Jiang *et al* synthesized a new series of helicid–pyrrolidine 2-one analogues (Figure 4) and examined them for their anticancer effect against human skov3 cell. The results showed that these analogues exhibit high anticancer effect against this cell line [13].

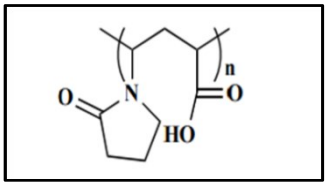


**Figure 3: Copolymer of N-vinyl Pyrrolidine-2-one (NVP) and acrylic acid (AA)**

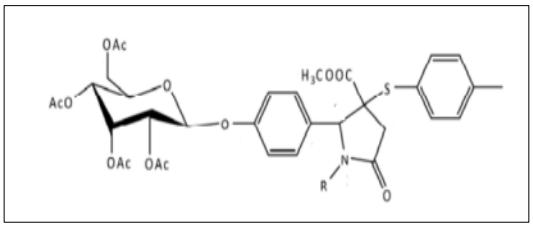



**Figure 4: Helicid–pyrrolidine- 2-one analogues**

Zhuang *et al* prepared highly potent pyrrolidine-2-one derivatives with improved P53−MDM2 inhibitory activity and in vitro anti-proliferative potency [14]. After the observation of the increasing bacterial resistance toward traditional β-lactam antibiotics, several groups have recently reported on the synthesis and antibacterial activity of compounds in which the β -lactam ring has been replaced by a chemically activated γ -lactam ring.

The aim of this study is to assess the effect of the new prepared pyrrolidine-2-one derivatives on the inhibition of Escherichia coli and Staphylococcus aureus and thus to explore the possibility of utilizing them as antibiotics.

## 2. MATERIALS AND METHODS

### *I. Apparatus*

The melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and were left uncorrected. FT-IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer, using KBr discs. $^1$H-NMR spectra of some prepared derivatives were recorded in DMSO or $CDCL_3$ with TMS as internal standard on a Varian-Mercury 300 MHz spectrometer. Mass spectra recorded by SHIMADZU model QP 1000EX using (SCI) mode. The starting chemicals were obtained from BDH, Sigma Aldrich and Fluka and were used as received without further purification.

### *II. Synthesis procedures*

**General procedure for the synthesis of compounds (N1-N3) [15]:** A mixture of (0.01mol.) of GBL and (0.01 mol.) of 80% hydrazine hydrate or (0.01 mol.) of ethylene diamine or (0.01 mol.) of ethanol amine was refluxed for (24 hrs.) in an oil bath at $220^0$C and afterwards a precipitate is observed. Each washed with petroleum ether and acetone and then recrystallized from ethanol.

**1-aminopyrrolidin-2-one (N1):** Yield (68%), m. p. (85-87°C), color (white), M. Wt. (100),FT-IR ν ($cm^{-1}$): (3294 and 3203) due to (sym. and asy.) stretching vibrations of (-$NH_2$), (2964 and 2877) due to stretching vibrations of (-CH aliph.) ,1703 due to stretching vibration of (C=O) of lactam ring and 1635 due to bending vibration of (-$NH_2$), $^1$H-NMR (ppm):1.3(m,2H,-$CH_2$ aliph.), 1.7 (t, 2H, -$CH_2$ aliph.), 2.1(t, 2H, -$CH_2$ aliph.) and 2.7(s,2H,-$NH_2$).Mass, the molecular ion peak (M+ , m/z) =100.

**1-(2-aminoethyl) pyrrolidine-2-one (N2):** Yield (63%), m. p. (130-132°C), color (white), M. Wt. (128),FT-IR ν ($cm^{-1}$): (3344 and 3207) due to (sym. and asy.) stretching vibrations of (-$NH_2$), (2926 and 2877) due to stretching vibrations of (-CH aliph.) and 1699 due to stretching vibration of (C=O) of lactam ring ,$^1$H-NMR (ppm): 1. 7 (m, 2H ,-$CH_2$ aliph. of lactam ring), 2.2 (t, 4H ,2(-$CH_2$) aliph. of lactam ring), 3. 0 (s, 4H ,-$CH_2CH_2$- aliph. bonded to nitrogen of lactam ring) and 3.3 (s, 2H ,-$NH_2$) .Mass ,the molecular ion peak (M+ , m/z) =128.

**1-(2-hydroxyethyl) pyrrolidine-2-one (N3):** Yield (58%), m. p. (20 - 22°C), color (yellowish white), M. Wt. (129),FT-IR ν ($cm^{-1}$): 3410 due to stretching vibration of (-OH), (2982 and 2854) due to stretching vibrations of (-CH aliph.) and 1718 due to stretching vibration of (C=O) lactam,$^1$H-NMR (ppm): 1.4 (m, 2H ,-$CH_2$ aliph. of lactam ring), 1. 8 (t, 4H, 2(-$CH_2$ aliph.) of lactam ring), 2.2 (s, 4H,-$CH_2CH_2$- aliph. bonded to nitrogen of lactam ring of lactam ring) and 3.20 (s, 1H, -OH).Mass, the molecular ion peak (M+, m/z) =129.

**General procedure for the synthesis of compounds (N4-N7)[16]**: To a solution of (0.01 mol.) of compound (N1) in (25 ml) absolute ethanol ,(0.01 mol.) of carbonyl compounds (pyrrole -2-carboxaldehyde or p-chloro benzaldehyde or p-nitro benzaldehyde or 2-bromo-4′-phenylacetophenone) was added in the presence of (4 drops) of glacial acetic acid and the mixture was refluxed for (3- 6 hrs.) .After cooling, the mixture was filtered and the solid recrystallized from ethanol to afford the wanted compound.

**1-{[(E)-1 H-pyrrol-2-ylmethylidene]amino}pyrrolidine-2-one (N4):** Yield (50%),m. p. (150-152°C),color (yellow),M. Wt. (177),FT-IR ν ($cm^{-1}$): 3109 due to stretching vibration of (-NH-) of pyrrole ring, 2845 due to stretching vibration of (-CH aliph.),1705 due to stretching vibration of (C=O) of lactam ring and 1606 due to stretching vibration of (C=N), $^1$H-NMR (ppm): 1.3 (m, 2H ,-$CH_2$ aliph.), 2.0 (m, 4H ,2(-$CH_2$) aliph.), 7.10 (m,3H,pyrrol ring) , 7.8 (s, 1H ,-NH pyrrole ring) and 8.80 (s, 1H ,N=CH) .Mass ,the molecular ion peak (M+ , m/z) =177.

