ORIGINAL ARTICLE

Preparation, characterization and antibacterial activity of the 5-membered ring via Schiff's bases

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ABSTRACT

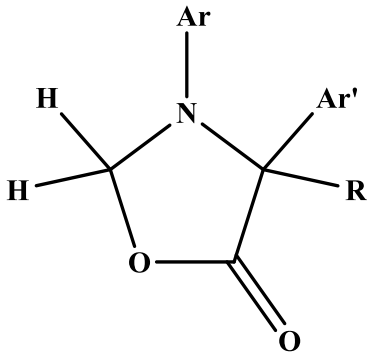
In this research, 5- membered heterocyclic compounds as oxazolidine-5-one J_1-J_5 derivatives were prepared using primary aromatic amine, aromatic carbonyl compounds and chloroacetic acid. Schiff's bases were synthesis by condensation of primary aromatic amine and aromatic carbonyl compounds. Schiff bases are used with the chloroacetic acid compound to prepare oxazolidine-5-one J_1-J_5 derivatives. The compounds J_1-J_5 were described using NMR spectroscopy and FT-IR. .The biological efficacy was evaluated according to maximum inhibitory concentrations (MICs) toward *Staphyloccoccus aureus* and *Esherichia coli*. The best MIC was 210 $\mu g.well^{-1}$ for J_4 against the two pathogenic bacteria, while J_1, J_4, and J_1 did not show any inhibitory effect against all bacteria. Finally, the 3'-(pyrimidin-2-yl) spiro[indoline-3,2'-oxazolidine]-2,5'-dione (J_4) is the best compound synthesized inhibited the growth of gram-negative and positive bacteria.

Keywords: Heterocyclic, Oxazolidine-5-one, Biological activity, MICs

INTRODUCTION

Schiff's bases are containing a double bond group between carbon and nitrogen (Mumtaz et al., 2016). Schiff's bases were prepared by the condensation reaction of a primary amine with an aldehyde or a ketone(Abid et al., 2017; Jiang and Ni, 2018; Muslim et al., 2018; Zohreh Ebrahimi, Abolghasem Davoodnia and Motavalizadehkakhky, 2020). The novelty of Schiff base comes from the imine group (-C=N), which forms the heart of these molecules as well as, acts a significant role in bioactivity. Schiff's bases have wide usage in pharmaceutical applications as antifungal (Bharti et al., 2010), anti-bacterial (Iqbal et al., 2007) anticancer (Makawana et al., 2014), antioxidant (Anouar et al., 2013; Taha et al., 2013), urease inhibitor (Aslam et al., 2011). As well as, their antiinflammatory (Nath et al., 2010; Rakesh et al., 2015), antiglycation activities (Taha et al., 2014), antiviral (Wang et al., 2018), anti-HIV-1 (Al-Abed et al., 2002), antitumor (Shebl et al., 2017; Zhang et al., 2014), antipyretic (Murtaza et al., 2017), antiproliferative (Prasanna Kumar et al., 2013; Song et al., 2014). The merging of carbon-nitrogen double bond with a heteroatom in a ring increases the scope of Schiff base in antimalarial, antitumor, antimicrobial, antipyretic, antiviral, antineoplastic and antiproliferative activity(Da Silva et al., 2011; Jesmin et al., 2010; Sunil et al., 2013). Therefore, many researchers synthesized heterocyclic from Schiff bases as quadruple, pentagonal or hexagonal rings containing at least two heteroatoms to increases the potential of Schiff bases as bioactivity.

