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PREPARATION, DIAGNOSIS AND EVALUATION OF THE BIOLOGICAL EFFICACY OF NEW DERIVATIVES OF THE OXAZEPINE RING

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Abstract: In the research ,new derivatives of the oxazepine heptacyclic ring were prepared by the reaction of equal moles of the prepared codebases with phthalic anhydride, nuclear magnetic resonance spectroscopy, infrared spectroscopy and physical measurements were used to confirm the compounds formed, in addition, the melting degrees of the prepared compounds were determined .It was also examined how several prepared compounds affect the growth of two types of bacterial isolates Klebsiella ,gram-negative and Gram-positive Staphylococcus aureus.

Keywords: Oxazepine, Biological activity.

1. Introduction

Oxazepine They are compounds with a heterogeneous and unsaturated seven-ring most often called oxazepine and may be saturated and called oxazepan(1) containing five carbon atoms and two heterogeneous atoms, an oxygen atom and a nitrogen atom(2) oxazepine compounds are non-aromatizing compounds and oxazepine compounds are of wide importance due to its biological activity in life, as in antihistamines (3), anticancer drugs (4), antivirals (5) painkillers (6), antifungals (7), antihistamines anticonvulsants (8), anticoagulants (9), antidepressants (10), non-narcotic antimicrobials (11), sedatives, and hypnotics (12).

2. Materials and Methode:

2.1. Material: All of the chemicals used in this study were obtained from BDH, Fluka, and Aldrich, without any further purification.

2.2. Equipment utilized: Melting points were measured with a thermoelectric melter 9300. KBr disk at 400–4000 cm-1 scale, Shimadzu FT-IR 8400S spectrophotometer; Bruker equipment running at 400 MHz for 1H-NMR and 13C-NMR spectra. Fluka silica gel plates with a thickness of 0.2 mm were used in thin-layer chromatography (TLC). UV light was used to achieve visibility after fluorescent silica gel G was used to activate the plates.

2.3. Preparation of Oxazepane [13]

The preparation was carried out by adding (0.01 mole) of the prepared five SHF bases with (0.01 mole) of the phthalic anhydride compound, after dissolving each of them in (15 ml) of dry benzene, mixing them in a conical flask, and the mixture was ascended for(12) hours, at a temperature of C 50, after which the reaction was cooled and obtained sediments of different colors and different percentages, purification and melting points were measured, as shown in Table (1).

Table (1) Some physical properties, percentage, reaction time, and Rf of oxazpine derivatives

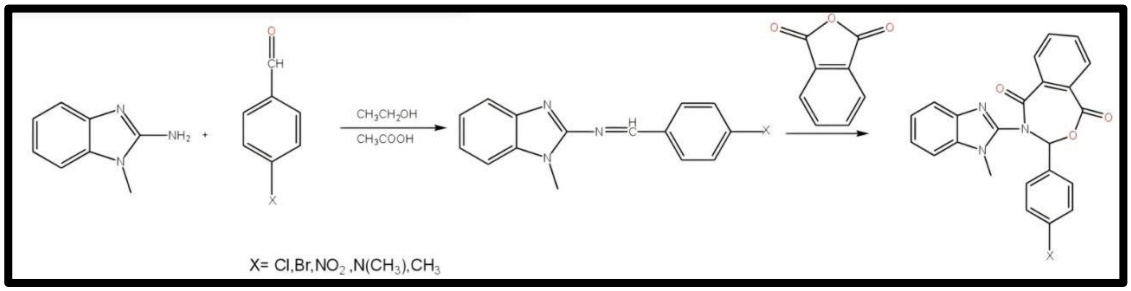
Comp.No	X	Molecular Furmola	M.P (C°)	Yield%	Color
Ar40	Cl-	$C_{22}H_{16}N_3O_3Cl$	178-180	80	Yellow
Ar42	NO_2	$C_{22}H_{16}N_4O_5$	190-192	82	Brown
Ar50	-Br	$C_{22}H_{16}N_3O_3Br$	176-178	78	White
Ar51	$-N(CH_3)_2$	$C_{24}H_{22}N_4O_3$	175-177	76	White
Ar52	CH_3-	$C_{23}H_{19}N_3O_3$	184-186	82	Yellow