**1-{[(E)-(4-chlorophenyl) methylidene]amino}pyrrolidine-2-one (N5):** Yield (54%),m. p. (158-160°C),color (yellow),M. Wt. (222),FT-IR ν ($cm^{-1}$): (2970 and 2955) due to stretching vibrations of (-CH aliph.),1672 due to stretching vibration of (C=O) of lactam ring and 1608 due to stretching vibration of (C=N), $^1$H-NMR (ppm): 0.9 (m, 2H ,-$CH_2$ aliph.), 1.2 (m, 4H ,2(-$CH_2$) aliph.), (7.4 and 7.8) (d. ,d. Para sub. benzene) and 8.70 (s, 1H ,N=CH).

**1-{[(E)-(4-nitrophenyl) methylidene]amino}pyrrolidine-2-one (N6):** Yield (83%),m. p. (215-217°C),color (yellow),M. Wt. (233),FT-IR ν ($cm^{-1}$): (2902 and 2816) due to stretching vibrations of (-CH aliph.), 1660 due to stretching vibration of (C=O) lactam ring and 1591 due to stretching vibration of (C=N), $^1$H-NMR (ppm): 0.8 (m, 2H ,-$CH_2$ aliph.) , 1.4 (t, 2H , -$CH_2$ aliph.), 2.0 (t, 2H ,-$CH_2$ aliph.), (7.8 and 8.2)(d. ,d. Para sub. benzene) and 8.6 (s, 1H,N=CH).

**1-{[(1Z)-1-(biphenyl-4-yl)-2-bromoethylidine]amino}pyrrolidine-2-one (N7 ):** Yield (78%),m. p. (85-87°C),color (orange),M. Wt. (357),FT-IR ν ($cm^{-1}$): 2955 due to stretching vibration of (-CH aliph.), 1708 due to stretching vibration of (C=O) of lactam ring and 1591 due to stretching vibration of (-C=N), $^1$H-NMR (ppm) :1.0 (m, 2H ,-$CH_2$ aliph.) , 1.3 (t, 4H ,2(-$CH_2$) aliph. ), 3.1 (s,2H,-$CH_2$ bonded to bromide atom ) and 7.0-8.0 (m, aromatic protons).

**Procedure for the synthesis of compound 2-(4-chlorophenyl)-2\, 5-dioxo-1, 1 \ -bipyrrolidine-3-carboxylic acid (N8) [17]:** (0.01mol.) of compound (N5) and (0.01 mol.) of succinic anhydride mixed together in (25 ml) of chloroform with heating in water bath at temperature range (55-60˚C) for about (18 hrs.) with continuous stirring. Solvent then was evaporated, formed solid was filtered and recrystallized from benzene ,yield (70%), m. p. (210-212°C),color (yellow), M. Wt. (321) ,FT-IR ν ($cm^{-1}$): 3342 due to stretching vibration of (-OH ,carboxylic acid ),(2972 and 2852) due to stretching vibrations of (-CH aliph.), 1732 due to stretching vibration of (C=O) of carboxylic acid and (1716 and 1699) due to stretching vibrations of other two (C=O) of this compound ,$^1$H-NMR (ppm) : 1.2-1.7 (m, 6H ,3(-$CH_2$) aliph. of lactam ring) , 3.5 (s, (1H ,-CH) ,( 2H,-$CH_2$) alpha and beta to C=O of carboxylic acid and (1H ,-CH benzylic proton)), 6.8-7.9 (m, aromatic protons) and 10.8 (s, 1H , -OH of carboxylic acid).

**Procedure for the synthesis of 1-{[(1-E)-1-phenyl-2-(2-phenylhydrazinyl) ethylidene] amino} pyrrolidin-2-one (N9) [18]**: (0.01 mol.) of phenyl hydrazine was added to (30 ml) ethanol containing (0.01 mol.) of compound (N7) then refluxed for about (15 hrs.). The reaction mixture was cooled to room temperature and poured into (ice/water) mixture containing few drops of HCl acid. Then the precipitate was filtered, dried and recrystallized by (ethanol : water) (10:1) mixture: yield (59%),m. p. (194-196°C),color (light orange),M. Wt. (384),FT-IR ν ($cm^{-1}$): (3300 and 3203) due to stretching vibrations of (-NHNH-) ,3045 due to stretching vibration of (-CH aromatic) , (2966 and 2877) due to stretching vibrations of (-CH aliph.) and 1699 due to stretching vibration of (C=O) of lactam ring, $^1$H-NMR (ppm) :1.2 (m, 2H ,-$CH_2$ aliph.), 2.6 (t, 4H ,2(-$CH_2$) aliph.) and (7.2-8.3) (m, aromatic protons and –NHNH-).

**Procedure for the synthesis of 1-naphthalen-1-yl-3-(2-oxopyrrolidin-1-yl) urea (N10) [19]:** (0.01 mol.) of compound (N1) dissolved in (20 ml) DMF and then (0.01 mol.) of naphthyl isocyanate was added and refluxed for about (7 hrs.). Then, (25ml) of diethyl ether was added to the solution and the formed precipitate was filtered immediately, a mixture of (ethanol: water (1:1)) was used for recrystallization, yield (80%),m. p. (132-134°C),color (light pink),M. Wt. (269),FT-IR ν ($cm^{-1}$): (3282 and 3203) due to stretching vibrations of (-NH-C=O-NH-) , 3037 due to stretching vibration of (-CH aromatic) , (2955 and 2879) due to stretching vibrations of (-CH aliph.) and (1701 and 1651) due to stretching vibrations of (C=O) groups of lactam ring and (NHC=ONH), respectively , $^1$H-NMR (ppm) :0.9 (m, 2H ,-$CH_2$ aliph.), 1.6 (t, 4H ,2(-$CH_2$) aliph. ) and (7.1-8.3) ( m, aromatic protons and protons of (-NHCONH-)).