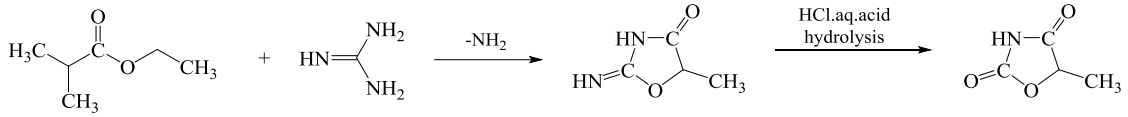
Oxazolidinone is a new antibiotic group; this synthetic drug is active against large species of Gram-positive bacteria, involving vancomycin- and methicillin-resistant Staphylococci, penicillin-resistant Pneumococci (Hussain, 2017). The synthesis of oxazolidine-5-one derivatives and their biological activities occupy a useful place in medicinal chemistry and heterocyclic chemistry. 4-substituted poly hydroxyllidine-2-phenyl oxazolidines-5-one and its derivatives have a wide range of different pharmaceutical and biological activities (Anupama et al., 2015). Oxazolidine-5-one derivatives are considered one of the important types of heterocyclic compounds (Hussain, 2017). Many of aryl- oxazolidine compounds are showed diverse biological activities (HAGEL et al., 2014), including hypoglycemic activity (Dey et al., 2011) and potent antimicrobial agents (Satyanarayana et al., 2008). However, Scheme 1 exhibited the general ring structure of oxazolidine-5-one derivatives.



Ar and Ar'= Aryl or Alkyl groups
R= H atom or C atom

Scheme 1. The general ring structure of oxazolidinone derivatives

Several 5-substituted-1,3-oxazolidine-dione derivatives carrying various substituents were synthesized and their anti-inflammatory activities were evaluated (Shankarananth et al., 2012). One of these derivatives shows in scheme 2.



Scheme 2. Synthesizing one of the oxazolidinone derivatives from guanidine

The aim of this research is preparing 5-membered ring derivatives from Schiff's bases. Each derivatives structure has been characterized by FT-IR and 1H-NMR spectra after measuring some physical properties such as melting points, yield percent and color. The antibacterial activity of the prepared derivatives J_1-J_5 was assessed against *Staphylococcus aureus* and *Escherichia coli*.

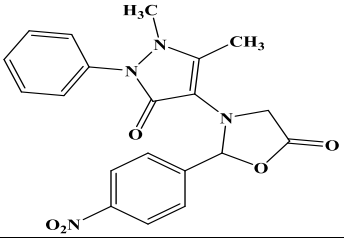
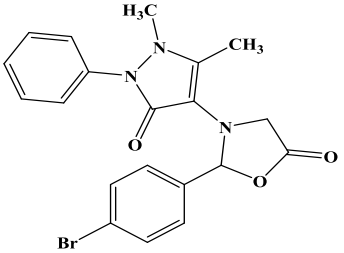
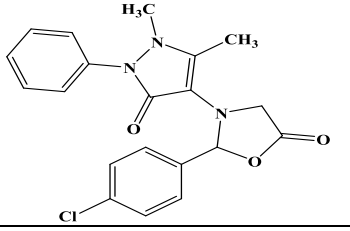
2. Experimental

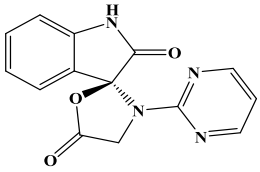
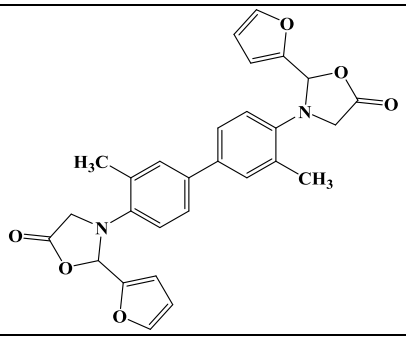
2. 1. Chemicals: In this research, the chemicals were obtained from some companies with their purity as in the following: Indoline-2,3-dione (Fluka, 99%), 4-Amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (Merck, 98%), Glacial Acetic Acid (Fluka, 98%), 3,3'-Dimethylbiphenyl-4,4'-diamine (Merck, 99%), Chloroacetic acid (Sigma Aldrich, 99.8%), Furan-2-carbaldehyde (Fluka, 98%), Absolute ethanol (Sigma Aldrich, 99.8%), Tetra Hydro Furan (Sigma Aldrich, 99.9%), Tri Ethyl Amine (Fluka, 99%), 4- Bromobenzaldehyde (Sigma Aldrich, 99.8%), 4-Chlorobenzaldehyde (Sigma Aldrich, 99.8%), and Pyrimidin-2-amine (Sigma Aldrich, 99.9%).