2.4. Evaluation of the biological activity

The effectiveness of the prepared compounds against bacteria was tested using the agar diffusion method[14-17]. After inoculating the culture medium with bacterial isolates, make holes in the Petri dishes using the cylinder-measuring method (according to USP 35). Using the driller: (40 microliters) of the prepared compounds in three concentrations are placed in each well and the plate is incubated at a temperature of (37 degrees Celsius) for (24) hours, then (24) hours and (48) hours later the results are read[18-22]. To demonstrate the sensitivity of the derivative used, which depends on the inhibitory diameter appearing in the Petri dish surrounding the well, where an increase in the inhibitory diameter means an increase[23-28]. The biological activity of the prepared compounds was compared with the inhibition diameter of standard antibiotics, using solutions such as amoxicillin and ciprofloxacin as control samples depending on the solutions used in the laboratory. Ministry of Health and based on World Health Organization tests[29-33].

3. Results and Discussion:

Several compounds had to be prepared for this investigation, as the scheme(1) shows.



Scheme (1): Path of the Ready Compounds

3.1. Characterization of Oxazepane derivatives[34]:

The infrared(IR) spectrum of the compound[Ar42] showed absorption beams within the range(1703 cm-1) belonging to the actin of the carbonyl group lactone(O–CO), the appearance of an absorption beam at the range (1686 cm-1), belonging to the actin of the carbonyl group lactam(lactam) (N–CO), absorption beams at the range(1517-1597 cm-1), belonging to the actin(C=C) aromatization, the appearance of a bundle at(2925 cm-1) belonging to the(CH3) group and an absorption bundle was also observed at(3106 cm-1), belonging to the (AR-h) aromatization range.

Table (2) shows the results of the infrared absorption (cm-1) of oxazpine derivatives.

IR(KBr) cm^{-1}						
Comp. No	**X**	**C=O Lacton**	**υ (Ar-H)**	**C---C**	**C=O Lacta, NBm**	**CH_3**
Ar40	**Cl-**	**1764**	**3066**	**1597**	**1681**	**2911**
Ar42	**NO_2**	**1703**	**3106**	**1517**	**1686**	**2925**
Ar50	**-Br**	**1708**	**3086**	**1600**	**1691**	**2934**
Ar51	**-$N(CH_3)_2$**	**1731**	**3006**	**1598**	**1698**	**2923**
Ar52	**CH_3-**	**1719**	**3074**	**1605**	**1688**	**2901**

