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Article

Synthesis, Characterization and Evaluation of New Oxazepine Derivatives for Antibacterial Activity

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Abstract: Maleic anhydride was reacted with previously synthesized Schiff bases in the presence of dry benzene, aiming to form a heptad ring derived from oxazepine. This study addresses the need for new bioactive compounds due to increasing bacterial resistance to traditional antibiotics. Physical characteristics such as yield, color, and melting point, along with spectral data (IR and NMR), confirmed the successful synthesis of the compounds. Their antibacterial activity was evaluated against Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive), showing comparative results to the antibiotic amoxicillin. The findings suggest potential applications of these oxazepine derivatives as antimicrobial agents.

Keywords: Heterocyclic, Oxazepine, Biological activity

Introduction

Oxazepines are mostly compounds with a seven-membered, unsaturated ring called Oxazepine [1], It is also known as oxazepine when it is saturated. They have two heteroatoms, nitrogen and oxygen, and five carbon atoms [2]. Furthermore, oxynitrogen heterocyclic compounds exist in three isomers, 1,2-, 1,3-, and 1,4-, the numbers of which vary according to the locations of the nitrogen and oxygen atoms in the hexagonal ring. Oxazepine [3].Compared with the hexagonal aromatic ring of benzene, the size of the hexagonal ring of the non-planar Oxazepine ring is larger, making it non-planar. Due to its larger size, the hexagonal ring has a boat-shaped shape in the spatial distribution of atoms and is therefore more stable. It reduces ring tension, so it is non-aromatic [4]. These compounds are non-planar and therefore non-aromatic.

We find that the percentage of formation of these compounds increases as the size of the ring increases, and they are also easy to prepare due to the difference in quantity. We find that a large number of heterogeneous compounds are prepared and produced in this field [5], and many studies have proven the possibility of using Oxazepine compounds in the treatment of many diseases and psychological disorders. This prompted many researchers to search for new ways to prepare them [6]. Oxazepines are heterogeneous organic compounds containing nitrogen in their structure, which makes

them of great biological importance, especially in the medical and pharmaceutical fields. The polymer is a chemical derivative of oxazepine that has heterogeneous effects on bacteria [7].

Materials and Methods

2.1. Chemicals Used:

Chemicals sourced from Aldrich, BDH Thomas, Fluka, and Merck were utilized.

2.2 Devices Used:

Melting points were determined using a thermoelectric melter 9300. A KBr disk on a 400-4000 cm^{-1} scale was employed. Shimadzu FT-IR 8400S spectrophotometer and Bruker equipment operating at 400 MHz were used for ^{1}H-NMR spectra. Fluka silica gel plates with a thickness of 0.2 mm were applied for thin-layer chromatography (TLC).

2.3. Preparation of Oxazepines derivatives (B6-B10).[8]

An equal amount (0.001 mol) of the prepared Schiff base was dissolved with maleic anhydride (30 ml) in dry benzene and the mixture was stirred for (9-12) hours. The mixture was cooled and the precipitate was filtered and recrystallized. The solvent was used as 1,4-dioxane. As shown in Table (1)

2.4. Biological activity study

Dissolve 39 g of Mueller Hinton agar in 1 litre of distilled water, then dissolve it by heating and stirring with a magnetic stirrer, and sterilize it using an autoclave at a temperature of 121 °C and a pressure of 1.5 bars[9-14]. It was cooled to 50 °C for 2 hours, then poured into Petri dishes and left to solidify at room temperature, and two bacterial isolates were tested, one of which was Gram-negative, E. coli. Gram-positive [Gr+ve] Using heat-sterilized carriers, two colonies of pure Gram-positive and Gram-negative bacteria isolates were moved to solid medium plates[15–20]. \

Test tubes with five millilitres of distilled water inside were incubated at 37 °C for sixteen to twenty hours. The turbidity was then diluted with physiological salt until it was comparable to the standard turbidity. Acquiring around 1.5 x 10^8 cells/ml as the cell count. Dimethyl sulfoxide (DMSO) solvent was used to generate chemical solutions of some of the prepared compounds at three different concentrations of each component (for each solid derivative): 0.1, 0.01, and 0.001 mg/ml[21–25].