**Procedure for the synthesis of compound 1-(2-oxopyrrolidin-1-yl)-3-phenylthiourea (N11) [20]:** (0.01 mol.) of phenyl isothiocyanate was added to (30ml) DMF containing (0.01 mol.) of compound (N1) and refluxed for about (10-12 hrs.). The solution was poured into ice water. The formed precipitate was filtered off and recrystallized from (ethanol: water (10:1)) mixture ,yield (68%),m. p.

(150-152°C),color (light brown),M. Wt. (235),FT-IR ν ($cm^{-1}$): (3371 and 3203) due to stretching vibrations of (-NH-C=S-NH-) , 3043 due to stretching vibration of (-CH aromatic) , (2965 and 2875) due to stretching vibrations of (-CH aliph.), 1693 due to stretching vibration of (C=O) lactam ring and 1320 due to stretching vibration of (C=S), $^1$H-NMR (ppm ): 1.5 (m, 6H ,3(-$CH_2$) aliph.), (7.5-7.8)(m, aromatic protons) and (8.5 and 9.2) ( s,2H,-NH-C=S-NH-).

**Procedure for the synthesis of compound 1-{[(2Z)-3, 5-diphenyl-1, 3-thiazol-2(3H)-ylidene] amino} pyrrolidin-2-one (N12) [21]**: (0.01 mol.) of 2-bromo-4′-phenylacetophenone was added to (30ml) ethanol containing (0.01 mol.) of compound (N11), the solution then refluxed for (16 hrs.), then cooled and neutralized with $NH_4OH$ solution. Cold water was added to the solution to complete the precipitation. The formed precipitate was filtered off, washed with water, and recrystallized from a mixture of (ethanol: water) (15:1) , yield (72%),m. p. (80-82°C),color (light brown),M. Wt. (411),FT-IR ν ($cm^{-1}$): 3088 due to stretching vibration of (-CH aromatic) , (2958 and 2858) due to stretching vibrations of (-CH aliph.), 1691 due to stretching vibration of (C=O) lactam ring and 1573 due to stretching vibration of (C=N), $^1$H-NMR (ppm ) :2.2 (m, 6H ,3(-$CH_2$) aliph.), 7.2 (s,1H, vinyl H) and (7.2-7.6) (m, aromatic protons).

**Procedure for the synthesis of compound 2-chloro-N(2-oxopyrrolidene-1-yl) (N13)[22]**: ( 0.01 mol.) of chloro acetyl chloride was added drop wise to (30 ml) benzene containing (0.01 mol.) of compound (N1), the mixture was refluxed for about (4 hrs.) , then the reaction mixture was cooled to room temperature and solvent evaporated under reduced pressure ,the solid formed was filtered off and recrystallized from ethanol , yield (73%),m. p. (128-130°C) color (creamy white) ,FT-IR ν ($cm^{-1}$):3352 due to stretching vibration of (-NH),1691 due to stretching vibration of (C=O) lactam ring and 1674 due to stretching vibration of (C=O) of amide group ,$^1$H-NMR (ppm): 1.6 (m, 2H ,-$CH_2$ aliph.), 2.2 (t, 2H ,-$CH_2$ aliph.), 2.8 (t, 2H ,-$CH_2$ aliph.), 4.4 (s, 2H ,-$CH_2$ between –NHCO- and chlorine atom) and 5.8 (s,1H,-NHCO-).

**Procedure for the synthesis of compound 1-[(2-hydrazinyl-1, 3-thiozol-4-yl) amino] pyrrolidin-2-one (N14) [23]:** A mixture of (0.01 mol.) of compound (N13) with (0.01 mol.) of thiosemicarbazide in (25ml) ethanol was refluxed for (12 hrs.). The mixture was concentrated and after cooling poured into ice water. The solid formed was filtered, washed with 2% $NaHCO_3$ solution followed by water, and recrystallized from ethanol , yield (81%),m. p. (245-247°C) color (yellowish white). FT-IR ν ($cm^{-1}$): (3371,3309 and 3203) due to stretching vibrations of (-$NHNH_2$ and -NH), (2955 and 2879) due to stretching vibrations of (-CH aliph.) and 1701 due to stretching vibration of (C=O) lactam ring .$^1$H-NMR (ppm): 1.0 (m, 2H ,-$CH_2$ aliph.), 1.3 (m, 2H ,-$CH_2$ aliph.), 1.8 (t, 2H ,-$CH_2$ aliph.), 6.6 (s, 3H ,-$NHNH_2$) and 7.1 (s, 1H ,-NH and 1H of thiophen ring ).

**Procedure for the synthesis of compound 5-amino-2-{4-[(2-oxopyrrolidin-1-yl) amino]-1,3-thiazol-2,4-dihydro-3H-pyrazol-3-one(N15)[24]**: (0.01 mol.) of compound (N14) and (0.01 mol.) of ethyl cyano acetate were added to a solution of ethanolic sodium ethoxide and reflux for (8 hrs.). After cooling the reaction mixture was poured onto crushed ice containing few drops of $CH_3COOH$. The solid obtained washed with water and recrystallized from methanol, yield (81%), m. p. (264-266°C) color(white),M. Wt.(280) ,FT-IR ν ($cm^{-1}$):(3317,3221 and 3140) due to stretching vibrations of (-NH,- $NH_2$), (2941 and 2837) due to stretching vibrations of (-CH aliph.),(1716 and 1697) due to stretching vibrations of carbonyl groups and 1614 due to stretching vibration of (C=N). Mass, the molecular ion peak (M+, m/z) =280.

### *III. Antibacterial Activities [25]*

The agar well-diffusion method was used to detect antibacterial activities for synthesized compounds against *Escherichia coli* and *Staphylococcus aureus* using one experiment. These isolates were obtained from Department of Biology/ College of Science / Mustansiriyah University. The concentrations for each compound were (1000, 500 µg /ml). Plates were prepared by spreading approximately 105 cfu/ml culture broths of each indicator bacterial isolates on Muller Hinton agar surface using sterile cotton swabs. The agar plates were left for about (15 min.) before aseptically dispensing the 50µl of each compound into the agar wells already bored in the agar plates. The plates were then incubated at 37°C for (18 - 24 hrs.). Zones of inhibition were measured and recorded in millimeter diameter. Dimethyl sulfoxide used as control. Amoxicillin was the antibacterial agent for comparison.