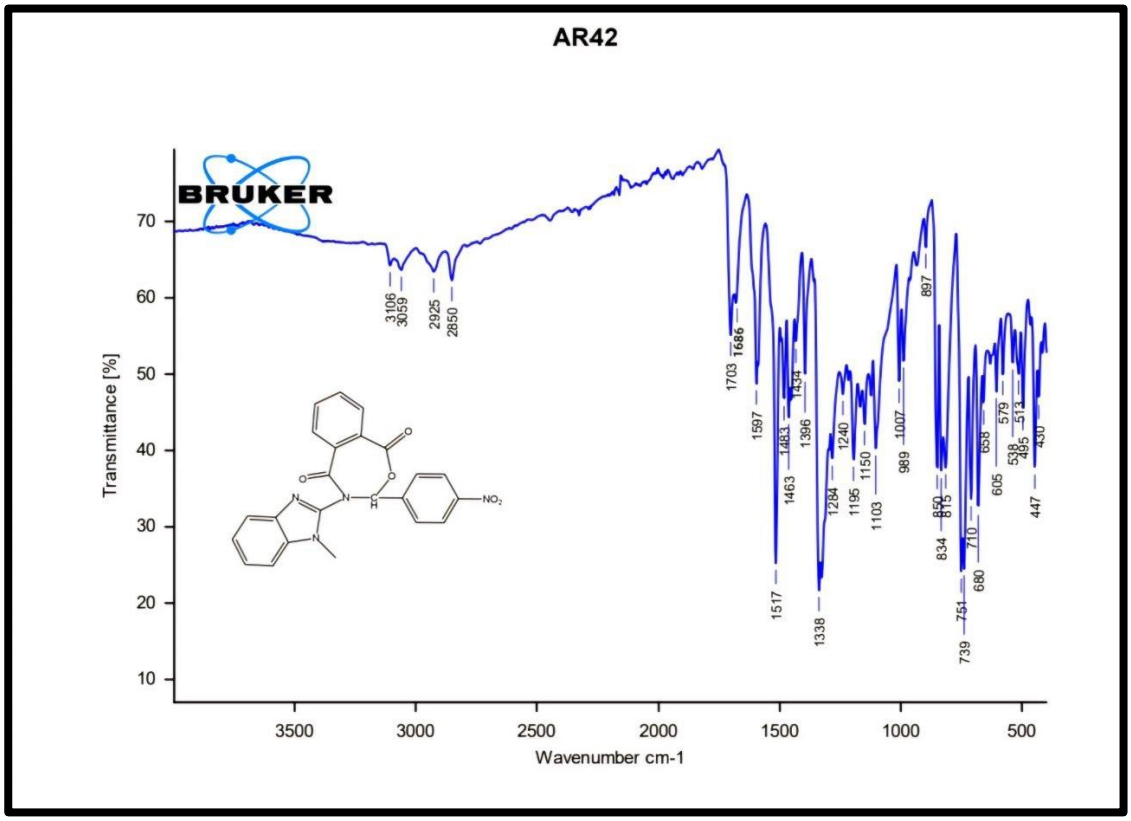


Figure (1) infrared spectrum of the compound (Ar42)

The NMR spectrum of the proton (1H-NMR) of the compound[Ar42] showed signals at (ppm 8.37 – 6.87) belonging to the protons of the aromatic ring,while the signal visible at (ppm 6.35) belongs to the Proton of the (N–CH–O) group in the heptagonal ring, and the signal visible at (ppm 3.36) belongs to the protons of the (CH3) group.

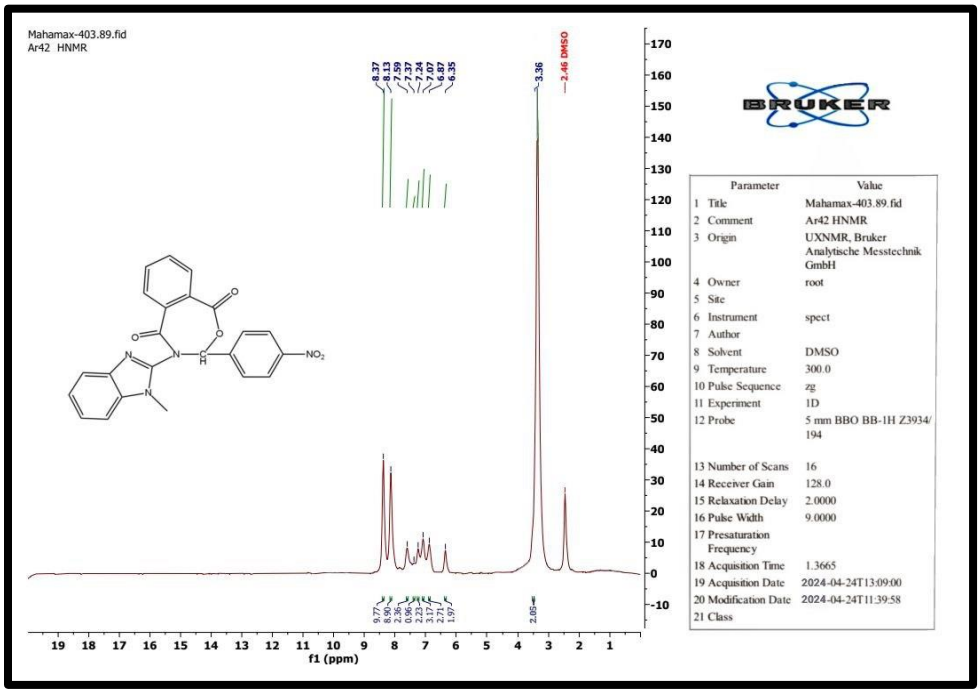


Figure (2): Proton NMR spectrum of the compound [Ar42]

