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Synthesis and Biological Activity of 1,3-Oxazpine-4,7-Dione Derivatives

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Abstract

The compounds 1,3-oxazepine-4,5-dione (C and D) are generated by reacting schiff base derivatives (A and B) with succinic anhydride. The Schiff bases (A and B) are obtained via the reaction between benzidine and 4-hydroxycinnamaldehyde, 4-dimethylaminocinnamaldehyde, resulting in the formation of Schiff bases. All synthesized derivatives are characterized based on their physical characteristics and spectrum methods, such as FTIR and ^{1}HNMR. These compounds were shown to possess antibacterial and antifungal properties and demonstrated significant effectiveness against all the microorganisms tested. The derivative of 1,3-oxazepine,4,5-dione (C) has an effect on zone inhibition on antimicrobial agents such as *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* at 34, 25, and 29 mm, respectively, which gives higher activity from the derivative (D). It was found that oxazepine derivatives (C and D) are more effective than Schiff base derivative (B) against all fungi that were tested, including *Aspergillus niger* and *Chalara corda*.

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1. Introduction

The scientific study of carbon-nitrogen double bonds has been fundamental to improving the field of chemical sciences [1]. These molecules have extensive uses in the area of chemistry due to the presence of a single pair of electrons on the nitrogen atom and the electron-donating nature of the double bond between them [2, 3]. Compounds having the >C=N group are often referred to as schiff bases, which include imines, azomethines, anils, and ligands [4]. Schiff initially synthesized these compounds and therefore named them in his honor [5]. An oxazepine derivative was introduced in 1965 as a treatment for mental conditions marked by worry and tension [6]. Oxazepine is a term used to describe a ring structure consisting of seven atoms, with one oxygen atom and one nitrogen atom included [7]. 1,3-oxazepine is a subset of many categories of heterocyclic oxazepine. 1,3-oxazepane-4,7-diones are composed of a seven-membered ring containing two carbonyl groups [8]. Extensive research and documentation have been conducted on the synthesis of oxazepine derivatives throughout the years. The significance of heterocyclic compounds lies in their substantial biological applications. Heterocyclic compounds, which include atoms from many elements inside their ring structure, have garnered significant interest in the development of medication-active chemicals and sophisticated organic compounds [9]. Antimicrobial resistance (AMR) poses a substantial risk to global health. In 2019, over 4.95 million fatalities were linked to antimicrobial resistance (AMR), with 1.95 million deaths attributed to illnesses caused by fungi, namely Candida, and Aspergillus [10]. The microorganisms that cause the most deaths due to antibiotic resistance include Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. The combined action of antibiotics and plant extracts against antibiotic-resistant bacteria may provide

novel therapeutic alternatives for the treatment of infectious illnesses in cases where the antibiotic alone is no longer effective [11]. The aim of this study was to synthesize new 1,3-oxazepine-4,5-dione derivatives (C and D) and characterize these derivatives by spectroscopic methods. These derivatives of oxazepine were tested as antibacterials and antifungals.

2. Materials and Methods

Benzidine, 4-dimethylaminocinnamaldehyde, and hydroxycinnamaldehyde were obtained from Sigma Aldrich Company, while ethanol absolute, dry benzene, succinic anhydride, glacial acetic acid, and malic anhydride were obtained from Merck Company.

2.1. Synthesis of Schiff base derivatives (A and B)

Dissolved Benzidine (0.01 mole, 1.84 g) in 15 ml of ethanol absolute with 4-hydroxycinnamaldehyde (0.02 mole, 2.96 g) and 4-Dimethyl-aminocinnamaldehyde (0.02 mole, 3.5 g), respectively in presence (2-3) drops of glacial acetic acid and the mixtures were stirred and refluxed for 6 hours. The precipitates were filtered to product derivatives of schiff base (A and B). The products were recrystallized from ethanol to give the Light-yellow color derivatives (A and B) [12, 13], as shown in scheme 1.

2.2. Synthesis of 1,3-Oxazepine-4,5-dione derivatives (C and D)

A mixture of derivatives A (0.01 mole, 4.44 g) and derivative B (0.01 mole, 4.94) and succinic anhydrides (0.01 mole, 0.1 g) was dissolved in 15 mL of dry benzene as solvent. The mixture was stirred and refluxed at overnight. The precipitates were filtered and recrystallized from ethanol to produce a 1,3-oxazpine derivatives (C and D), respectively [7, 16] as shown scheme 2.

