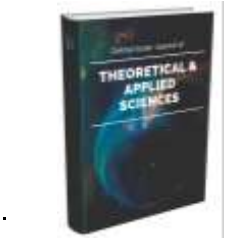

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Article

Synthesis and Characterization of New Derivatives of The Seven-Ring Oxazepine and Study of Their Bacterial Activity

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Abstract: This article deals with the preparation and characterization of new derivatives of oxazepine compounds using the traditional method of sublimation. This study of this type of seven-membered rings comes due to its wide-ranging pharmacological and biological importance in various medical and pharmaceutical fields. These compounds were prepared by reacting 2-aminophenol with chalcones (prepared by reacting acetophenone substitutes with 4-chlorothiazole-5-carbaldehyde, which was considered the main core of this study). The results showed that these compounds have good physical properties and stability in laboratory conditions. Some spectroscopic methods such as (F.T-I.R , H-N.M.R and C-N.M.R) were used to prove the validity of the structures of these materials in addition to their purity. When testing their biological activity against two types of Gram- negative (*Escherichia coil*) and Gram- positive bacteria (*Staphylococcus aureus*). The results showed that the antibacterial activity varied, as compound M8 had the highest activity against negative bacteria, followed by compound M10, while the activity against positive bacteria was less clear compared to the antibiotics used as a control. *Ciprofloxacin* was used as a control sample, and its activity was higher than the prepared compounds. Despite this, the compounds can be considered promising materials for use as pharmaceutical antibiotics.

Keywords: Oxazepine, Biological Activity, Ciprofloxacin

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1. Introduction

Heterocyclic compounds are among the most diverse and important classes of organic molecules and have found a wide range of applications in medicinal and pharmaceutical sciences. Of these, seven-membered heterocycles, like oxazepines, have garnered particular interest due to the intricate structure and wide ranges of biological activity. The most common of such compounds contain a heterocyclic scaffold with nitrogens and oxygens that add to their wide-ranging pharmacological potential [1]. This class of compounds has indeed been investigated over the past decades, as potential antimicrobial agents, anticancer and modulators of neurological disorders, see Figure 1 [2]. Appropriate functional substitutions generate structural diversity that not only serves as a basis for future research into new derivatives with improved potential to circumvent known forms of microbial resistance but also to generate more effective therapeutic outcomes [3].

In other words, oxazepine compounds have a broad spectrum of biological activities, such as antioxidant, anti-inflammatory, and antibacterial activities. Subamination on oxazepine rings have been shown in multiple studies to alter pharmacological activity [4]. Pyrrolo-based oxazepines, in particular, have displayed potent antimicrobial activity and have been reported as potential antihypertensive and opioid analgesic agents. While such results are promising, the relationship between the molecular modification and biological activity is still poorly characterized, particularly in the case of derivatives created through

sublimation [5]. These highlight the need for experimental studies in a systemic manner to demonstrate their bioactivity and structural stability.

The literature overview shows that many of the fundamentals on oxazepines are based on classical syntheses and limited biological assays. More recent endeavours, however, have made similar compounds functional which then appear better soluble, stable and with a more extended therapeutic index [6]. However, there is a lack of integration of spectroscopic characterization followed by broad-spectrum in vitro antibacterial assessment against Gram-positive and Gram-negative strains. In addition, very few comparisons have been made between newly synthesized oxazepines and clinically proven antibiotics like ciprofloxacin, leaving their direct therapeutic potential unclear [7].

To fill this void, the current study will synthesize and characterize new oxazepine derivatives through the condensation of the reaction of 2-aminophenol with different chalcones. This rigmarole utilizes all mundane sublimation procedures and then followed by recrystallization; products thereafter are characterized in detail structurally via spectra such as FT-IR, ^1H-NMR, and ^13C-NMR. Then the antibacterial activity of obtained compounds is determined through agar well diffusion method against two kinds of bacteria including Gram-negative bacteria (Escherichia coli) and Gram-positive bacteria (Staphylococcus aureus). Ciprofloxacin is the standard control antibiotic to which therapeutic outcomes are directly benchmarked under laboratory conditions [8].