The NMR spectrum of the carbon (13C-NMR) of the compound[Ar42] showed a signal at (ppm174.23) belonging to the carbon atom of the carbonyl group (O–C=O) in the heptagonal ring, while the signal seen at (ppm163.34) belonging to the carbon atom of the carbonyl group (N–C=O) in the heptagonal ring, and the signals seen at (ppm151. 02 - 112.50) belonging to the carbon is in the aromatic ring, while the signal visible at PPM 110.95 is due to the carbon atom of the N–Ch–o group in the heptagonal ring. While the signal visible at PPM 29.32)) is due to the carbon atom of the CH3 group.

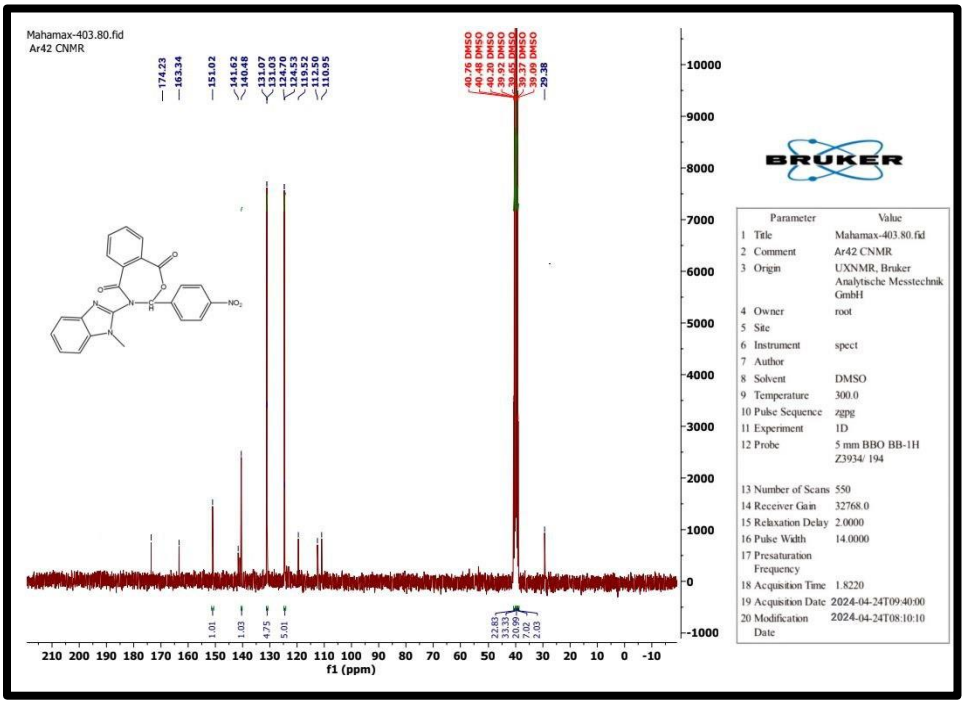


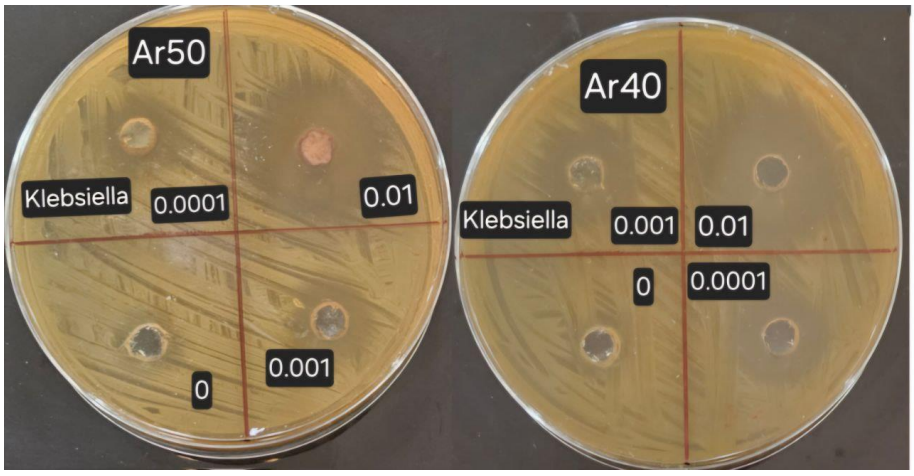
Figure (3): carbon NMR spectrum of the compound [Ar42]

3.4. Evaluation of Biological activity

These germs were chosen for their medical importance, as they cause many diseases, as well as where these germs differ in their resistance to antibiotics.the bioeffectiveness of some compounds prepared using the etching method was evaluated[35-40], and the level of inhibition (inhibition zone) was measured, where it was found that the prepared compounds have the ability to inhibit the growth of bacteria used with positive and negative types of