2.3. Antibacterial

The bacterial cultures of *Staphylococcus aureus, Escherichia coli,* and *Bacillus subtilis* were acquired from the Baghdad laboratory, Baghdad, Iraq. The bacterial cultures were incubated at a temperature of 30 ± 0.1 °C for 24 hours by introducing them into nutritional agar. The 1,3-oxazepine-4,5-dione derivatives (C and D) were maintained in a dry environment at room temperature and dissolved at 25 mg/ml in dimethylsulfoxide (DMSO). The ability of each compound to kill bacteria was evaluated using the agar disc-diffusion method. The Mueller Hinton Agar Media (15 cm^3) was poured onto Petri plates and then solidified at a temperature of 45 °C. 9 cm Petri plates were inoculated with 5 0µL of a standard saline solution containing a culture media with a concentration of microbes of 105–106 bacteria per ml.

The prepared Schiff bases (50 µL) were injected into discs and then firmly pushed into the solid agar media. The Petri plates were incubated at a temperature of 37 degrees Celsius for a duration of 24 hours. The inhibitory zones created on the medium were measured at the conclusion of the time using a zone reader, and the measurements were recorded in millimeters.

2.4. Antifungal

The Department of Microbiology at the Baghdad laboratory, Baghdad, Iraq, provided pathogenic strains of *Asperigillus niger* and *Chalara corda*. The 1,3-oxazepine-4,5-dione derivatives (C and D) and schiff base derivative (B) were maintained in a dry environment at room temperature and dissolved in dimethylsulfoxide (DMSO) at a concentration of 25 mg/mL. The antifungal activity of each drug was assessed using the agar disc-diffusion technique. The Sabarod agar medium (15 cm^3) was put into the petri dishes and allowed to harden at a temperature of 45 °C. Discs of filter paper, measuring 10 mm in diameter, were soaked with prepared 1,3-oxazepine-4,5-dione derivatives (C and D) and schiff base derivative (B) (50 µL) and then positioned onto the fungus-seeded substrate. The plates were thereafter incubated at a temperature of 27 degrees Celsius for a duration of 1 to 7 days. The inhibitory zones that developed on the medium were measured at the conclusion of the time using a zone reader, and the measurements were recorded in millimeters.

3. Result and Discussion

The mechanism of Schiff base manufacturing is an unique type of nucleophilic addition to the carbonyl group, in which the amine acts as the nucleophile. The amine undergoes a reaction with the carbonyl group, resulting in the formation of an unstable addition product known as carbinolamine. The carbinolamine undergoes dehydration by either acid or base catalyzed mechanisms. Due to its alcohol nature, the carbinolamine experiences dehydration by acid catalysis as shown in figure 2. Oxazepine derivatives prepared in this paper were by cycloaddition reaction [2+5] of the prepared imines with succinic anhydride by refluxing the reaction

mixture in dry benzene.In FTIR, the amino group peaks of the amine derivative and the carbonyl group of the amine derivative disappear after characterization of these derivatives (A and B) and appear of the azomethine group. In the characterization of 1,3-Oxazepine-4,5-dione derivatives (C and D), the azomethine group of Schiff base disappears and the carbonyl group of lactam and lactone for Oxazepine appears. In 1H-NMR, the derivative A and B appeared the protons of azomethine group, which that disappeared at formation of derivative C and D. Schiff base derivative (A): Yield: 74%, Color: Light yellow, Melting point: 219 °C. FTIR (cm-1): 3002 C-H (Aromatic), 2925, 2849 C-H (Aliphatic), 1633 Azomethine, 1617, 1597 C=C (Aliphatic and Aromatic) [14]. Schiff base derivative (B): Yield: 71%, Color: Yellow, Melting point: 204 °C. FTIR (cm-1): 3039 C-H (Aromatic), 2983, 2843 C-H (Aliphatic), 1638 Azomethine, 1619, 1583 C=C (Aliphatic and Aromatic) [15].

From results of FTIR, the azomethine group of Schiff base disappears and the carbonyl group of lactam and lactone for Oxazepine appears. In 1H-NMR disappeared protons of azomethine groups. 1,3-Oxazepine-4,5-dione derivative (C): Yield: 78%, Color: Orange, Melting point: 234 °C. FTIR (cm-1): 3042 C-H (Aromatic), 2988, 2852 C-H (Aliphatic), 1691 (C=O lactam), 1717 (C=O lactone), 1601, 1593 C=C (Aliphatic and Aromatic). 1H-NMR: (DMSO-d6), δ, ppm: 9.13 (s, 2H, OH), 6.88 – 7.53 (m, 24H, Aromatic ring), 6.68 – 6.70 (m, 4H, HC=CH), 2.69 – 2.76 (m, 4H, CH2) [17]. 1,3-Oxazepine-4,5-dione derivative (D): Yield: 76%, Color: Dark orange, Melting point: 229 °C. FTIR (cm-1): 3060 C-H (Aromatic), 2981, 2832 C-H (Aliphatic), 1694 (C=O lactam), 1718 (C=O lactone), 1602, 1572 C=C (Aliphatic and Aromatic). 1H-NMR: (DMSO-d6), δ, ppm: 9.13 (s, 2H, OH), 6.88 – 7.53 (m, 24H, Aromatic ring), 6.68 – 6.70 (m, 4H, HC=CH), 2.69 – 2.76 (m, 4H, CH2) [18].