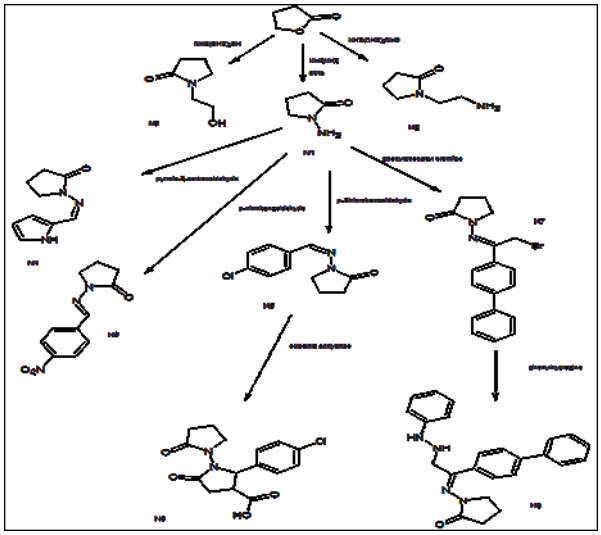
**TABLE I: Antibacterial activity for compounds N1-N15 against *E. coli* and *S. aureus***

| | *E. coli*, Conc. ( µg /ml) Inhibition zone diameter (mm | | *S. aureus,* Conc. ( µg /ml) Inhibition zone diameter (mm) | |
|---|---|---|---|---|
| Comp. no. | 1000 | 500 | 1000 | 500 |
| N1 | - | - | 12 | - |
| N2 | 11 | 9 | 12 | - |
| N3 | 17 | - | - | - |
| N4 | 10 | - | - | - |
| N5 | 15 | - | - | - |
| N6 | 13 | - | - | - |
| N7 | - | - | 10 | - |
| N8 | - | - | - | - |
| N9 | 11 | - | - | - |
| N10 | 14 | - | 22 | - |
| N11 | 20 | - | 18 | - |
| N12 | 13 | - | 21 | - |
| N13 | - | - | - | - |
| N14 | 11 | 7 | 12 | - |
| N15 | - | - | 12 | - |
| Amoxicillin | 20 | 18 | 14 | 12 |

## 3. RESULTS AND DISCUSSION

### *I. Spectra*

The preparation of compounds (N1-N3) through lactamization of GBL with hydrazine hydrate, ethylene diamine and ethanol amine, respectively was approved by FT-IR, $^{1}$H-NMR and some by Mass spectroscopy. According to FT-IR ($cm^{-1}$) spectra, The disappearance of (C=O) vibration at 1760 that belonged to GBL (Figure 5) and appearance of new bands at (1703, 1699 and 1718) due to stretching vibration bands of (C=O) of lactam rings of (N1, N2 and N3), respectively besides appearance of new bands at (3294 and 3203) and (3344 and 3207) due to (sym. and asy.) stretching vibration bands of ($-NH_2$) in the spectra of compounds (N1 and N2), respectively and appearance of broad band at 3410 due to (-OH) stretching vibration in the spectra of compound (N3) affirm the formation of these compounds.



**Scheme 5: General steps for synthesizing of compounds N1-N9**

Figure 6 and 7 show the FT-IR spectra of compounds (N1 and N3), respectivel.$^{1}$H-NMR (ppm) for compound N1 showed multiplate, triplet and another triplet at (1.3 ,1.7 and 2.1 respectively) due to aliphatic protons of lactam ring and showed singlet at 2.7 due to (2H, $-NH_2$) (Figure 8) ,the

molecular ion peak in Mass spectra of compound (N1) showed (M+, m/z) =100 which was corresponded to its molecular weight (Figure 9) . $^{1}$H-NMR (ppm) for compound N2 showed multiplate and triplet at (1.7 and 2.2, respectively) due to aliphatic protons of lactam ring and showed singlet at 3 and 3.3 due to (4H,-$CH_2CH_2$-, bonded to nitrogen of lactam ring) and (2H, -$NH_2$), respectively. $^{1}$H-NMR (ppm) for compound N3 showed multiplate and triplet at (1.4 and 1.8), respectively due to aliphatic protons of lactam ring and showed singlet at 2.2 and 3.2 due to (4H,-$CH_2CH_2$-, bonded to nitrogen of lactam ring) and (1H, -OH), respectively .The Mass spectra of compound (N3) showed the molecular ion peak (M+, m/z) =129 which was corresponded to its M. Wt. (Figure 10). The formation of Schiff bases (N4-N7) has been proved by their FT-IR, $^{1}$H-NMR and some by Mass spectroscopy.

