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Article

Synthesis, Characterization, and Evaluation of the Biological Activity of Novel Oxazepine Compounds Derived From Indole-5-Carboxylic Acid

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Abstract: This study focuses on the synthesis and characterization of novel oxazepine compounds derived from indole-5-carboxylic acid. Indole-5-carboxylic acid, a compound known for its diverse biological activities, was used as a starting material to address the need for new antimicrobial agents. The research involved a multi-step process, beginning with the esterification of indole-5-carboxylic acid, followed by the preparation of hydrazide derivatives using benzaldehyde derivatives. These were then subjected to a cyclization reaction with maleic anhydride to produce oxazepine derivatives. The structures of the synthesized compounds were confirmed by Fourier Transform Infrared Spectroscopy (FTIR), and Nuclear Magnetic Resonance (H1-NMR, C13-NMR), ensuring their structural integrity. The biological activity of these oxazepine derivatives was evaluated using the diffusion plate method, revealing significant antibacterial activity. These findings suggest that the synthesized compounds have potential as new antimicrobial agents, contributing to the ongoing search for effective treatments against resistant bacterial strains.

Keywords: Heterocyclic, Oxazepine, Biological activity.

Introduction

Heterocyclic compounds are compounds that have a ring structure containing different atoms, such as oxygen, sulfur, or nitrogen. These compounds are widely distributed in nature. They are of multiple importance and are used in many fields, including industrial and medical. These compounds enter into the composition of sugars and their derivatives, as well as enzymes, proteins, and nucleic acids [1]. because these compounds contain a heterogeneous atom. Heterocyclic compounds can

contain more than one hetero atom and are classified according to the type and number of atoms contained in the ring [2].

Oxazepine compounds are unbranched, heterocyclic, seven-ring compounds containing five carbon atoms, one oxygen atom, and one nitrogen atom. There are also three isomers of the oxazepine compounds: 1,2, 1,3, and 1,4-oxazepine, and this depends on the numbering of The position of the oxygen and nitrogen atoms in the heptagonal ring[3]. And the increase in the size of the ring makes it uneven when compared to the hexagonal aromatic ring of benzene, as a result, the ring takes the shape of a boat in the spatial distribution of atoms, and this characteristic (uneven) was the reason for these compounds to be non-aromatic[4].

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 [5]. Oxazepine derivatives are heterogeneous organic compounds containing nitrogen in their structure, which makes them of great biological importance, especially in the medical and pharmaceutical fields, as they have shown anti-cancer [6] and antibacterial efficacy[7].

Materials and Methods

All the compounds utilized in this investigation were acquired from BDH, Fluka, and Aldrich.

Synthesis of Oxazepine derivatives (AB12-AB17).[8]

The maleic anhydride and the hydrazone derivative were mixed in an equivalent molar ratio in a suitable heat-resistant glass beaker without the use of a solvent, where the mixture was heated quietly and slowly until melting, with stirring and mixing well for 15-20 minutes until the nature of the reactants changed in terms of color and texture, collect The product was recrystallized from a suitable solvent. as shown in Table 1

Table 1. Some physical properties of Oxazepine derivatives (AB12-AB17)

Compounds	X	Chemical Formula	Color	m.p. C°	Yield (%)
AB13	-H	$C_{22}H_{17}N_7O_3S_2$	Brown	207-209	78
AB14	-Cl	$C_{22}H_{16}ClN_7O_3S_2$	Deep red	208-209	83
AB15	$-NO_2$	$C_{22}H_{16}N_8O_5S_2$	Magenta	242-244	81
AB16	-OH	$C_{22}H_{17}N_7O_4S_2$	Brown	263-265	76
AB17	-Br	$C_{22}H_{16}BrN_7O_3S_2$	Deep red	213-215	86