Results from this research will broaden knowledge of oxazepine derivatives and their prospect as antimicrobial agents. Some of the synthesized compounds are expected to show high-level inhibition, especially against gram-negative bacteria, indicating that they may be utilized as alternative or additive therapies with existing antibiotics [9]. This study provides not only an estimated structure–activity relationship but also supports the pharmacological study in the future. In the end, this has repercussions for drug discovery and the global struggle for protection against antibiotic resistance [10].

2. Materials and Methods

2.1. Material: All materials used were fully supplied by BDH, Fluka and Aldrich.

2.2.Devices: FT-IR 8400S disc 400-4000 cm-1 scale. 1H-NMR and 13C-NMR Bruker equipment operating at 300 MHZ.

2.3. synthesis of Oxazepine compounds (M_6-M_{10})[13]:

In a round-bottomed flask, 2-aminophenol (0.004 mol, 0.432 g) was solubillized in ethanol, while the chalcone derivatives (0.004 mol) were solubillized in 10 ml of ethanol. After that, the mix was agitated for 12 to 14 hours. Methanol was used to concentrate, filter, wash, and recrystallize the mix. The compounds' physical and chemical characteristics are listed in Table 1.

Table 1. physical properties of the compounds (M_6-M_{10})

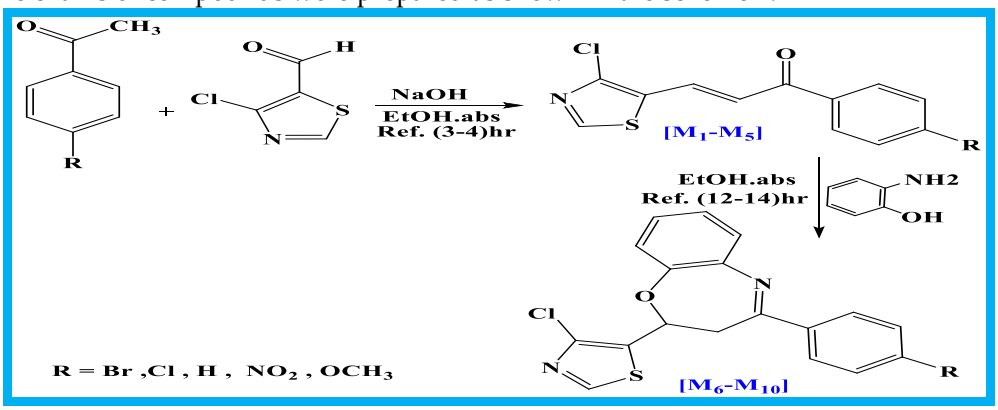
Comp No.	Ar	Molecular Formula/	Color	M.P (^{0}C)	R.T hr	R_f	Yield (%)
M_6	Br	$C_{18}H_{12}BrClN_2OS$	Orange	239-231	12	0.89	64
M_7	Cl	$C_{18}H_{12}Cl_2N_2OS$	Yellow	228-231	14	0.93	63
M_8	H	$C_{18}H_{13}ClN_2OS$	Light Brown	257-259	13	0.86	61
M_9	NO_2	$C_{18}H_{12}ClN_3O_3S$	Light yellow	216-218	14	0.94	59
M_{10}	OCH_3	$C_{19}H_{15}ClN_2O_2S$	Light yellow	257-260	12	0.87	65

2.4.Biological activity study:

The method for evaluating the antibacterial activity of compounds relies on a precise procedure that begins with the preparation of Mueller-Hinton agar (MHA) medium, followed by sterilization and pouring into Petri plates[11]. Next, two pure bacterial isolates are prepared: *Escherichia coli* and *Staphylococcus aureus*[12]. Bacterial suspensions are prepared by titrating the turbidity to 1.5 × 10^8 cells/mL. Compound solutions are then prepared in DMSO at concentrations of 0.1, 0.01, and 0.001 mg/mL. The medium is then inoculated with a cotton swab and evenly distributed. Using the agar well diffusion method, 40 µl of each solution is then added to the prepared wells[13][14]. The plates are incubated at 37°C for 24–48 hours, and the results are read to determine biological activity by comparing the diameter of the zone of inhibition surrounding the wells with that produced by standard antibiotics, such as ciprofloxacin[15].