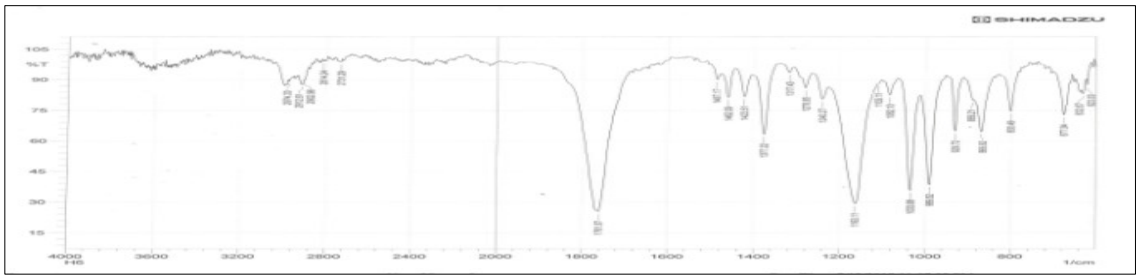


**Figure 5: FT-IR spectra for GBL**

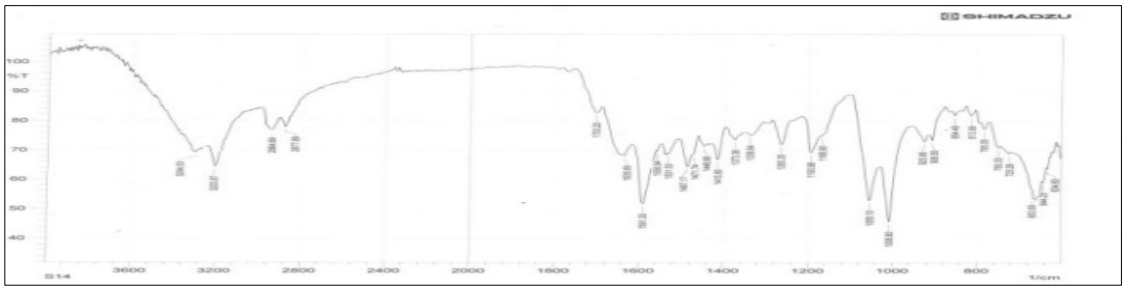


**Figure 6: FT-IR spectra for compound N1**

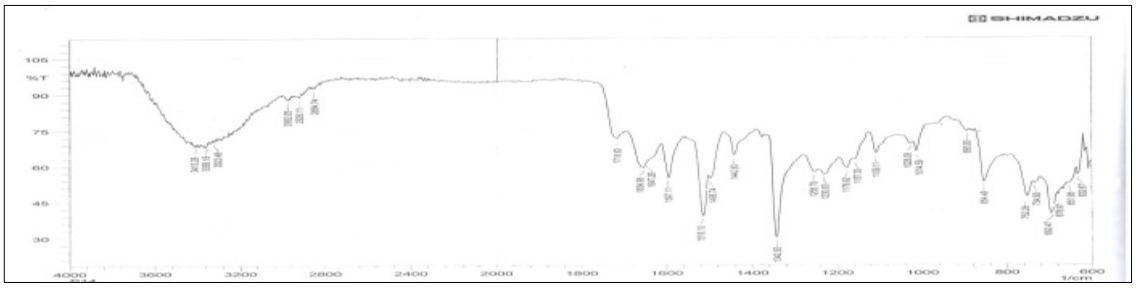


**Figure 7: FT-IR spectra for compound N3**

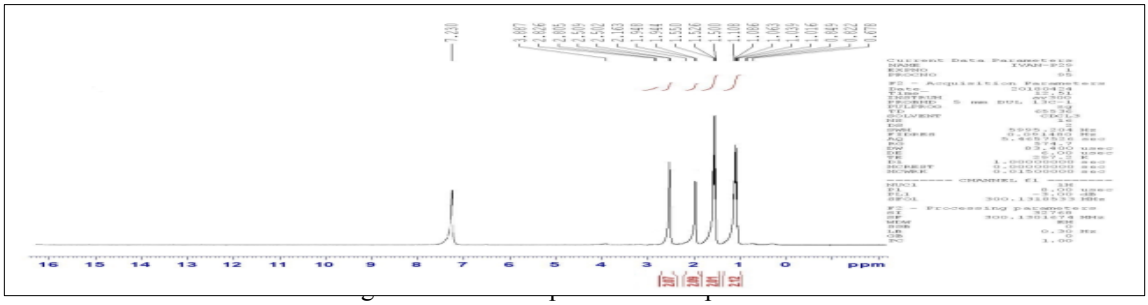


**Figure 8: $^{1}$H-NMR spectra for compound N1**

FT-IR ($cm^{-1}$) showed presence of stretching vibration bands of imine (N=CH) for compounds (N4-N6) at range (1591 - 1608) and band at 1591 due to stretching vibration of (C=N) of compound (N7) besides disappearance of (-$NH_2$) stretching vibration bands that appeared in FT-IR spectra of compound (N1). (Figure 11) shows FT-IR spectra of compound (N6). $^1$H-NMR (ppm) of compounds (N4-N6) showed singlet peaks at the range (8.6-8.8) due to imine group (CH=N).

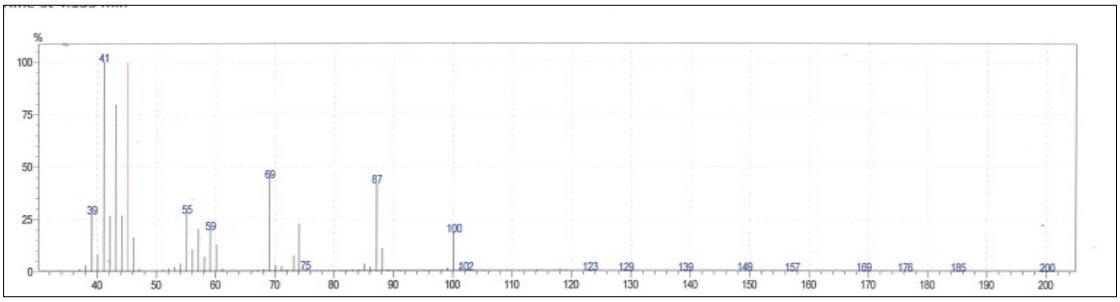


**Figure 9: Mass spectra for compound N1**

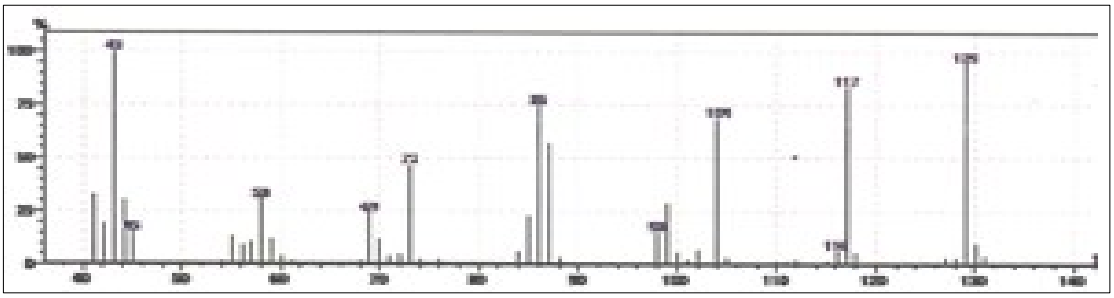
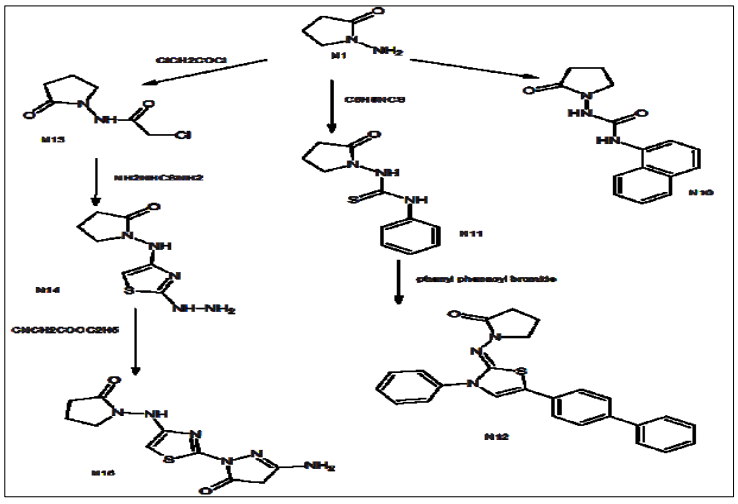