Results and Discussion

The Scheme shows the series of prepared compounds.

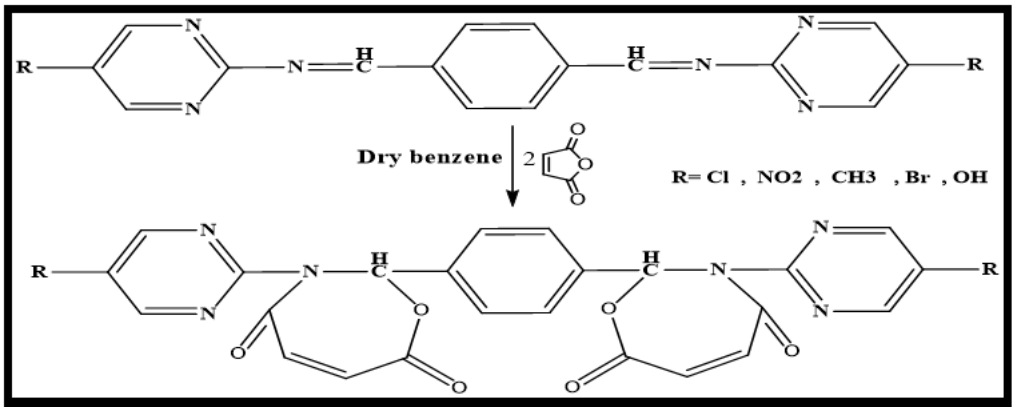


Figure 1. Path of the Ready Compounds (B6-B10)

Characterization of Oxazepine Derivatives (B6-B10)

The FT-IR spectrum of compounds (F6-F10) showed two bands at (1697-1690) cm-1, (1654-1643) cm-1 Due to (C=O) lactone and lactam respectively, two bands at (2976-2930) cm-1, (2903-2812) cm-1 Due to aliphatic (CH), two bands at (1564-1515) cm-1, (1509-1467) cm-1 Due to aromatic (C=C), a band at (1342-1315) cm-1 Due to (C-O), and a band at (1228-1215) cm-1 Due to (C-N)[26]. as shown in Table 2 and Figure 1.2

The 1H-NMR spectrum of compound B6 showed two Double signals at (6.66-6.92) ppm for (CH=CH) oxazepine, a signal at (7.38) ppm for (CH) oxazepine, signals at (7.76,8.11) ppm for aromatic rings, [27,28]. as shown in Figure3. The 1H-NMR spectrum of compound F8 showed a signal at (2.36) ppm for (CH3), two Double signals at (6.43-6.81) ppm for (CH=CH) oxazepine, a signal at (7.44) ppm for (CH) oxazepine, signals at (7.77,8.17) ppm for the aromatic rings, and a signal at (8.83) ppm for (NH). as shown in Figure 4. The 1H-NMR spectrum of compound B10 showed two Double signals at (6.54-6.91) ppm for (CH=CH) oxazepine, a signal at (7.23) ppm for (CH) oxazepine, signals at (7.80,8.17) ppm for aromatic rings, and a signal at (9.66) ppm for (OH). as shown in Figure 5

Evaluation of the Biological Activity of Prepared Compound

Insert a sterile cotton swab into the test tube containing the diluted bacterial culture and remove excess inoculum by pressing the swab against the inner wall of the tube. Inoculate Mueller Hinton agar (MHA) with the sterile cotton swab and wipe it over the culture[29-35]. Leave the Petri dish aside (10-15 days) for a few minutes to absorb the culture and dry the medium. The agar diffusion technique was used to assess the synthesized compounds' antibacterial activity. Create holes in the Petri plates using the cylinder measurement method (per USP 35) [36–41] after introducing the bacterial isolates into the culture medium.

