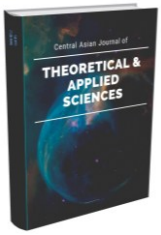

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Article

Synthesis and Design of Novel Oxazolidinone Rings and Evaluation of Their Biological Activity

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Abstract: In this study, a new, environmentally friendly, solvent-free technique—which is cost-effective and easy to use—was employed to synthesise a number of compounds containing an oxazolidinone ring, by reacting hydrazone with chloroacetic acid via a fusion reaction without the use of any solvent. Basic organic chemistry analyses (FT-IR, ^{1}H and ^{13}C-NMR) showed a clear disappearance of azomethine, indicating complete consumption of the reactants and confirming the validity of the synthesis. In addition, antimicrobial activity was evaluated against two common bacterial species: Escherichia coli and Staphylococcus aureus. Compared with the antibiotic ampicillin, which was used as a control for inhibition, compound M2 exhibited the strongest antimicrobial activity against Gram-positive bacterial strains; against Gram-negative bacteria, compound M1 was more effective than the other compounds, The results showed that inhibition improved with increasing concentration. Based on the above, these compounds show promising potential for future medical applications.

Keywords: heterocyclic, hydrazone, oxazolidinone, bacterial bioactivity

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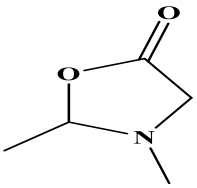
1. Introduction

One of the fascinating branches of science is heterocyclic chemistry, which is a great source for both theoretical and Heterocyclic chemistry is one of the most interesting branches of science, which is not only great source for theoretical but also practical applications. Hence, it constitutes a big part of research in chemistry and chemical sciences. Heterocyclic compounds are natural compounds, having biological features. Heterocyclic chemistry is one of the broad and developing areas in chemistry. It is because of the obvious importance of molecules derived from heterocyclic compounds, which are utilized in plastics, polymers, pharmaceuticals, agriculture and other industries. Biological features of heterocyclic compounds make them used in treating infectious diseases [1-3]. New generation antibiotics are oxazolidinones, which belong to the synthesized chemicals and are effective against several gram-positive bacteria like vancomycin-resistant staphylococci and penicillin-resistant pneumococcus. The design and biological features of oxazolidin-5-ones are important for medicinal chemistry and chemical biology [4]. The compounds of oxazolidin-5-ones that are substituted with polyhydroxylidin-2-phenyl and their derivatives possess multiple biological activities. The oxazolidin-5-one derivatives constitute significant classes of chemical substances with heterocyclic structure. Numerous derivatives of aryl-oxazolidinone possess various biological activities, such as hypoglycemic and strong antibacterial activity for different bacterial strains. Nevertheless, figure 1 represents the general ring structure of oxazolidin-5-one chemical compounds[5,6]. Numerous derivatives of 5-substituted-1,3-oxazolidindiones with different groups have been synthesized and tested for anti-inflammatory



this work aims to prepare novel pentathlonal oxazolidinone-5-one compounds by reacting prepared hydrazones with chloroacetic acid using an environmentally friendly solvent-free melting method. The biological activity of these compounds will be evaluated against two different types of bacteria, one Gram-positive and one Gram-negative.

2. Materials and Methods

2.1. Materials: Reputable and industry-leading businesses including BDH, Aldrich, and FLUKA provided the research materials, which were used without further screening.

2.2. Preparation of hydroquinazoline derivatives (M_1-M_5) [7,8]

Neutral hydrazones (0.001 mol) were mixed with chloroacetic acid in a heat-resistant flask, and the mixture was heated for 20 minutes with continuous stirring, then allowed to dry. Table 1 shows the procedure described therein, whereby the contents of the flask were dried, collected, and recrystallized using ethanol.

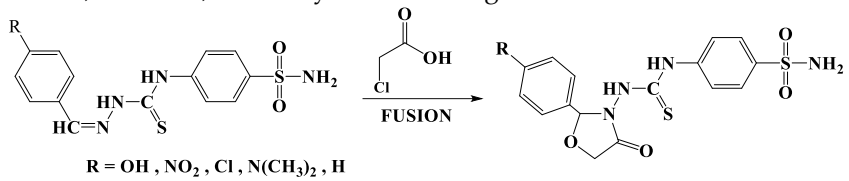


Table 1. Information on the useful aspects of synthetic substances(M1-M5)

