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ORIGINAL ARTICLE

Preparation, Characterization and Antibacterial Activity of some New Oxazolidin-5-one Derivatives Derived from Imine Compounds

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KEYWORDS

Heterocyclic;
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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. By combining primary aromatic amines and aromatic carbonyl compounds, Schiff's bases were synthesized. 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 µg ml^{-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 best chemical created, 3'-(pyrimidin-2-yl) spiro[indoline-3,2'-oxazolidine]-2,5'-dione (J4), inhibited the development of both gram-negative and positive bacteria.

INTRODUCTION

Schiff's bases are containing a double bond group between carbon and nitrogen [1]. Schiff's bases were created by combining an aldehyde or a ketone with primary amine in a condensation process. [2-4]. The novelty of Schiff base comes from the group of imine (-C=N), It serves as the heart of these molecules and also plays an important part in bioactivity Schiff's bases are widely used as antifungal agents in medicinal applications [5], antibacterial [6]anticancer [7], antioxidant [8,9], urease inhibitor [10]. As well as, their antiinflammatory [11,12], antiglycation activities [13], antiviral [14], anti-HIV-1 [15], antitumor [16,17] , antipyretic [18], antiproliferative [19,20]. 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[21-23]. 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.

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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 [24]. The synthesis of oxazolidine-5-one derivatives and their biological effects are important in medicinal 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 [25]. Oxazolidine-5-one derivatives are considered one of the important types of heterocyclic compounds. Many of aryl- oxazolidine compounds are showed diverse biological activities [26], including hypoglycemic activity [27] and potent antimicrobial agents [28]However, Figure 1 exhibited the general ring structure of oxazolidine-5-one derivatives.

Several 5-substituted-1,3-oxazolidine-dione derivatives carrying various substituents were synthesized and their anti-inflammatory activities were evaluated [29]. One of these derivatives shows in Figure 2.

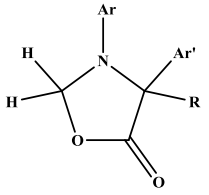


Figure 1. The general ring structure of oxazolidinone derivatives.

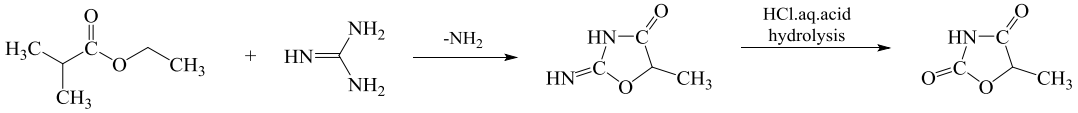


Figure 2. Synthesizing one of the oxazolidinone derivatives from guanidine.

The goal of this study is to create 5-membered ring derivatives from Schiff's bases. After evaluating physical parameters such as melting temperatures, yield percent, and color, each derivative structure was characterized using IR and ^{1}H-NMR spectra. The antibacterial activity of compounds J1-J5 against Staphylococcus aureus and Escherichia coli was evaluated.

MATERIALS AND METHODS

Chemicals

In this research, the chemicals were obtained from some companies with their purity as in the following: Indoline-2,3-dione (Fluka, 99%), 1,5-dimethyl-4-Amino--2-phenyl-1H-pyrazol-3-one (Merck, 98 percent), Glacial Acetic Acid (Fluka, 98 percent), 3,3'-Dimethylbiphenyl-4,4'-diamine (Merck, 99 percent), Chloroacetic acid (Sigma Aldrich, 99.8 percent), Furan-2-carbaldehyde (Fluka (Sigma Aldrich, 99.9 percent).