Using a cork drill, fill each well with 40 microliters of each of the three concentrations of the produced compounds. Next, incubate the dish for 24 hours at 37 degrees Celsius in an incubator, and then for another 24 hours[42–45]. and (48) analyzed the data after four hours to demonstrate the sensitivity of the derivative used, which is dependent on the inhibitory diameter that develops in the culture dish surrounding the well used. An increase in the inhibitory diameter indicates a higher bioavailability of the compound and is compared to the inhibitory diameter of common antibiotics, some of which are already used in solution form, like amoxicillin, based on tests conducted by the World Health Organization and Ministry of Health laboratories[46–53]. as shown in Table 3 and Figure 6.7

Table 1. Some physical properties of for prepared compounds (B6-B10)

Comp. No.	R	Molecular formula	m.p. °C	Yield%	Color
B6	4-Cl	$C_{25}H_{16}Cl_2N_6O_5$	218-220	71	Yellow
B7	4-NO2	$C_{25}H_{16}N_8O_9$	246-248	74	Light Brown
B8	4-CH3	$C_{27}H_{22}N_6O_5$	267-265	76	Yellow
B9	4-Br	$C_{25}H_{16}Br_2N_6O_5$	256-254	78	Dark Yellow
B10	4-OH	$C_{25}H_{18}N_6O_7$	236-234	75	Red

Table 2. FT-IR absorption results for Prepared compounds (B6-B10)

Comp. No.	R	ν(C-H) Arom.	ν(C-H) Aliph.	ν(C=O) Lactone Lactam	ν(C-O) ν(C-N)	ν(C=C) Arom.	Others
B6	4-Cl	3034	2976 2812	1697 1645	1315 1224	1533,1487	ν(C-Cl) 756
B7	4-NO2	3045	2955 2890	1695 1651	1310 1221	1564,1488	ν(NO_2) *asy*. (1521) *sym*. (1351)
B8	4-CH3	3050	2930 2903	1691 1654	1317 1228	1551,1492	--
B9	4-Br	3028	2933 2869	1690 1643	1326 1219	1557,1509	ν (C-Br) 590
B10	4-OH	3082	2931 2844	1695 1645	1342 1215	1515,1467	ν (OH) 3421

Table 3. Biological efficacy of produced substances and control methods (measured in cm of inhibition)

Comp. No.	E. Coil Conc. mg/ml			Staph. Aureus Conc. mg/ml		
	0.01	0.001	0.0001	0.01	0.001	0.0001
B6	1.8	1.5	0.3	2.8	2.8	1.5
B7	1.7	1.3	1	3	2.7	0.4
B8	3.5	3.5	1	2	1.5	1
B9	1.3	2.1	0.5	1.5	1	0.5
B10	2.5	2.1	1.5	2.6	2	0.8
Amoxicillin	3.8	3.5	1.8	3.5	3	2

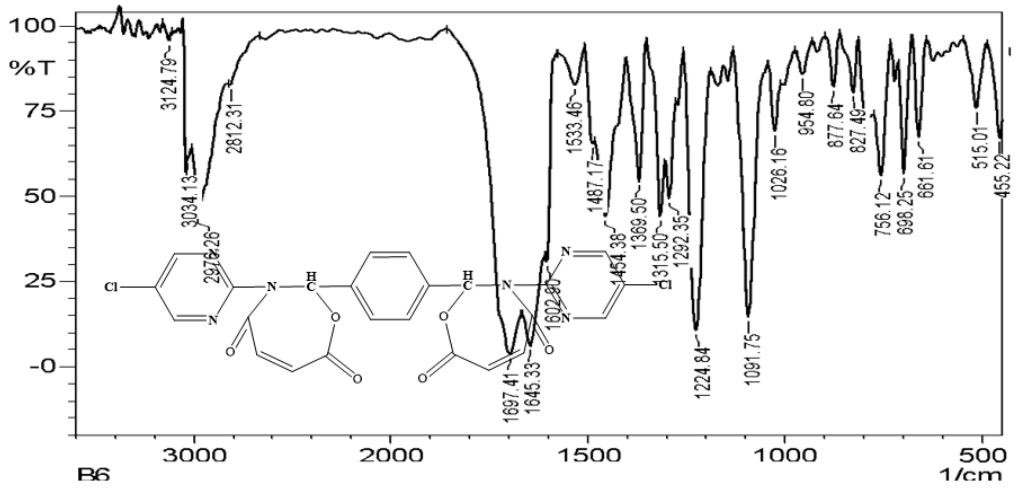


Figure 1. The compound's FT-IR spectra (B6).