2. 2. Bacterial isolates: Two bacterial isolates, including *Staphylococcus aureus* and *Escherichia coli* were obtained from the Ministry of Science and Technology, Baghdad, Iraq.

2. 3. Preparation of 1,3-oxazolidinone-5-one derivatives (J_1-J_5): Mixtures of (1 mmol) of aldehyde and (1 mmol) of amine were dissolved in 30mL absolute ethanol with two drops of glacial acetic acid as a catalyst and refluxed in a round bottom flask (50mL) for 3hrs, (1 mmol) of the chloroacetic acid was placed on the round bottom flask contents. Then, the mixture was refluxed again for a period of 4hrs (Ayfan et al., 2019; Tawfeeq et al., 2019b, 2019a). The products were cooled in an ice bath and filtered. The solid products were dried and recrystallized from absolute ethanol to obtain derivatives of J_1-J_5 (Ayfan et al., 2019; Saygili, 2011; Selvam et al., 2011; Tawfeeq et al., 2019a, 2019b), see table 1.

Table 1. The molecular formula, nomenclature, percentage of the product and some physical properties of the prepared 1,3-oxazolidine-5-one compounds

Compound	Structure formula	Yield %	m.p. °C	Color
J_1		**75%**	**224-226**	**Bright yellow**
J_2		**87%**	**228-230**	**Bright yellow**
J_3		**79%**	**236-237**	**Bright Light yellow**

J_4		**88%**	**162-164**	**Light nutty**
J_5		**81%**	**196-198**	**Bright Light gray**

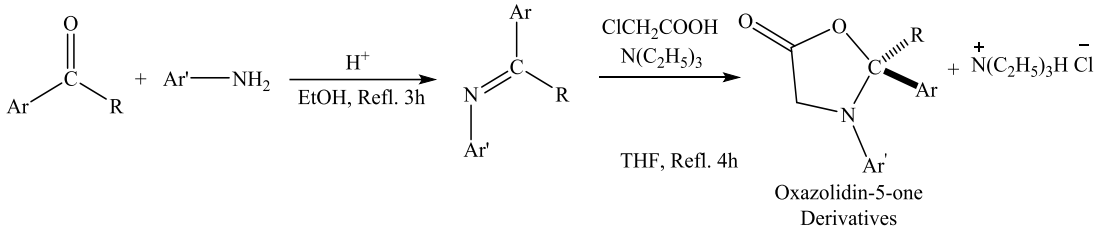
2. 4. Identification of 1,3-oxazolidinone-5-one derivatives (J_1-J_5): FT-IR analysis was done using FT-IR spectroscopy device, Bruker - Tensor 27, Germany. [1] HNMR spectra were measured in DMSO-D6 on an Agilent NMR spectrometer (300 MHz) Bruker - Ultra shield 300 MHz, Germany. Measuring the melting points of the prepared compounds was done by the Electro thermal device (m. p.) Galan Kamp by a capillary tube

2. 5. Biological activity: Antibacterial efficacy of Oxazolidine-5-one compounds (J_1-J_5) was done using Mueller Hinton Agar toward *E. coli* and *S. aureus*. The holes have a diameter of 6 mm and the volume of J_1-J_5 was 50 µl per hole in DMSO with concentrations ranged from 30 µg to 600 µg. The culture dishes were dependent on calculating the zone of inhibition (Owaid et al., 2015). Besides, 50 µg.well^{-1} of Gentamycine as a positive control and 50 µl.well^{-1} of DMSO as negative control were used in this experiment.