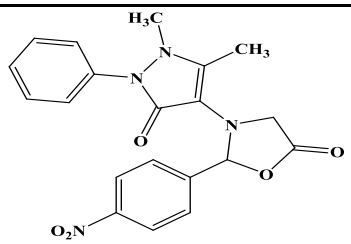
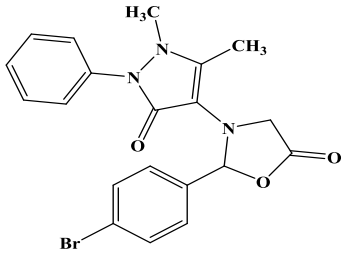
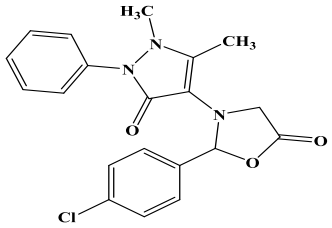
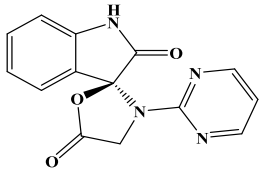
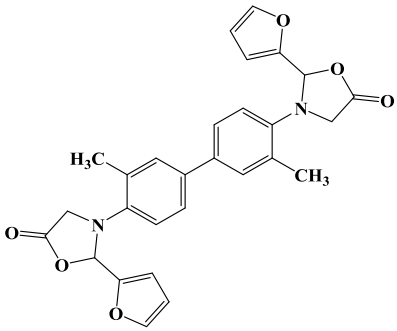
Bacterial isolates

The Ministry of Science and Technology in Baghdad, Iraq, provided two bacterial isolates, including Staphylococcus aureus and Escherichia coli.

Preparation of 1,3-oxazolidinone-5-one derivatives (J_1-J_5)

In a round bottom flask, 1 mmol aldehyde and 1 mmol amine mixtures were dissolved in 30mL 100% ethanol with few drops of GAA as a catalyst and heated at refluxed for 3 hours (50mL). A mixture was then refluxed for another 4 hours.[30-32]. The goods were filtered after being chilled in an ice bath. To get J1-J5 derivatives, the products were dried and purified from 100% ethyl alcohol. 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

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] On an Agilent NMR spectrometer (300 MHz) Bruker - Ultra shield 300 MHz, Germany, HNMR spectra were measured in DMSO-D6. A melting points of compounds (J1-J5) were measured using Electro thermal device (m. p.) Galan Kamp.

Biological activity

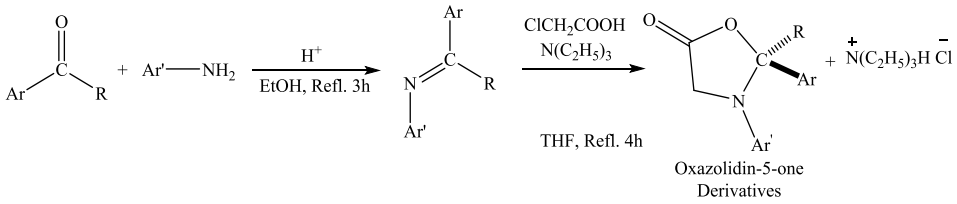
Using Mueller Hinton Agar, oxyazolidine-5-one compounds (J1-J5) were tested for anti-bacterial activity against S. aureus and E. coli. The holes are 6 mm in diameter, and the volume of J1-J5 in DMSO varies from 30 g to 600 g per hole. Calculating the zone of inhibition was necessary for the culture dishes (Owaid et al., 2015). In addition, 50 g.well-1 Gentamycine was utilized as a

positive control, while 50 l.well-1 DMSO was employed as a negative control in this experiment.

RESULTS AND DISCUSSION

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

The following general equation, scheme 3, shows the guidelines for recovering the preparation directly from the interaction of various primary amines and aldehydes in ethanol because GAA acts as a catalyst (Figure 3).



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

Figure 3. 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 revealed that absorption at 1699-1799 was returned to the lactone (carbonyl), absorption at 3042-3100cm-1 was returned of C=C-H in the phenyl moiety, absorption at 1480-1543cm-1 was returned to the aromatic (C=C), absorption at 1160-1211cm-1 was returned to the group of C-O [33].

Moreover, The FT-IR frequency of 1,3-oxazolidine-5-one compounds revealed that absorption at 1699-1799 cm-1 returned to the Lactone (C=O), 3042-3100cm-1 returned to the vibration group of C=C-H in the phenyl ring, 1480-1543cm-1 returned to the aromatic group (C=C), absorption at 1160-1211cm-1 returned to the C-O, and absorption at 1.

(J2) compound yielded 87 percent, was bright yellow, and had a melting point of 229-231 C. The FT-IR (KBr) detected 1130 cm-1 (C-N), 1178 cm-1 (C-O), 1482 (C=C phenyl), 2930 (Symmetric Aliphatic C-H), 2987 cm-1 (Asymmetric Aliphatic C-H), 3090 cm-1 (C-H aromatic), 1749 cm-1 (carbonyl lactone), 1642 cm-1 (carbonyl lactam), and 585 cm-1 (C-H phenyl) (C-Br). ^{1}H-NMR spectroscopy (dimethylsulfoxide-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 (d, J=8Hz, 2H) (m, 5H) 7:81–7:83 (d, J=8Hz, 2H).