Biological activity study

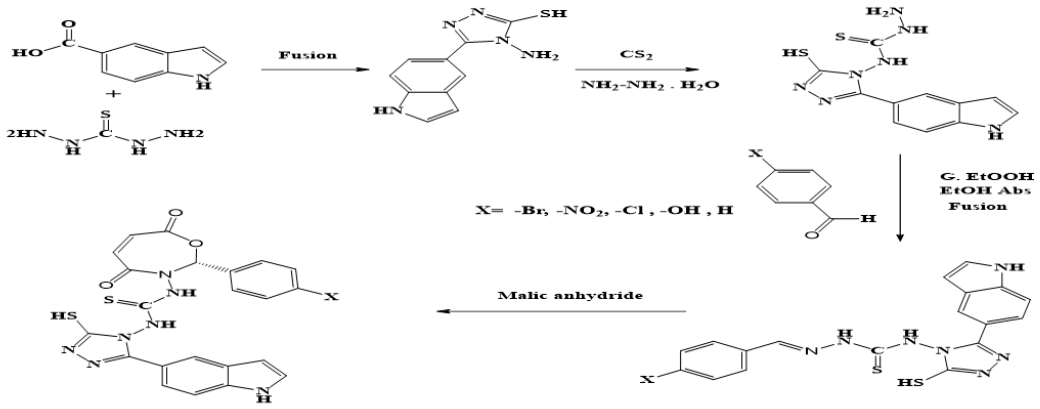
Two pure bacterial isolates of two bacterial species (Staphylococcus aurous-positive and E. coli-negative) were transferred from solid culture plates to test tubes containing (5 ml) distilled water using heat-sterilized holders [9,10]. The tubes were incubated (16-20 h) at (37 °C) and then diluted with physiological saline until the turbidity reached standard turbidity levels to obtain a cell count of approximately (1.5 × 108) cells/ml. Chemical solutions of some of the prepared compounds were prepared using dimethyl sulfoxide (DMSO) solvent, and each substance was inoculated into Mueller-Hinton agar (MHA) medium at three concentrations (0.01, 0.001, 0.0001) mg/ml.

Sterile cotton was inserted into the tube containing the diluted bacterial growth and excess inoculum was removed by pressing the swab against the inner wall of the tube, then the culture medium was wiped in three directions to achieve distribution. Leave the Petri dish aside for (10-15) minutes to absorb the culture and dry the medium[11,12]. The effectiveness of the prepared compounds against bacteria was tested using the agar diffusion method. After inoculating the culture medium with the bacterial isolates, a cork punch was used to make a hole in the Petri dish using the cylindrical measurement, where (40 µl) was placed.

The compounds were prepared in each well to three concentrations, and then the Petri dishes were incubated (24 hours) at a temperature of (37°C), and the results were read after (24) hours and (48) hours. Hour to show the sensitivity of the derivatives used according to the diameter[13,14]. The inhibition appears clearly in the Petri dish surrounding the well-used, as the increase in the inhibition diameter means an increase in the bioavailability of the prepared compound. For comparison, some standard antibiotics were used in the form of a solution, such as amoxicillin, as an antibiotic Control sample[15,16].

Results and Discussion

Oxazepine derivatives were prepared according to the following scheme:



Scheme 1. Path of the Ready Compounds (AB12-AB17)

Characterization of oxazepine derivatives (AB12-AB17)

The FT-IR spectrum showed stretching bands for the lactone group (C=O) (–O–CO) at (1691-1704) cm-1, as well as stretching bands for the carbonyl lactam group (–N–CO–) at (1643-1671) cm-1, stretching bands for the (NH) group appeared at (3164-3269) cm-1, stretching bands for the (C=C) group of the aromatic ring appeared at (1504-1562) cm-1, and stretching bands for the (=C-H) group appeared at (3025-3060) cm-1. Stretching bands for the (C-O) group appeared at (1193-1228) cm-1, and stretching bands for the (C=S) group appeared at (1089-1143) cm-1[17,18], as shown in Table 2 and Figures 1 and 2.

Table 2. Shows The most important absorbance of the prepared compounds

Comp. No.	R.	=C-H Ar.	C=C Ar	C=S	C=O L.N	C=O L.M	C-O E.R	N-H	Others
AB13	-H	3060	1562	1126	1692	1665	1204	3199	-------
AB14	-Cl	3025	1504	1143	1698	1669	1193	3197	C-Cl 812
AB15	$-NO_2$	3030	1546	1136	1702	1671	1228	3269	$-NO_2$ 1360
AB16	-OH	3037	1525	1089	1691	1647	1222	3201	OH 3323
AB17	-Br	3038	1519	1093	1704	1643	1217	3253	C-Br 783

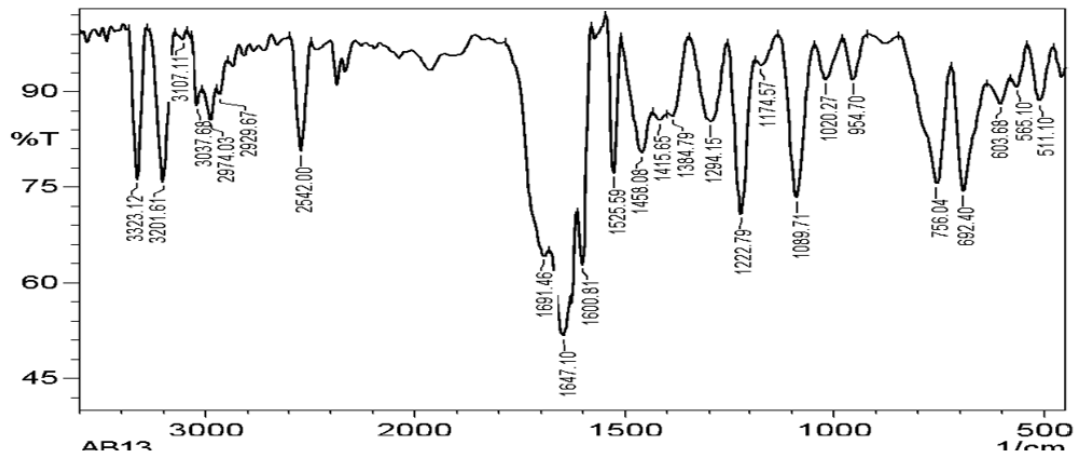


Figure 1. The compound's FT-IR spectra (AB13)