**Figure 10: Mass spectra for compound N3**



**Scheme 6: General steps for synthesizing of compounds N10-N15**

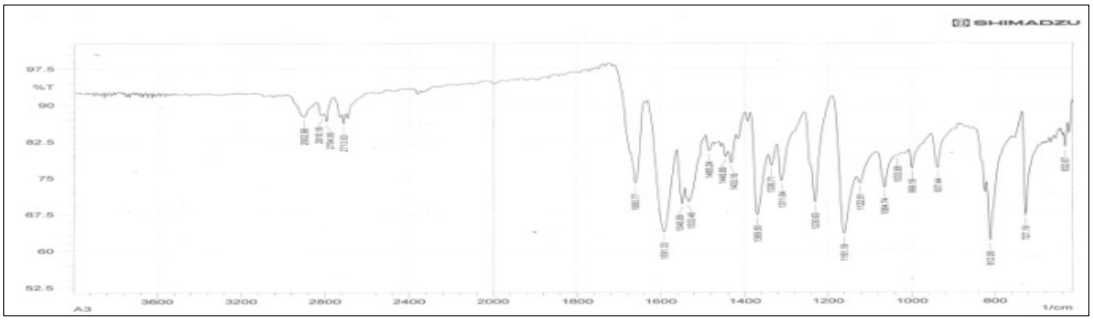


**Figure 11: FT-IR spectra for compound N6**

Figure 12 and 13 show Mass and $^{1}$H-NMR spectra of compounds N4 and N5, respectively. The formation of compound (N8) has been proved by FT-IR and $^{1}$H-NMR spectra, FT-IR ($cm^{-1}$) showed a broad band at 3342 and band at 1732 due to hydroxyl and carbonyl groups of ( C=O-OH),respectively and showed bands at (1716 and 1699) due to carbonyl groups of the two lactam rings.

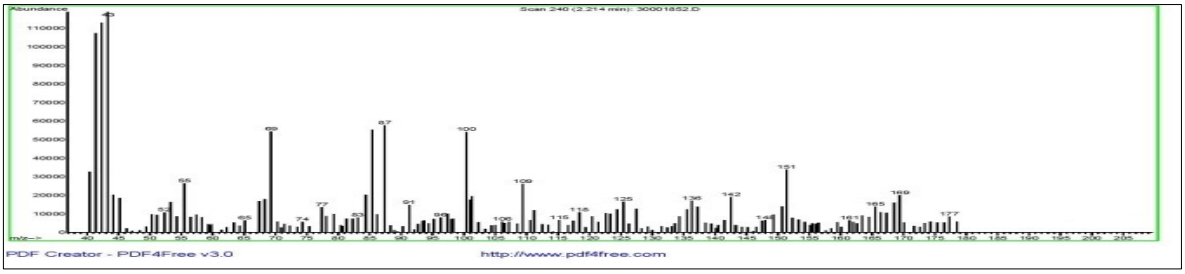



**Figure 12: Mass spectra for compound N4**

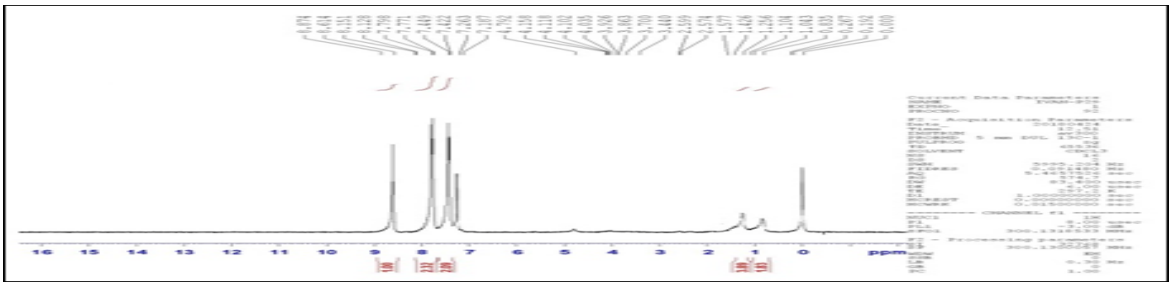


**Figure 13: $^{1}$H-NMR spectra for compound N5**

$^{1}$H-NMR (ppm) of compound (N8) (Figure 14) showed disappearance of imine singlet peak which was at 8.7 in the spectra of compound (N5) and appearance of a singlet peak at 10.8 due to proton of (-COOH). FT-IR ($cm^{-1}$) spectra of compound (N9) showed new bands at (3300 and 3203) due to stretching vibrations of (-NHNH-) of phenyl hydrazine moiety, while $^{1}$H-NMR (ppm) showed multiplate and triplet at (1.2 and 2.6 respectively) due to aliphatic protons of lactam ring and showed multiplate at (7.2 - 8.3) due to aromatic protons and (-NHNH-).The formation of compounds (N10 and N11) has been proved by FT-IR and $^{1}$H-NMR spectroscopy. FT-IR ($cm^{-1}$) showed disappearance of stretching vibration bands at (3294 and 3203) that belonged to ($-NH_2$) group of compound (N1) and appearance of new bands at (3282 and 3203) and (3371 and 3203) due to stretching vibrations of ((-NH) in (NH-C=O-NH) and (NH-C=S-NH)) moieties, respectively.