Comp. No.	R	Molecular formula	m.p. °C	Yield %	Color
M1	OH	$C_{16}H_{16}N_4O_5S_2$	234-236	69	White
M2	NO_2	$C_{16}H_{15}N_5O_6S_2$	217-219	68	Brown
M3	Cl	$C_{16}H_{15}ClN_4O_4S_2$	225-227	70	Orange
M4	$N(CH_3)_2$	$C_{18}H_{21}N_5O_4S_2$	219-221	65	Yellow
M5	H	$C_{16}H_{16}N_4O_4S_2$	211-213	73	Off-white

2.3. Evaluation of bacterial bioactivity

Because of their abundance and ease of acquisition from the Biology Laboratories of Tikrit University, we used two of the most common bacteria which are found mostly in soil and water including the positive bacteria which are called ***Staphylococcus aureus*** and the negative bacteria called ***Escherichia coli***. First, we prepared the growth medium for the bacteria which we call as Mueller-Hinton agar, by dissolving 40 grams of this substance with one liter of distilled water [9-12]. This medium was sterilized using heat method at 121°C temperature under 1.5 bar pressure in an autoclave; then this medium was cooled and poured into Petri dishes under normal conditions. Bacteria obtained using three methods were contaminated in order to assure uniform contamination, then this dish was punctured in three holes which are 1 mm in diameter[13-15]. Chemical solutions were prepared using the constant addition of DMSO solvents at 3 different concentrations (0.01, 0.0001, and 0.001) mg/ml. After that, each concentration was added to a well, and three distinct concentrations were added to one plate. After that, the plates were incubated for a whole day at 37°C in a dedicated incubator. The inhibition's diameter was measured in millimeters [16].

3. Results

3.1. Characterization of hydroquinazoline derivatives (M1-M5)

When tests were carried out, beginning with Fourier transform infrared spectroscopy (FT-IR), it became apparent that the azomethine bond had disappeared, indicating that

reactions had taken place within the material. New bands appeared in the spectra which had not previously been present, such as the aliphatic bond, which was identified at (2987–2958 and 2935–2894) cm^{-1} and which always forms a double band as a result of symmetric and asymmetric stretching. Another characteristic of the new compound is the presence of the carbonyl bond of the formed oxazolidinone compound at (1687–1675) cm^{-1}. In addition, another band has appeared, confirming that the target ring has been successfully synthesised; this is the (C–O) band found at (1373–1358) cm^{-1}. The remaining bonds retained their original positions without being affected, as in the primary and secondary amine groups as well as the aromatic rings; all bands are shown in Table 2 [17, 18], as well as in Figures 1 and 2.

Table 2. Metadata of the FT-IR spectrum for compounds (M1-M5)

Comp. No.	R	ν(NH_2)	ν(N-H)	ν(C-H) Arom	ν(C-H) Aliph.	ν(C=O) ν(C=S)	ν(C=C) Arom.	ν(C-O)	Others
M1	OH	3425 3414	3241	3013	2982 2933	1687 1087	1529 1479	1373	ν (OH)3456
M2	NO_2	3378 3335	3298	3046	2987 2935	1679 1088	1558 1478	1370	ν (NO)1331,1525
M3	Cl	3381 3342	3256	3067	2958 2894	1685 1093	1521 1471	1358	ν (C-Cl)721
M4	$N(CH_3)_2$	3367 3319	3201	3073	2980 2910	1675 1097	1530 1490	1362	ν (C-N)1257
M5	H	3338 3261	3197	3062	2970 2905	1681 1092	1554 1484	1367	--

Proton ^{1}H-NMR analysis of compound M_1 confirmed the disappearance of the proton normally associated with the azomethine group, as well as signals indicating the formation of products following confirmation of the consumption of the reactants. A signal at 6.78 ppm appeared, indicating the presence of a CH group in the target ring. The information did not stop there, however, as another signal was detected at 4.37 ppm, indicating a CH_2 group in the target ring, which is the oxazolidone ring. The other groups, including the benzene ring, remained at their expected positions at 7.33–7.95 ppm. Furthermore, NH groups were detected at 9.30 and 10.19 ppm, whilst the final signal, at 12.42 ppm, corresponded to the hydroxyl (OH) group bound to the aldehyde [19]. As shown in Figure 3.

The use of ^{13}C-NMR spectroscopy for compound M1 revealed the disappearance of the azomethine group, whilst the signals indicated the formation of the desired ring structure; the signal at 108.83 parts per million corresponded to a carbon atom (CH) in the desired ring structure, and another signal at 67.65 parts per million corresponded to CH_2 in the same ring, whilst the signal at 169.70 parts per million indicated the formation of a carbonyl group in the desired ring structure. The (C=S) signal appeared at 178.27 parts per million, whilst the benzene signals were present at their usual positions, ranging from 127.79 to 135.39 parts per million, as shown in Figure 4.