3. Results and Discussion

The chains of compounds were prepared as shown in the scheme 1.



Scheme (1): Shown prepared compounds.

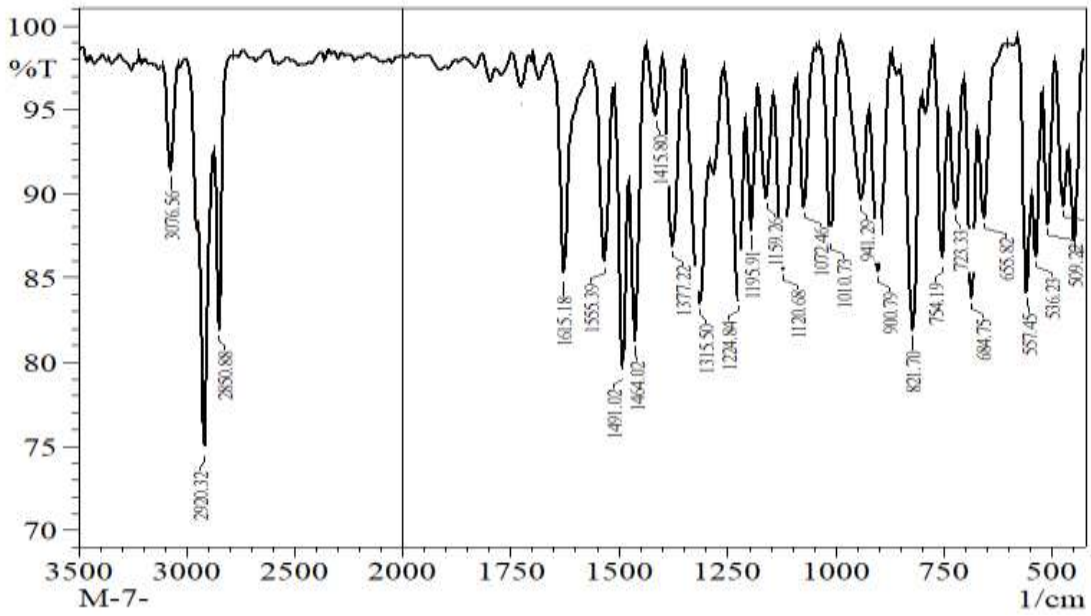
3.1. Characterization of Oxazepine derivatives [M6-M10]:

The compounds' infrared spectra [M6-M10] showed uptake lines in the (3083-3053) cm-1 area due to the elongation of the aromatic (C-H) link. Additionally, the elongation of the aliphatic (CH) link resulted in the appearance of two uptake lines in the span (2960-2920) cm-1 and (2831-2874) cm-1, while the elongation of the (C=N) link inside the seven-membered ring caused an uptake lines to arise in the span (1615-1623) cm-1 [16][17]. In addition to the formation of uptake lines at (1338-1377) cm-1 and (1224-1264) cm-1 due to the symmetric elongation, two uptake lines in the span of (1583-1548) cm-1 and (1491-1476) cm-1 were also seen as a result of the elongation of the aromatic (C=C) link. Additionally, as table 2 and figure 1, 2 demonstrate, the asymmetrical sequential formation of the (C-O-C) link inside the seven-membered ring and the creation of an uptake lines in the span of (1209-1190) cm-1 are caused by the elongation of the (C-N) link [18], see Table 2.