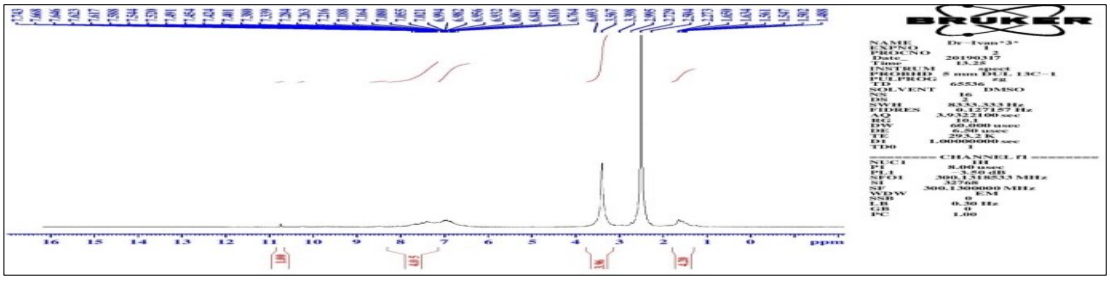


**Figure 14: $^{1}$H-NMR spectra for compound N8**

$^{1}$H-NMR (ppm) of compound (N11) (Figure 15) showed two singlet peaks at 8.5 and 9.2 due to protons of (NH-C=S-NH) .The formation of compound (N12) has been confirmed by FT-IR ($cm^{-1}$) that showed disappearance of the bands at (3371 and 3203) that belonged to stretching vibration of (NH-C=S-NH) of compound (N11) and appearance of new band at 1573 due to (C=N), while $^{1}$H-NMR (ppm) showed disappearance of the two singlet peaks at (8.5 and 9.2) that belonged to protons of (NH-C=S-NH). FT-IR ($cm^{-1}$) of compound (N13) showed new bands at ( 3352 and 1674) due to (-

NH) and (-C=O) of new amide group, respectively and showed disappearance of (-$NH_2$) stretching vibration bands that belonged to compound (N1), $^1$H-NMR showed singlet peak at 5.8 that attributed to (1H, -NHCO-) which is a proof to formation of this compound.

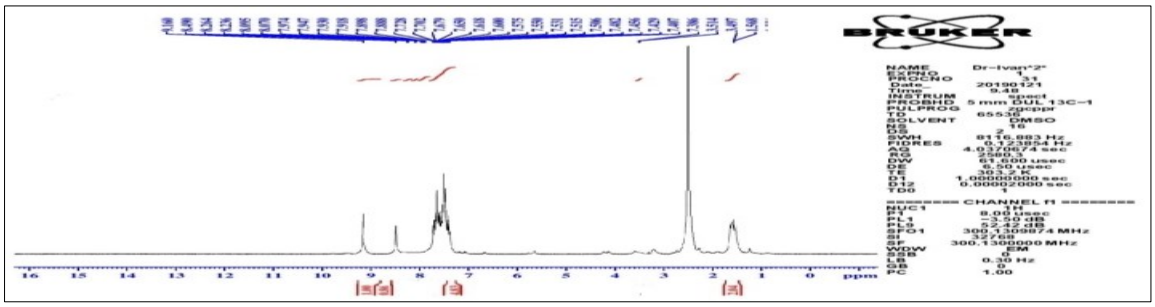


**Figure 15: $^1$H-NMR spectra for compound N11**

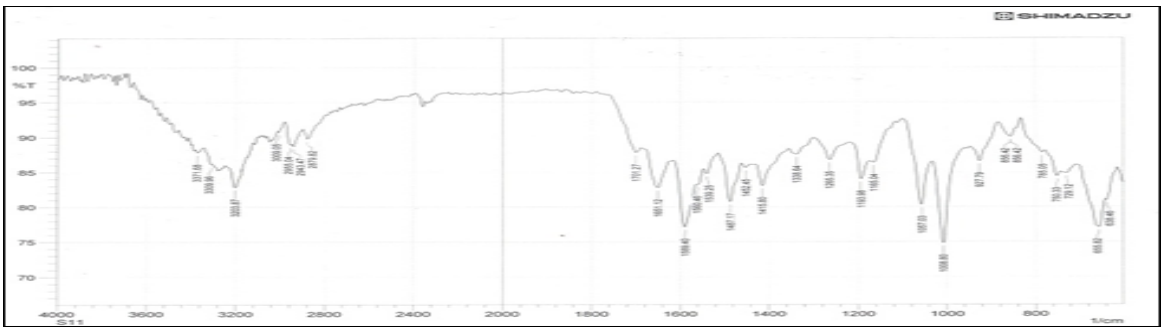


**Figure 16: FT-IR spectra for compound N14**

FT-IR (cm$^{-1}$) spectra of compound (N14) (Figure 16) showed disappearance of stretching vibration band of (C=O) of amide group of compound (N13) that was at 1674 and appearance of new bands at (3371, 3309 and 3203) that belong to (-$NHNH_2$ and -NH), $^1$H-NMR (ppm) showed disappearance of singlet peak at 5.8 that belonged to (1H, -NHCO-) of compound (N13) and appearance of new singlet peaks at 6.6 and 7.1 due to (3H, -$NHNH_2$) and (1H, -NH and 1H, thiophen ring),respectively (Figure 17). Formation of compound (N15) was confirmed by FT-IR (cm$^{-1}$) spectra that showed appearance of new bands at (3317, 3221 and 3140) due to (-$NH_2$ and -NH) and appearance of band at 1716 due to (C=O) of new five membered ring besides a band at 1697 due to (C=O) of original lactam. Mass spectra also confirmed formation of compound (N15), the molecular ion peak (M+, m/z) =280 which was corresponded to its molecular weight.