3.1. Antibacterial activity

The antibacterial evaluation of the 1,3-oxazepine at a dosage of 25 mg/ml has yielded data indicating their effectiveness against all microorganisms. The diameter of the inhibitory zones was measured in millimeters, and the corresponding findings are shown in table 1. The antimicrobial testing results demonstrate that 1,3-oxazepine derivatives exhibit notable activity against *Staphylococcus aureus, Escherichia coli,* and *Bacillus subtilis*. Derivative (C) was particularly effective against all tested bacterial strains due to a hydroxyl group in his structure, which possesses inherent antimicrobial properties. The antibacterial activity of these chemicals demonstrates an increasing order. As concentration increases, the region of growth inhibition likewise increases.

3.2. Anti-fungal activities

The results of the study of the antifungal activity demonstrate that the 1,3-oxazepine derivative (C, D) exhibit greater potency against all tested fungi, such as *Aspergillus niger* and *Chalara corda*, compared to the Schiff base derivative (B). derivative (D) exhibit the highest level of effectiveness against all types of fungus that were tested. The findings of the antifungal activity are shown in table 2. The present study focuses on the in-silico investigation of the inhibitory effects of oxazepine derivatives on GP6 synthase. It is interesting to note that the functional amine group of the diazepine and the carboxylate group formed two regular hydrogen bonds. This is one of the main reasons why both derivatives had a strong ability to bind to the receptor. Additionally, the interaction diagram reveals the presence of other interactions, such as van der Waals forces and π-alkyl interactions.

3.3. Calculation van der waals (vdw radius)

The van der waals (vdw radius) for each atom were 1.20 for hydrogen atom, 1.52 for oxygen atom, 1.70 for carbon atom and 11.80 for Sulphur atom that calculate by used pymol software with 3 dimension structures of oxazepine derivative C [19], as shown in figure 1.