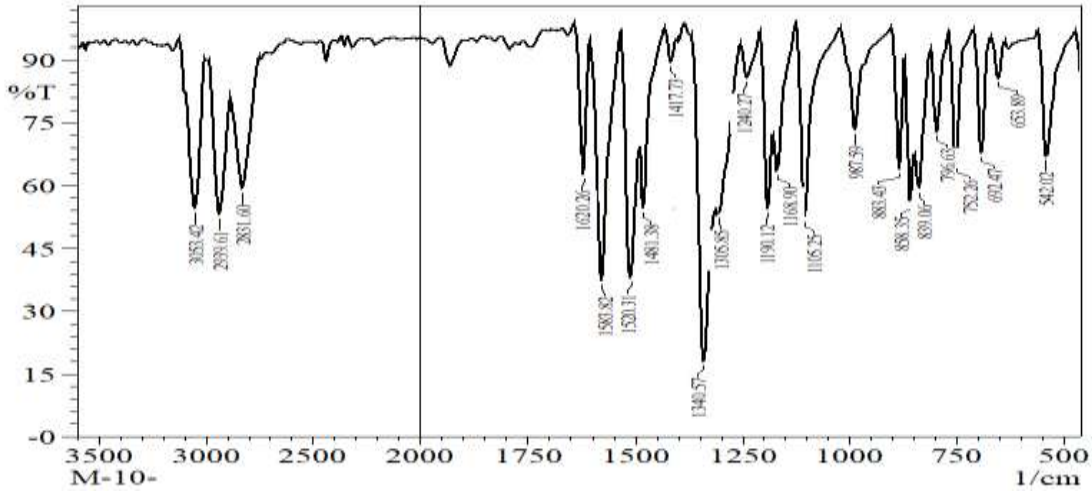
Table 2. IR absorption spectra values of compounds (M6-M10)

Comp. No.	Ar	ν (C-H) Arom.	IR (KBr) cm^{-1}					
			ν(C-H) Aliph.	ν(C=N)	ν(C=C) Arom.	ν (C-O).	ν (C-N)	Others
M6	Br	3056	2956 2859	1623	1567 1487	1367	1209	ν (C-Br)613
M7	Cl	3076	2920 2850	1615	1555 1491	1377	1195	ν (C-Cl)723
M8	H	3068	2931 2874	1618	1563 1481	1348	1197	---
M9	NO_2	3083	2960 2852	1621	1548 1476	1338	1207	ν(NO_2) *asy*. (1520)

								sym. (1340)
M10	OCH_3	3053	2939 2831	1620	1583 1481	1340	1190	---

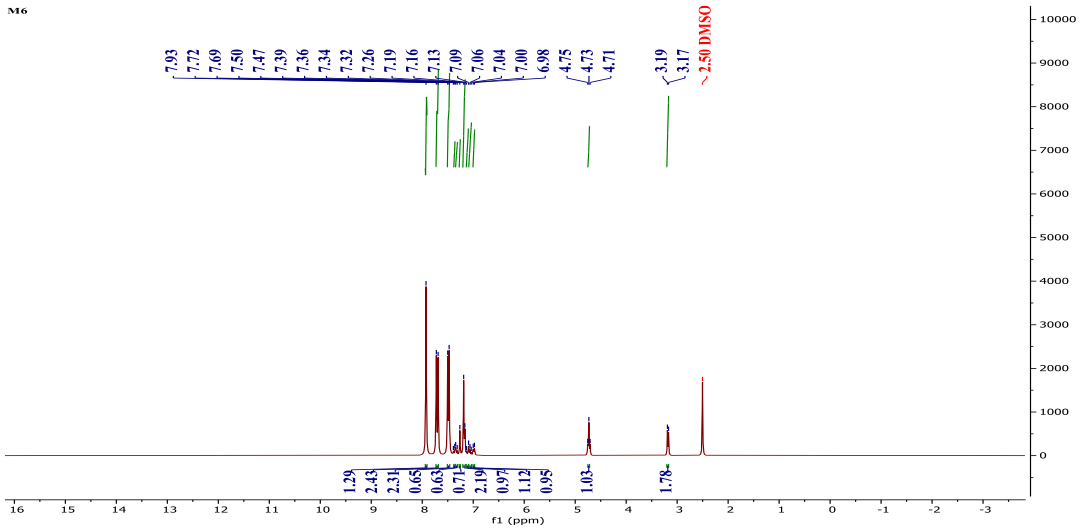


Fig(1): FT-IR of (M_7)