cram dye in different proportions, and four compounds were used in the study of bacterial effectiveness (Ar52 Ar51, Ar50, Ar42. Ar40), so was the direct relationship between concentration and inhibition[41-44], as shown by Table(3).

Table (3): Antibiotics and other generated chemicals can prevent the growth

	Conc. m/m	Staphylococcus aureus+	Klebsiella-
Ar40	0.01	18	23
	0.001	6	17
	0.0001	2	15
Ar42	0.01	24	22
	0.001	10	18
	0.0001	6	16
Ar50	0.01	22	20
	0.001	16	16
	0.0001	10	10
Ar51	0.01	22	22
	0.001	14	16
	0.0001	10	12
Ar52	0.01	23	22
	0.001	16	14
	0.0001	11	10



Figure(4): shows the bioeffectiveness of some compounds prepared on the bacterium Klebsiella pneumonia

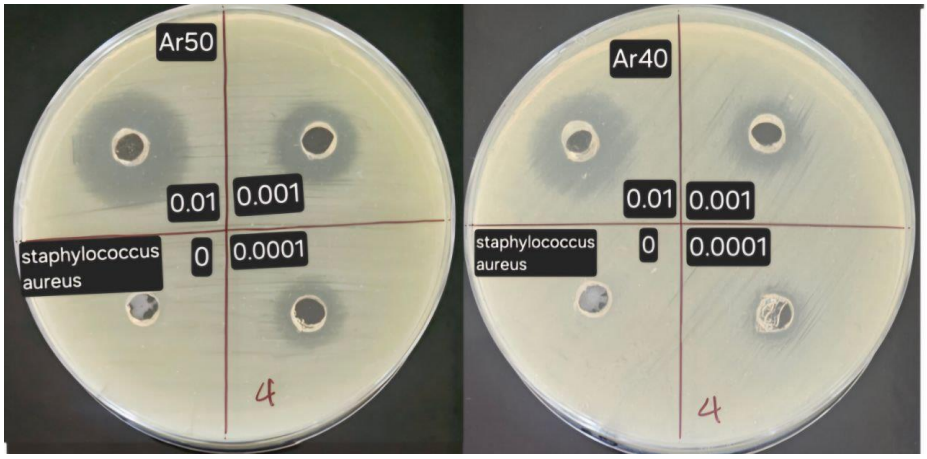


Figure (5): shows the bioeffectiveness of some compounds prepared on Staphylococcus aureus bacteria

Conclusion:

Using nuclear magnetic resonance spectroscopy, infrared spectroscopy, and spectrophotometry, the generated compounds were validated. In addition, its effectiveness against two different types of Gram-positive and Gram-negative bacteria has been proven, and it was found to be equivalent to that of the antibiotic amoxicillin.

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