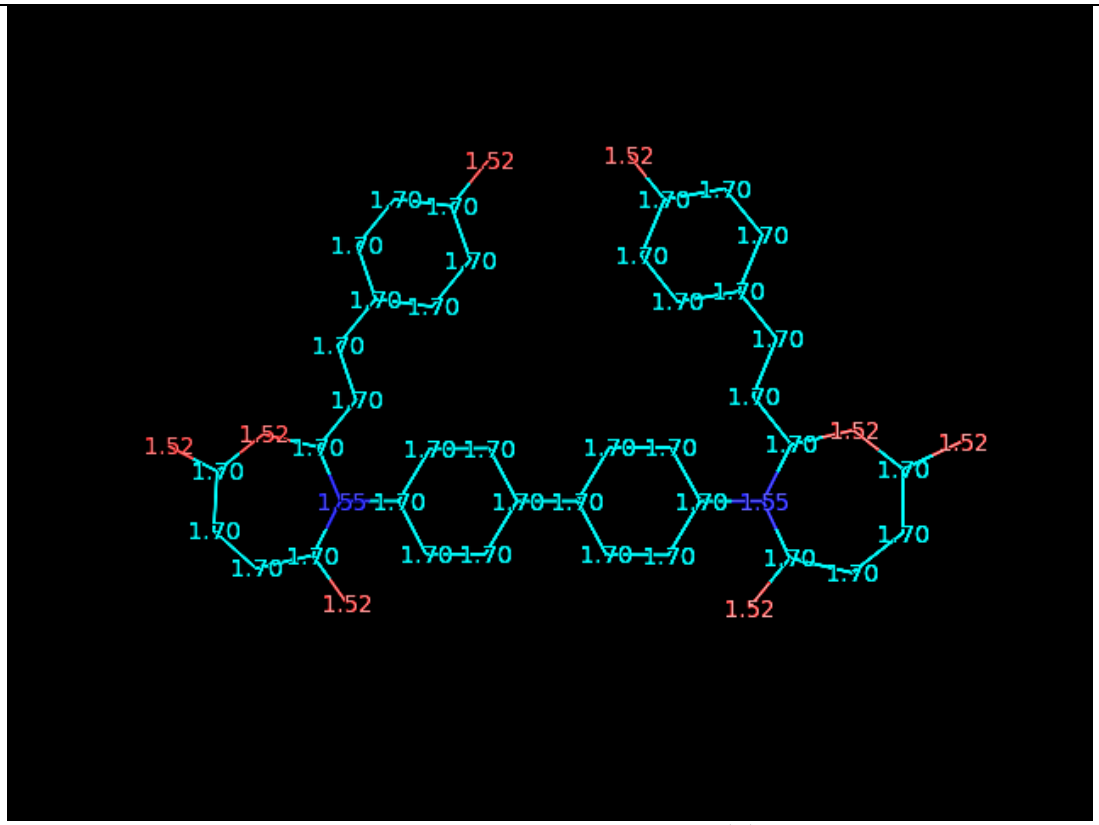


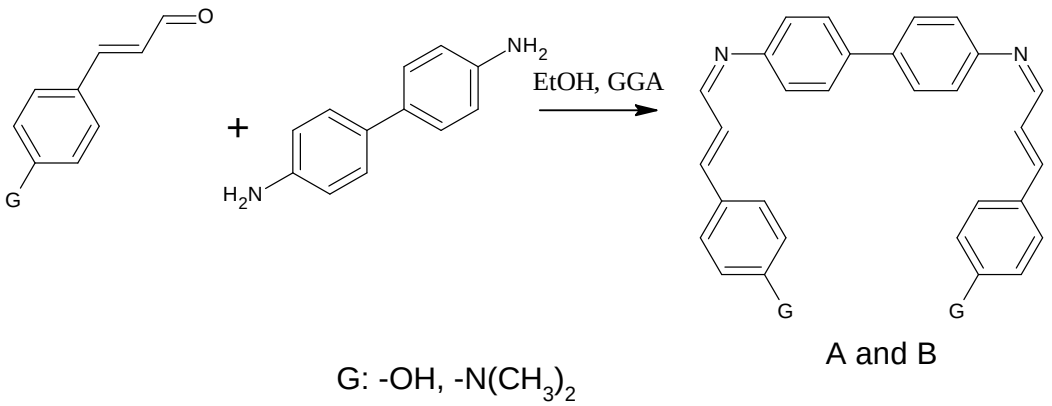
Figure 1. Van der Waals for Oxazepine derivative (C) by Pymol analysis.

Table 1. Antibacterial activity of oxazepine derivatives (C and D).

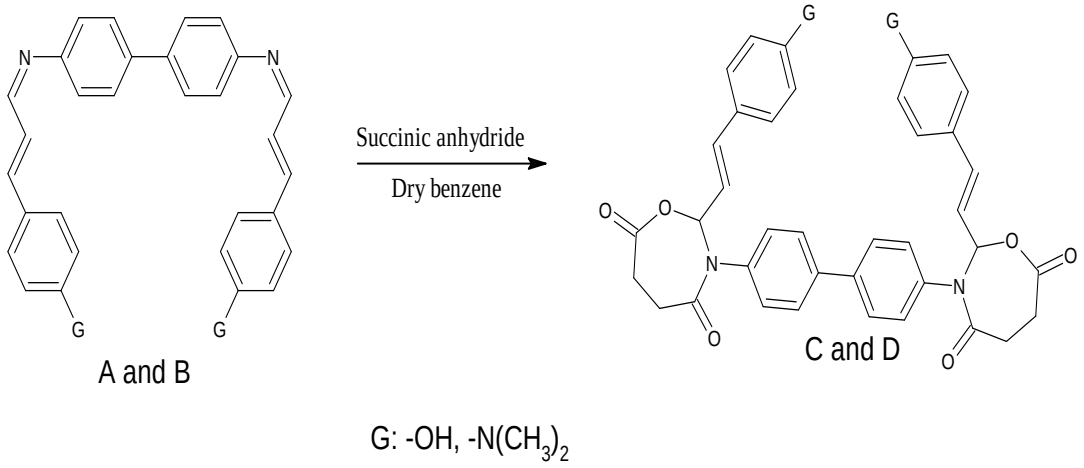
Compound	Zone inhibition (mm)		
	Staphylococcus aureus	*Escherichia coli*	*Bacillus subtilis*
C	34	25	29
D	21	18	23

Table 2. Antifungal activity of oxazepine derivatives (C and D) and schiff base derivatives (B).

Compound	Zone inhibition	
	Aspergillus niger	*Chalara corda*
B	23	21
C	27	29
D	26	21



Scheme 1. Synthesized schiff bases (A and B).



Scheme 2. Synthesized oxazepine (C and D).

4. Conclusion

Schiff bases (A and B) are formed by reacting benzidine with 4-hydroxycinnamaldehyde, 4-dimethylamino-cinnamaldehyde. The derivative of 1,3-oxazepine,4,5-dione (C) inhibits antimicrobial agents such Staphylococcus aureus, Escherichia coli, and Bacillus subtilis at 34, 25, and 29 mm, respectively, increasing its action. Oxazepine derivatives (C and D) outperformed Schiff base derivative (B) against all fungus, including Aspergillus niger and Chalara corda.

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Conflicts of Interest: The authors declare no conflict of interest.

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