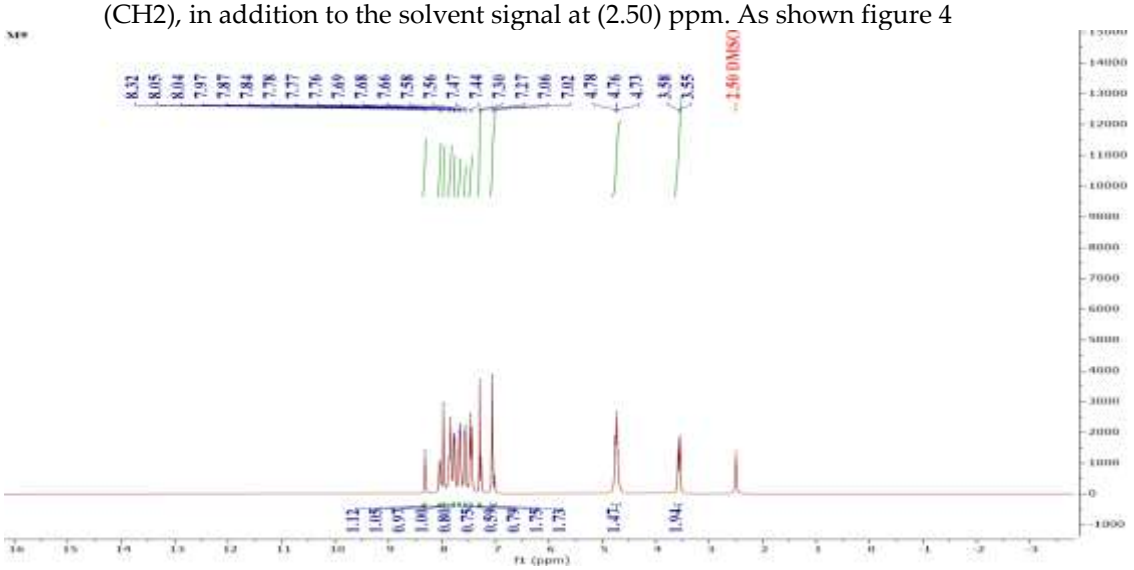
Fig(2): FT-IR of (M_{10})

Through 1H-NMR analysis of compound M_6, multiple signals were found that were attributed to hydrogen in the aromatic rings at the range (7.93-6.98) ppm, with a triple signal carrying two splits that was attributed to hydrogen (CH) at (4.75-4.71) ppm, and the presence of a double signal with one split at (3.19-3.17) ppm that was attributed to (CH2), in addition to the solvent signal at (2.50) ppm. As shown figure 3