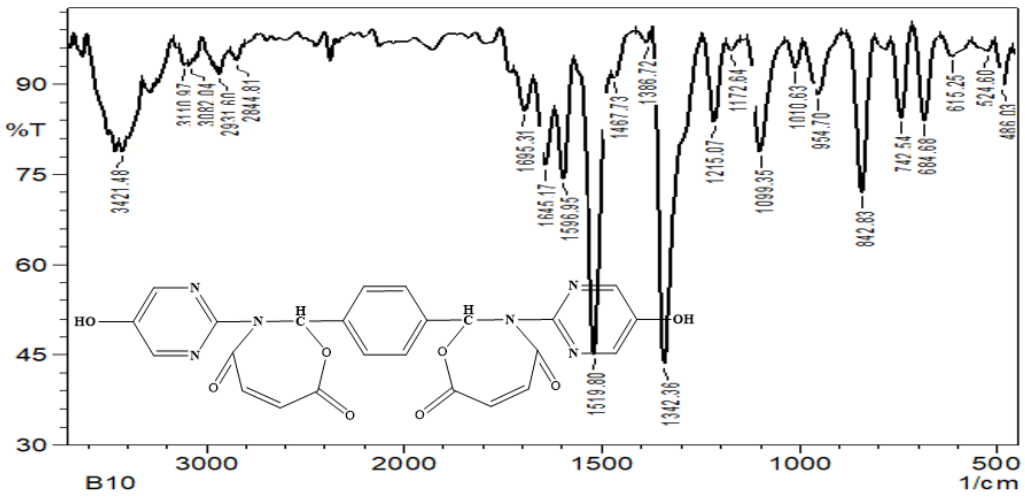


Figure 2. The compound's FT-IR spectra (B9)

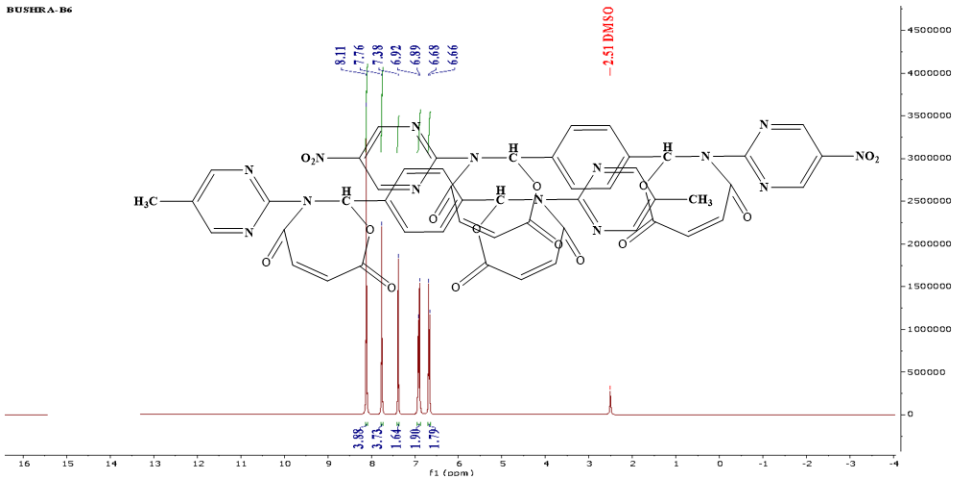


Figure 3. 1-H NMR spectra of the substance (B7)