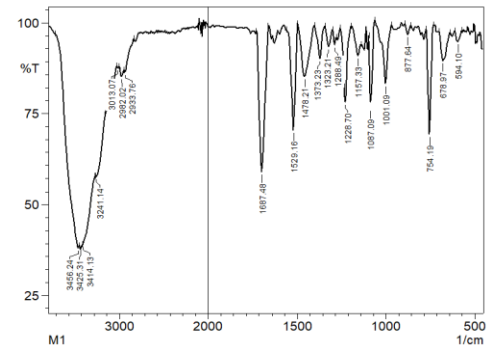


Figure 1. FT-IR OF (M1)

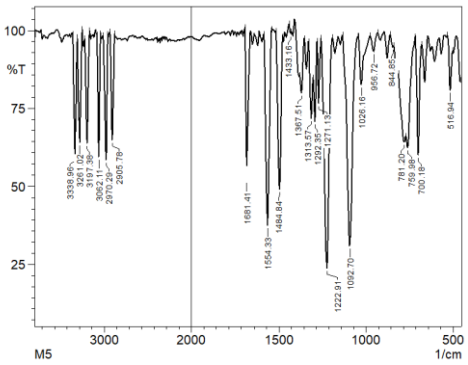


Figure 2. FT-IR OF (M5)

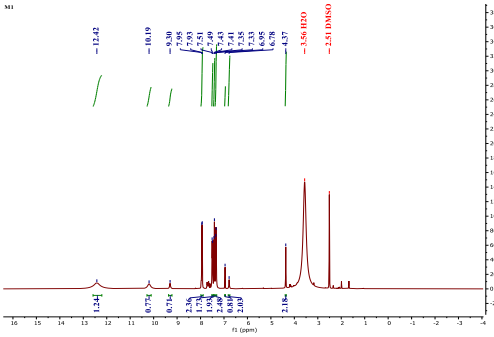


Figure 3. ^{1}H-NMR OF (M1)

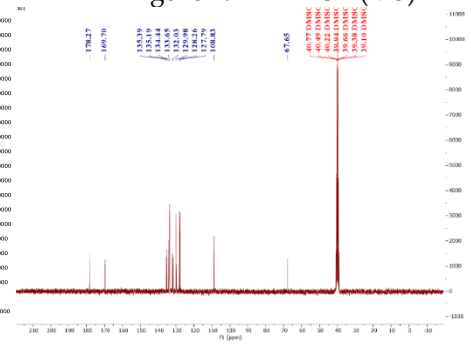


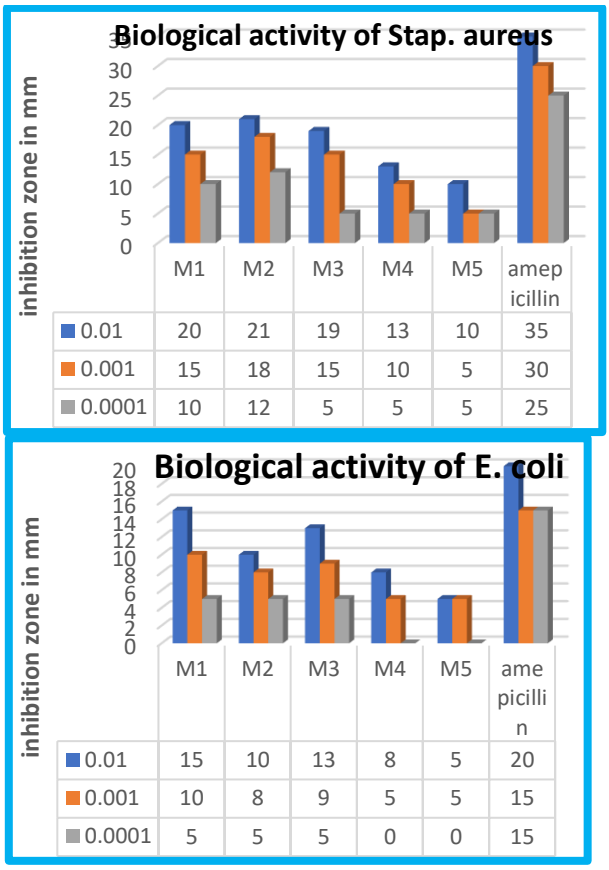
Figure 4. ^{13}C-NMR OF (M1)