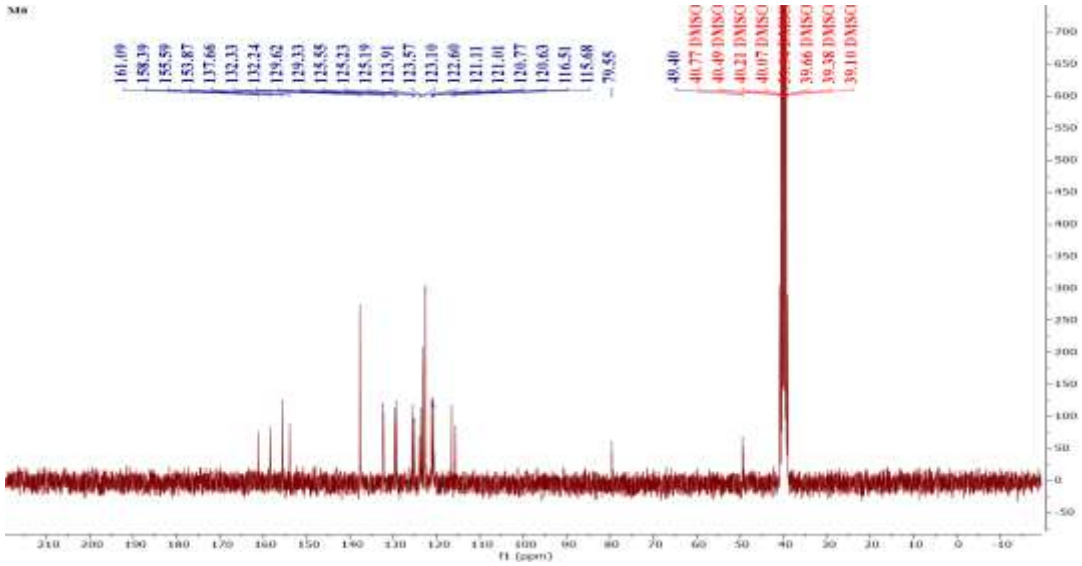
Fig(3): 1H-N.M.R of (M_6)

Through 1H-NMR analysis of compound M9, multiple signals were found that were attributd to hydrogen in the aromatic rings in the range (8.32-7.02) ppm, with a triple signal carrying two spliets that was attributed to hydrogen (CH) at (4.78-4.73) ppm, and the presence of a double signal with one split at (3.58-3.55) ppm that was attributed to (CH2), in addition to the solvent signal at (2.50) ppm. As shown figure 4



Fig(4): 1H-N.M.R of (M_9)

The 13C-NMR spectrum of compound M6 showed a signal that was included for azomethine in oxazepine (C=N) at (161.09) ppm, and a group of signals that were included for aromatic rings at (158.39-115.68) ppm, while the signal at (79.55) ppm was included for (CH), and the other signal at (49.40) ppm was included for the (CH2) group in the oxazepine ring. As shown figure 5



Fig(5): 13C-N.M.R of (M_6)

3.2. Evaluation of Biological Activity:

Due to the different properties of bacterial membranes, the prepared compounds exhibited different antibacterial effects[19]. The compounds exhibited the best antibacterial effects against Gram-negative bacteria, among which compound (M_8) showed the highest antibacterial activity against Gram-negative bacteria, with an inhibition diameter of (1.5 cm) at a high concentration of 0.1 mg/mL; followed by compound (M_{10}), with an inhibition diameter of (1.2 cm). In comparison, the antibiotics *ciprofloxacin* had inhibition diameters of 1.9 cm and 1.4 cm, respectively[20][21]. The antibacterial effects of the compounds on Gram-positive bacteria were not as good as those on Gram-negative bacteria. This inhibition was attributed to bacterial resistance to these compounds, against which the antibiotics showed activity, with the inhibition diameters of *ciprofloxacin* reaching 1.5 cm and 1.3 cm, respectively [22][23]. As shown in Table 3 and Figures 6, 7.

Table (3): Biological effectiveness of compounds (inhibition in cm).

Comp. No.	*Escherichia coil*			*Staphylococcus aureus*		
Conc. mg/ml	0.1	0.01	0.001	0.1	0.01	0.001
M_6	0.6	0.9	0.5	0.6	0.3	0.4
M_7	0.8	0.2	0.7	0.5	0.3	0.3
M_8	1.5	0.5	0.5	0.7	0.5	0.8
M_9	1	0.4	0.4	0.8	0.4	0.2
M_{10}	1.2	0.6	0.3	0.5	0.5	0.5
Ciprofloxacin	3.5	3	2.1	3.8	3.2	2.7