RESULTS AND DISCUSSION

3. 1. 1,3-Oxazolidinone-5-one derivatives (J_1-J_5)

The rules for recovering the preparation directly from the interaction of some primary amines and aldehydes in ethanol by the existence of glacial acetic acid as a catalyst (Wade Jr, 2013), as shown in the following general equation, scheme 3:



Ar and Ar'= Aryl groups
R= H in [Furan, 4-Chloro benzaldehyde, 4-Bromobenzaldehyde, 4-Nitrobenzaldehyde]
R= C in [Indoline-2,3-dione]

Scheme 3. The general equation of the preparation of oxazolidinone-5-one derivatives

The double bond of the (-C=N) in Schiff's base attacks the alpha carbon of Chloroacetic acid to form an intermediate (carbonium ion), which reacts implicitly to create the final product

The FT-IR frequency of 1,3-oxazolidine-5-one compounds showed absorption at 1699-1799 cm^{-1} returned to Lactone (C=O), the absorption at 3042-3100cm^{-1} returned to the vibration group of C=C-H in the benzene ring, the absorption at 1480-1543cm^{-1} returned to the aromatic group (C=C), the absorption of 1160-1211cm^{-1} belonged to the group of C-O and the absorption at 1100-1147cm-1 returned to the vibration of the C-N group (Wade and Simek, 2013).

Moreover, (J_1) had a yield of 75%, Bright yellow, m. p. 224-226 °C. Its FT-IR (KBr) showed the presence of 1100 cm^{-1} (C-N), 1160 cm^{-1} (C-O), 1543 cm^{-1} (C=C aromatic), 2956 cm^{-1} (Symmetric Aliphatic C-H), 2996 cm^{-1} (Asymmetric Aliphatic C-H), 3069 cm^{-1} (C-H aromatic), 1756 cm^{-1} (C=O lactone), 1638 cm^{-1} (C=O lactam), and 1336 cm^{-1}, and 1546 cm^{-1} (-NO_2). 1H-NMR (DMSO-D6) 2.15 (s, 3H) 3.24 (s, 3H), 5.76 (s, 2H), 7.38 (s, 1H), 7.54 (m, 2H), 8.05-8.03 (d, J=7.3, 2H) 8.29-8.26 (d, J=7.7Hz, 2H).

(J_2) compound showed a yield of 87%, Bright yellow, m. p. of 228-230 °C. The FT-IR (KBr) exhibited the existence of 1130 cm^{-1} (C-N), 1178 cm^{-1} (C-O), 1482 (C=C aromatic), 2930 cm^{-1} (Symmetric Aliphatic C-H), 2987 cm^{-1} (Asymmetric Aliphatic C-H), 3090 cm^{-1} (C-H aromatic),

1749 cm^{-1} (C=O lactone), 1642 cm^{-1} (C=O lactam), and 585 cm^{-1} (C-Br). 1H-NMR (DMSO-D6) 2.45 (s, 3H) 3.19 (s, 3H), 5.67 (s, 2H), 7.35 (s, 1H), 7.39-7.49 (d, J=8Hz, 2H), 7.52 (m, 5H) 7.81-7.83 (d, J=8Hz, 2H).

(J_3) had a yield of 79%, Bright Light yellow, m. p. of 236-237 °C. Its FT-IR (KBr) exhibited the presence of 1129 cm^{-1} (C-N), 1167 cm^{-1} (C-O), 1484 cm^{-1} (C=C aromatic), 2933 (Symmetric Aliphatic C-H), 2987 cm^{-1} (Asymmetric Aliphatic C-H), 3060 cm^{-1} (C-H aromatic), 1799 cm^{-1} (C=O lactone), 1645 cm^{-1} (C=O lactam), and 956 cm^{-1} (C-Cl). 1H-NMR (DMSO-D6) 2.45 (s, 3H) 3.18 (s, 3H), 5.76 (s, 2H), 7.37 (s, 1H), 7.65-7.63 (d, J=7.3Hz, 2H), 7.74 (m, 5H) 7.86-7.84 (d, J=7.2Hz, 2H).