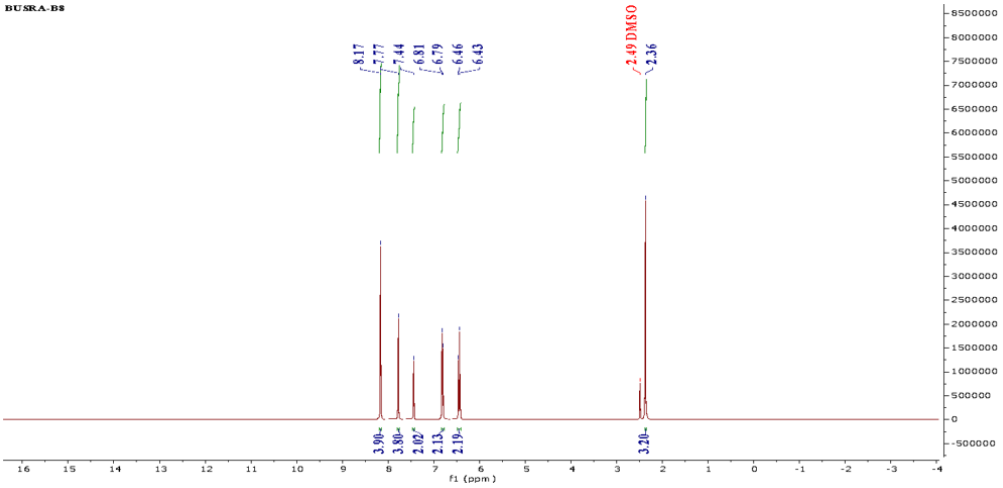
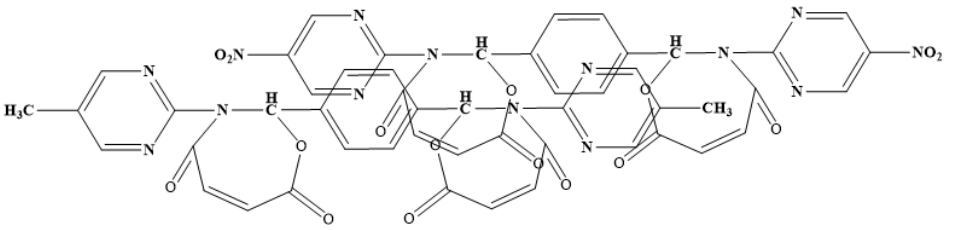


Figure 4. 1-H NMR spectra of the substance (B8)



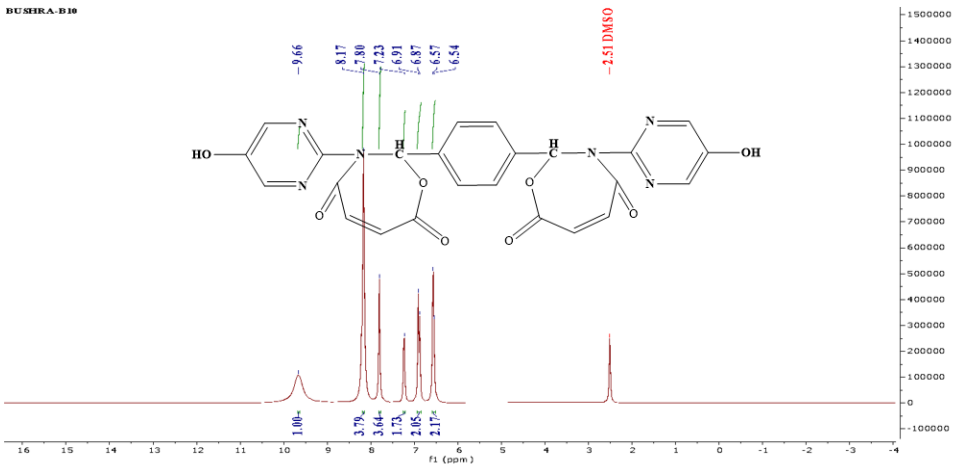


Figure 5. 1-H NMR spectra of the substance (B10)