3.2. Bacterial susceptibility to prepared compounds

The compounds produced at three different concentrations varied in their effectiveness in inhibiting growth of the target microorganisms, as seen in Table 4. It was observed that the capability of the compounds to inhibit growth of the target microorganisms on agar plates increased with increased concentrations [20, 21]. All in all, these compounds were found to be more effective against Gram-positive bacteria than Gram-negative bacteria. This is because Gram-positive bacteria lack outer wall preventing diffusion of chemicals within the cell compared to Gram-negative bacteria [22]. Concerning bacterial species, the most active compound M2 inhibited Gram-positive bacteria by up to 21 mm at the highest concentration tested. Even in medium and low concentrations, M2 maintained very high activity but lower than antibiotics. Thus, despite having lower activity than antibiotics, M2 is a highly promising compound for the use as antibiotic in the future [23]. However, in case of Gram-negative bacteria, M1 was the most potent and had an inhibition of 15 mm. We observe that pull group-based compounds are more efficient compared to push group-based ones due to the pull groups being instrumental in helping with cell membrane penetration [24].

Table 4. Data concerning the effectiveness of compounds (M1-M5) against microbes

Comp	**E.coli mg/ml**			**Staph. aureus mg/ml**		
No.	**0.01**	**0.001**	**0.0001**	**0.01**	**0.001**	**0.0001**
M1	15	10	5	20	15	10
M2	10	8	5	21	18	12
M3	13	9	5	19	15	5
M4	8	5	0	13	10	5
M5	5	5	0	10	5	5
amepicillin	20	15	15	35	30	25



Scheme 2. Information on how well substances (M1–M5) work against microorganisms

4. Discussion

The present findings demonstrate that the solvent-free fusion method successfully produced the targeted oxazolidinone derivatives (M1–M5), as supported by both spectroscopic characterization and biological evaluation. The disappearance of the characteristic azomethine signal together with the appearance of new carbonyl and C–O absorption bands in the FT-IR spectra provides strong evidence for cyclization and formation of the oxazolidinone ring [17], [18]. This structural assignment was further supported by the ^1H-NMR and ^13C-NMR spectra of M1, particularly the appearance of signals attributable to the CH and CH_2 groups within the newly formed heterocyclic ring and the carbonyl carbon signal associated with the oxazolidinone system [19]. These observations indicate that the solvent-free procedure is not only operationally simple but also sufficiently effective for obtaining the desired heterocyclic products. The antimicrobial results further demonstrate a clear concentration-dependent response, with larger inhibition zones generally observed at 0.01 mg/mL than at 0.001 and 0.0001 mg/mL [20], [21]. Overall, the synthesized compounds exhibited greater inhibitory activity against Staphylococcus aureus than against Escherichia coli. This difference may be associated with the more complex outer membrane of Gram-negative bacteria, which acts as an additional permeability barrier and can restrict the penetration of antimicrobial molecules [22]. Among the synthesized derivatives, M2 showed the highest activity against S. aureus, producing an inhibition zone of 21 mm at 0.01 mg/mL, whereas M1 exhibited the strongest activity against E. coli, with an inhibition zone of 15 mm at the same concentration. Although these values remained below those of ampicillin, the results suggest that structural modification of the oxazolidinone scaffold significantly influences antibacterial activity [23]. In particular, differences among the substituent groups of M1–M5 may alter electronic properties, lipophilicity, and interactions with bacterial membranes or intracellular targets, thereby accounting for the observed variation in activity. The comparatively better activity of compounds bearing electron-withdrawing substituents also suggests a possible contribution of electronic effects to antimicrobial

performance [24]; however, this structure–activity relationship should be interpreted cautiously because the present study did not directly investigate membrane permeability or molecular targets. Consequently, further studies involving minimum inhibitory concentration and minimum bactericidal concentration determination, broader bacterial panels, cytotoxicity evaluation, and molecular mechanism studies are required before these oxazolidinone derivatives, particularly M1 and M2, can be considered potential candidates for further antibacterial drug development.

5. Conclusion

In addition to economy and solventless, using the environmental-friendly reaction process increases the speed of synthesis of the chemicals thereby saving money. In addition to purity of the chemical products, this process provides a convenient and safe method for the reactions. The hydrazone azomethine molecule is combined with chloroacetic acid in the process forming five-membered rings based on oxazolidinone structure. All the synthesized substances have high purity especially in nuclear magnetic resonance and infrared spectra with total absorbance of the reagents used as well as the existence of different chemical groups of the desired ring. Also, these chemical substances exhibit good activity on the ***Staphylococcus aureus*** strain and moderate activity on ***Escherichia coli***, increasing in activity with concentration. Specifically, substance M2 was active enough to be considered in the future as antibacterial, and M1 was highly active against Gram-negative bacteria.

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