(J_4) compound had a yield of 88%, Light brown, m. p. 162-164 °C. while its FT-IR (KBr) showed the existence of 1129 cm^{-1} (C-N), 1208 cm^{-1} (C-O), 1508 cm^{-1} 1617 cm^{-1} (C=O lactam), 1699 cm^{-1} (C=O lactone), (C=C aromatic), 2952 cm^{-1} (Symmetric Aliphatic C-H), 2992 cm^{-1} (Asymmetric Aliphatic C-H), 3100 cm^{-1} (C-H aromatic), and 3198 cm^{-1} (N-H). 1H-NMR (DMSO-D6) 3.06 (s, 2H), 6.58-6.85 (d, J=8Hz, 1H), 7.23 (m, 4H), 7.68-7.74 (d, J=8Hz, 2H), 10.60 (s, 1H).

Finally, (J_5) had a yield of 81%, Bright Light gray, m. p. of 196-198 °C. Its FT-IR (KBr) had 1131 cm^{-1} (C-N), 1211 cm^{-1} (C-O), 1480 cm^{-1} (C=C aromatic), 1757 cm^{-1} (C=O lactone), 2957 cm^{-1} (Symmetric Aliphatic C-H), 2996 cm^{-1} (Asymmetric Aliphatic C-H), 3042 cm^{-1} (C-H aromatic), and 3110 cm^{-1} (=C-H of furan ring). 1H-NMR (DMSO-D6) 2.4 (s, 6H), 3.16 (s, 4H), 6.60-6.63 (d, J=13Hz, 2H), 6.94-6.98 (d, J=13Hz, 2H), 7.34-7.36 (d, J=3Hz, 2H), 7.40 (dd, J=7.6 Hz, 2H), 7.49-7.51 (d, J=11 Hz, 2H), 7.52-7.54 (d, J=3Hz, 2H), 7.84 (s, 2H).

3. 2. The antimicrobial activity and MICs of 1,3-oxazolidine-5-one compounds J_1-J_5: The bacterial activity and MICs of 1,3-oxazolidine-5-one compounds J_1-J_5 were recorded in table 2. However, the concentration 600 μg.$well^{-1}$ of compound J_3 showed the biggest inhibition zone (16 mm) against *S. aureus*, but it did not show any inhibitory effect against *E. coli*. The compound J_4 (600 μg.$well^{-1}$) exhibited a zone of inhibition reached 13 mm and 12 mm against *S. aureus* and *E. coli*, respectively. Gentamycin (50 μg.$well^{-1}$), as a control, exhibited a zone of inhibition reached 25 mm and 28 mm toward *S. aureus* and *E. coli*, respectively, as in table 2. Other prepared compounds did not exhibit any inhibitory effects against the studied pathogenic bacteria. Besides, the best MIC was 210 μg.$well^{-1}$ for J_4 against the two pathogenic bacteria. Also, the compound J_4 recorded MIC reached 240 μg.$well^{-1}$ against the *S. aureus* growth. While other prepared compounds J_5, J_2, and J_1 didn't record any inhibitory effect toward all bacteria species. See anti-bacterial efficacy of various concentrations of J_3 against *S. aureus* (a) and J_2 against *E. coli* (b) in figure 1.

The role of active compounds returns to connect the cell wall of bacteria and to reduce the replication of bacterial DNA (Mcdonnell and Russell, 1999). However, the prepared heterocycles have significant benefits toward various diseases which included the viral diseases too (El-Shehry et al., 2018; Elshehry et al., 2009). The tetrazol derivatives are efficient to synthesize various inflammatory agents (El Shehry et al., 2010). Thus, many new complexes of metals and derivatives of 1,3-oxazepine were used in the medical aspect, which exhibited remarkable positive results to kill the pathogenic bacteria (Ahmed et al., 2016; Ibtisam, 2009).