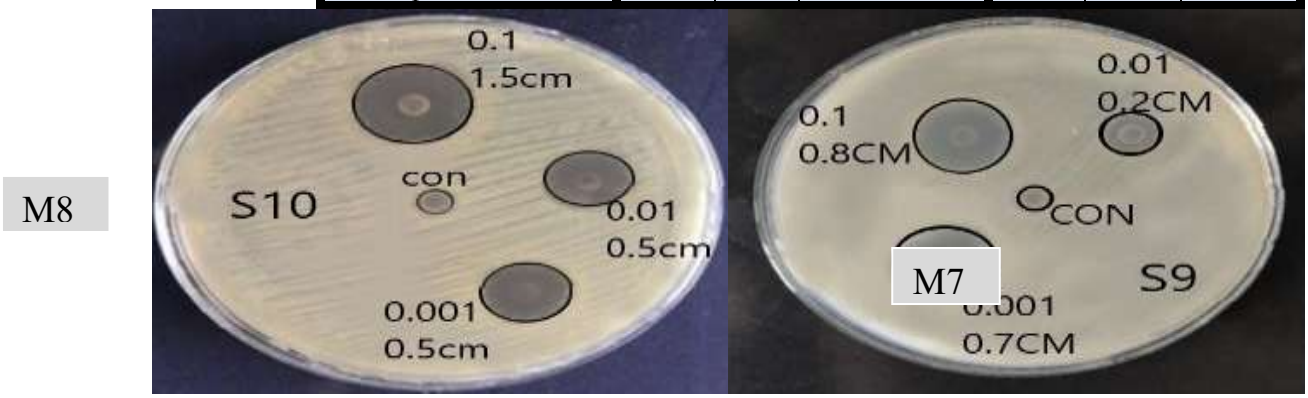


Fig 6: Efficacy of compounds (M7, 8) against Escherichia coli bacteria.

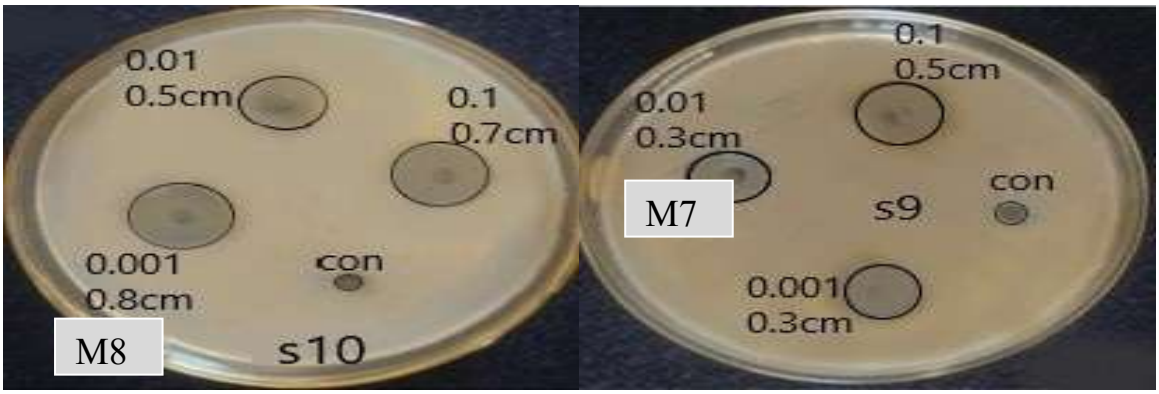


Fig 7: Efficacy of compounds (M7, M8) against Staphylococcus aureus bacteria.

4. Conclusion

Here, we report the sublimation synthesis of new derivatives of seven-membered oxazepine compounds, whose integrity and purity were confirmed by FT-IR, ^1H-NMR, and ^13C-NMR. Biological assays confirmed that the compounds synthesized were remarkable in terms of anti-bacterial activity against Escherichia coli, with the highest inhibition being associated with compound M8 but still lower compared to the standard antibiotic ciprofloxacin. These results highlight oxazepine derivatives as possible scaffolds for new antimicrobial classes, notably bypassing resistance mechanisms in Gram-negative bacteria. These solutions suggest that structural alterations, followed by functionalization, may improve their pharmacological activity and expand their applications. It is recommended that these derivatives be optimized through molecular docking, as well as in vivo studies and SAR before they can be applied for broader pharmaceutical development.

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