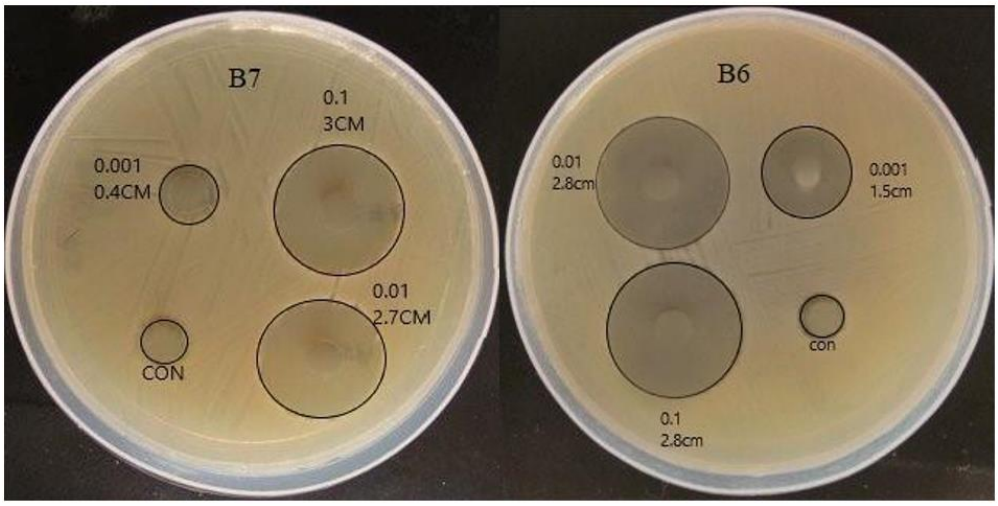


Figure 6. Biological effectiveness of the compound B6, B7 against becteral staph. Aurous

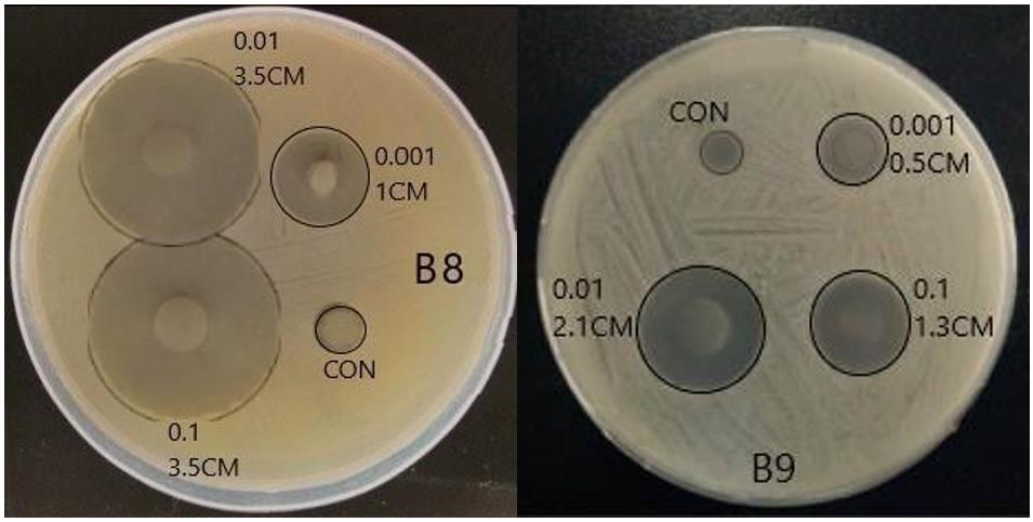


Figure 7. Biological effectiviness of the compound B8, B9 against becteral E.coli

Conclusion

In conclusion, the study successfully synthesized oxazepine derivatives through the reaction of the (C=N) group with maleic anhydride, confirmed by FT-IR and H-NMR spectra, which demonstrated high purity and yield of the compounds. The biological activity tests revealed that these synthesized compounds exhibited significant antibacterial effects, surpassing the inhibition performance of standard antibiotics. Notably, compound B8 showed the strongest inhibition against E. Coli with a zone of inhibition of 3.5 cm, while compound B7 inhibited Staphylococcus aureus by 3 cm. These findings imply the potential of these compounds as promising antibacterial agents. Further research is warranted to explore the molecular mechanisms underlying their antimicrobial efficacy and to evaluate their potential applications in medicinal chemistry.

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