Table 2. MICs and anti-bacterial efficacy of the prepared compounds J_1-J_5 against two pathogenic bacteria

Compounds	Species of bacteria	MICs μg.$well^{-1}$	Zone of Inhibition (mm)			
			150 μg.$well^{-1}$	300 μg.$well^{-1}$	450 μg.$well^{-1}$	600 μg.$well^{-1}$
J_1	*S. aureus*	-	0	0	0	0
	E. coli	-	0	0	0	0
J_2	*S. aureus*	-	0	0	0	0
	E. coli	-	0	0	0	0
J_3	*S. aureus*	240	0	12	13	16
	E. coli	-	0	0	0	0
J_4	*S. aureus*	210	0	11	11	13
	E. coli	210	0	10	11	12
J_5	*S. aureus*	-	0	0	0	0
	E. coli	-	0	0	0	0
DMSO 50 μg.$well^{-1}$	*S. aureus*	-	0			
	E. coli	-	0			
Gentamycin 50 μg.$well^{-1}$	*S. aureus*	-	28			
	E. coli	-	25			

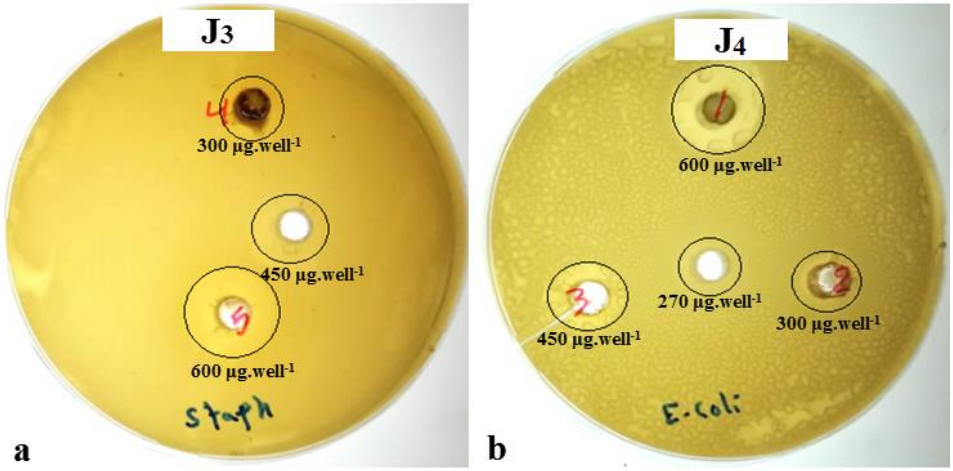


Figure 1. Anti-bacterial efficacy of various concentrations of J_3 against *S. aureus* (a) and J_4 against *E. coli* (b)

CONCLUSIONS

The heterocyclic compounds (1, 3 -oxazolidine - 5 - one derivatives) were prepared by the reaction of primary aromatic amino compounds, aromatic carbonyl compounds and Chloroacetic acid. The compounds of 1,3-oxazolidine-5-one derivatives were characterized by ^{1}H-NMR and FT-IR analyses. The best MIC was 210 µg.well^{-1} for J_4 against the two pathogenic bacteria. Also, the compound J_4 recorded MIC reached 240 µg.well^{-1} against the *S. aureus* growth. However, the concentration 600 µg.well^{-1} of compound J_3 showed the biggest inhibition zone (16 mm) against *S. aureus*. The compound J_4 (600 µg.well^{-1}) exhibited a zone of inhibition reached 13 mm and 12 mm against *S. aureus* and *E. coli*, respectively. Finally, the 3'-(pyrimidin-2-yl) spiro[indoline-3,2'-oxazolidine]-2,5'-dione (J_4) is best compound synthesized inhibited the growth of gram negative and positive bacteria.

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