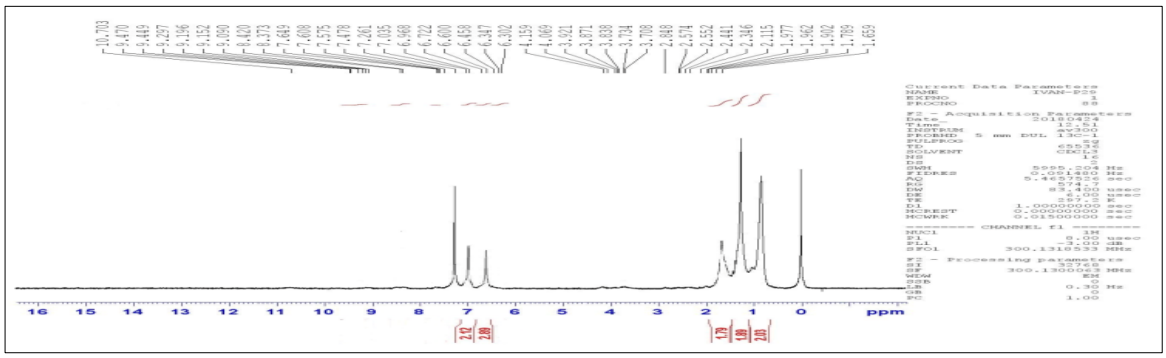


**Figure 17: $^1$H-NMR spectra for compound N14**

### *II. Antibacterial Activities*

Among the various properties of chemical compounds, antibacterial activity plays a crucial role since it suggests uses of the compounds in the medical applications such as antibiotics [26]. Since

antibiotics are inhibitors of bacterial growth, this situation has an impact on the structure and the activity of bacterial populations. Structural properties such as the number and location of various functional groups on a modified compound compared to their parent compounds usually exhibit great effect on the antibacterial activity of these antibiotics [27]. Gram-negative bacteria have an outer membrane rich in lipopolysaccharide. Several antibacterial have been found to inhibit the synthesis of this lipid in addition; antibacterial peptides can bind to the outer membrane of Gram-negative bacteria and block passage of solutes between the periplasm and the cell exterior, resulting in bacterial toxicity. There are antimicrobial agents that directly target a component of bacterial cytoplasmic membranes that can act on both Gram-negative as well as Gram-positive bacteria. Many of these are cyclic peptides with a rigid binding site capable of binding a lipid component. This binding targets antibacterial agents to bacteria, rather than being toxic to host cells [28]. We see from Table 1 that all synthesized compounds show antibacterial activity against one or two types of bacteria used (*E. coli* and *St. aureus*) except N8 and N13 that show no antibacterial activity at all. Compounds N2, N10, N11, N12 and N14 show antibacterial activity against two types of bacteria. Compounds N3, N5, N6 and N9 show antibacterial activity against *E. coli* only. Compounds N1, N7 and N15 show antibacterial activity against *St. aureus* only. Figures (18-21) show images exhibiting antimicrobial activities of some synthesized compounds. The bacterial responses to antibiotic drug treatments that contribute to cell death are not as well understood and have proven to be complex as they involve many genetic and biochemical pathways [29] so the suggested mechanism for cell death by the synthesized compound in this study could involve inhibition of production of the bacterial cell wall that involves the partial assembly of wall components inside the cell, transport of these structures through the cell membrane to the growing wall, assembly into the wall, and finally cross-linking of the strands of wall material .The result is an alteration in the cell wall and shape of the organism and eventually the death of the bacterium [30]. Other suggested mechanism is that antibiotics inhibit protein synthesis in bacteria. Those antibiotics that are selectively toxic bind to or inhibit the function of the proteins of the bacterium, thereby preventing the synthesis of new proteins and new bacterial cells or interferes with ribonucleic acid (RNA) synthesis in bacteria by binding to a subunit on the bacterial enzyme responsible for duplication of RNA [31].

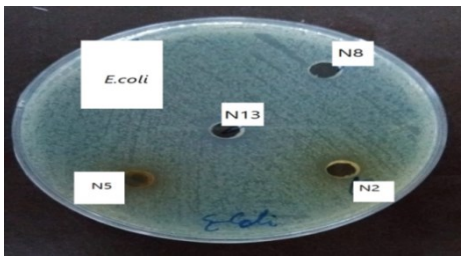



**Figure 18: Effects of compounds N2, N5, N8 and N13 on *E. coli***

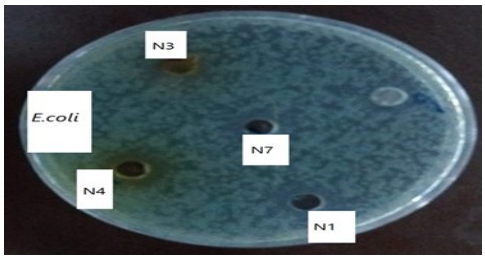



**Figure 19: Effects of compounds N1, N3, N4 and N7 on *E. coli***

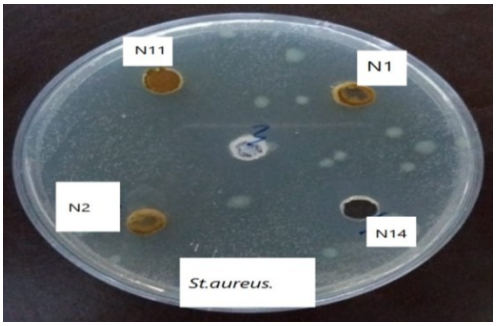



**Figure 20: Effect of compounds N1, N2, N11 and N14 on *St. aureus***

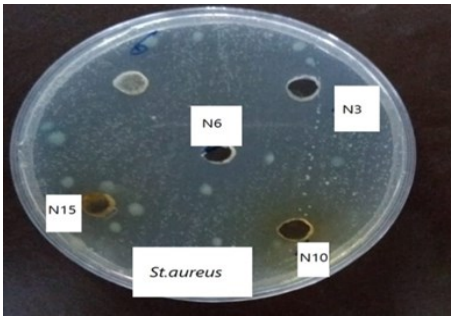



**Figure 21: Effect of compounds N3, N6, N10 and N15 on *St. aureus***

## 4. CONCLUSION

We conclude the possibility of synthesizing some pyrrolidine-2-one derivatives through lactamization of γ –butyrolactone with amines derivatives of good nucleophilic properties using high temperature and also conclude that these derivatives may have moderate biological activity compared to amoxicillin. The future study of the biological efficacy of prepared derivatives can be expanded using animal model such as contamination of rabbit skin wounds by bacteria then we examine the effect of synthesized compounds in the treatment of inflammation. Measurement of lethal dose 50 %( LD50) and studying the histological effect for prepared compounds may be investigated on mice in the future studies.

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