(J3) had a yield of 79 percent, was Bright Light yellow, and had melting point of 236-237 C. Its FT-IR (KBr) spectrum revealed the presence of 1129 cm-1 (C-N), 1167 cm-1 (C-O), 1484 cm-1 (C=C aromatic), 2933 cm-1 (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 (C-Cl). 1H-NMR spectroscopy ,2.45pm (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 (d, J=7.3Hz, 2H), 7.74 (d, J=7.3Hz, 2H), 7.74 (d, J=7.3Hz, 2H), 7.74 (d, J=7.3Hz, 2H (m, 5H) 7.86 to 7.84 (d, J=7.2Hz, 2H).

(J4) compound exhibited an 88 percent yield, light brown, m. p. 161-163 C., and its IR revealed the presence of 1129 cm-1 (C-N), 1208 cm-1 (C-O), 1508 cm-1 (carbonyl lactam ring), 1699 cm-1 (carbonyl lactone), (C=C phenyl), 2952 cm-1 (Symmetric Aliphatic C-H), 2992 cm-1 (Asymmetric Aliphatic (N-H). 1H-NMR spectroscopy 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 (m, 4H), 10.60 (m, 4H), 10.60 (m, 4H), 10.60 (m, 4H), 10.60 (m, 4H), 10.60 (m, 4H), 10.60 ((s, 1H).

Finally, (J5) exhibited an 81 percent yield, Bright Light gray, with a m. p. of 197-198 C. It 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) FT-IR (KBr). Proton NMR spectroscopy 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, 2 H), 7.84 (d, J=3Hz, 2H) (s, 2H).

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, Compound J3 at 600 g well-1 concentration displayed the largest inhibition zone (16 mm) against S. aureus, but no inhibitory impact against E. coli. The chemical J4 (600 g m^{-1}) inhibited S. aureus and E. coli with zones of inhibition of 13 mm and 12 mm, respectively. Gentamycin (50 µg ml^{-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 ml^{-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 4.

The role of active compounds returns to connect the cell wall of bacteria and to reduce the replication of bacterial DNA [34]. However, the prepared heterocycles have significant benefits toward various diseases which included the viral diseases too [35,36]. The tetrazol derivatives are efficient to synthesize various inflammatory agents [37]. 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 [38,39].

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 ml^{-1}	Zone of Inhibition (mm)			
			150 µg $well^{-1}$	300 µg ml^{-1}	450 µg ml^{-1}	600 µg ml^{-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			

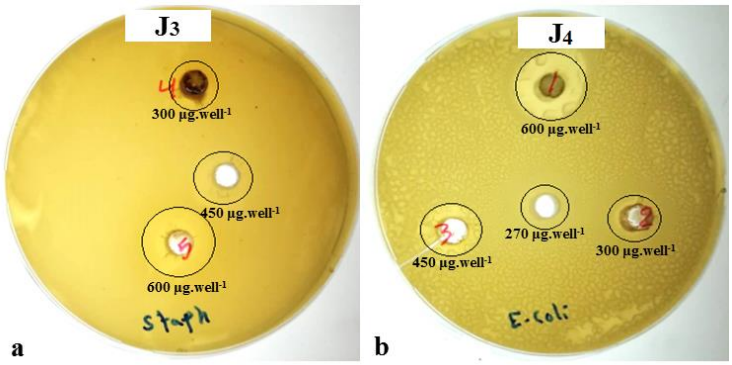


Figure 4. Anti-bacterial efficacy of various concentrations of J_3 against ***S. aureus*** (a) and J_4 against ***E. coli*** (b)

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 ml^{-1} for J_4 against the two pathogenic bacteria. Also, the compound J_4 recorded MIC reached 240 µg ml^{-1} against the *S. aureus* growth. However, the concentration 600 µg well^{-1} of compound J_3 showed the highest inhibition zone (16 mm) against *S. aureus*. The compound J_4 (600 µg ml^{-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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Conflict of interests

No conflict.

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