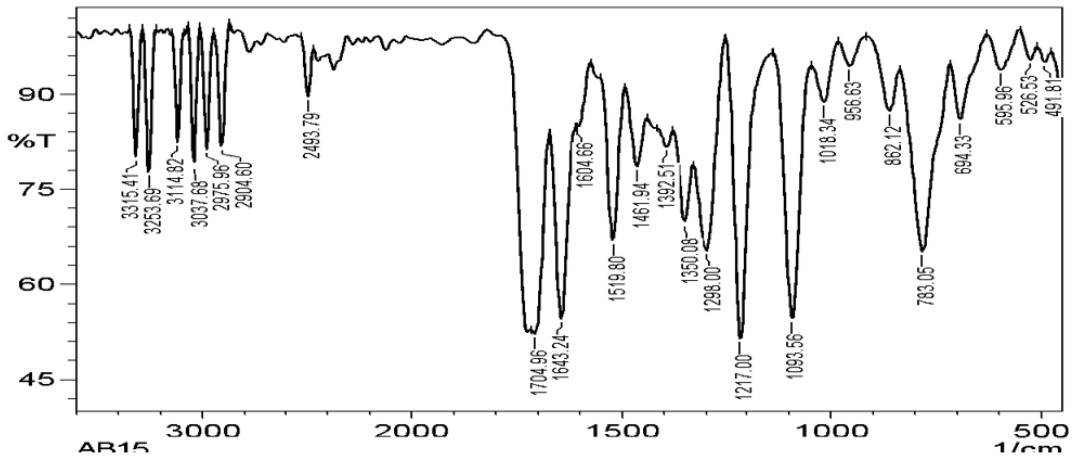


Figure 2. The compound's FT-IR spectra (AB15)

Discussion of the nuclear magnetic spectra of the proton (1HNMR) and carbon (13C-NMR):

Discussion of the proton NMR and carbon-13 spectrum. Measurement was studied using DMSO (1H-NMR). A group of analyses for the prepared compounds. The proton (1HNMR) and carbon (13C-NMR) nuclear magnetic analysis results agreed with those of the IR spectra.

Table 3. The proton NMR and carbon-13 spectrum

Com p. No	^{1}H-NMR\$^{13}$C-NMR Spectrum , δ , p.p.m , 300MHz
AB13	6.25-6.81 (H-C=C-H),7.32 -8.18 (m, Ar-H), 6.74 (S, N-CH),9.52 (b, N-H), 10.68 (b, Ar N-H), 12.13 (b, S-H). 112 (N-CH), 119-121 (H-C=C-H), 127-149 (C-Ar), 169(C=O), 172(C=O), 186(S=C)
AB14	6.37-6.92 (H-C=C-H),7.18 -8.27 (m, Ar-H), 6.92 (S, N-CH),9.61 (b, N-H), 10.87 (b, Ar N-H), H).12.34 (b, S-H). 112 (N-CH), 121-128 (H-C=C-H), 129.09-157 (C-Ar), 163.63(C=O), 166.39(C=O), 182.28(S=C)
AB15	6.38-6.96 (H-C=C-H),7.12 -8.16 (m, Ar-H), 6.84 (S, N-CH),9.42 (b, N-H), 10.18 (b, Ar N-H),.12.53 (b, S-H). 112 (N-CH), 118-123 (H-C=C-H), 128-152 (C-Ar), 165(C=O), 171(C=O), 186(S=C))
AB16	6.32-6.95 (H-C=C-H),7.53 -8.76 (m, Ar-H), 6.97 (S, N-CH),9.54 (b, N-H), 10.01 (b, Ar N-H), 11.11 (b, O-H).13.47 (b, S-H). 115 (N-CH), 122-125 (H-C=C-H), 129-161 (C-Ar), 168(C=O), 164(C=O), 167(C=O), 184(S=C)
AB17	6.13-6.73 (H-C=C-H),7.24 -8.16 (m, Ar-H), 6.73 (S, N-CH),9.63 (b, N-H), 10.93 (b, Ar N-H), 12.06 (b, S-H). 113 (N-CH), 118-123 (H-C=C-H), 128-151 (C-Ar), 17(C=O), 173(C=O), 181(S=C)

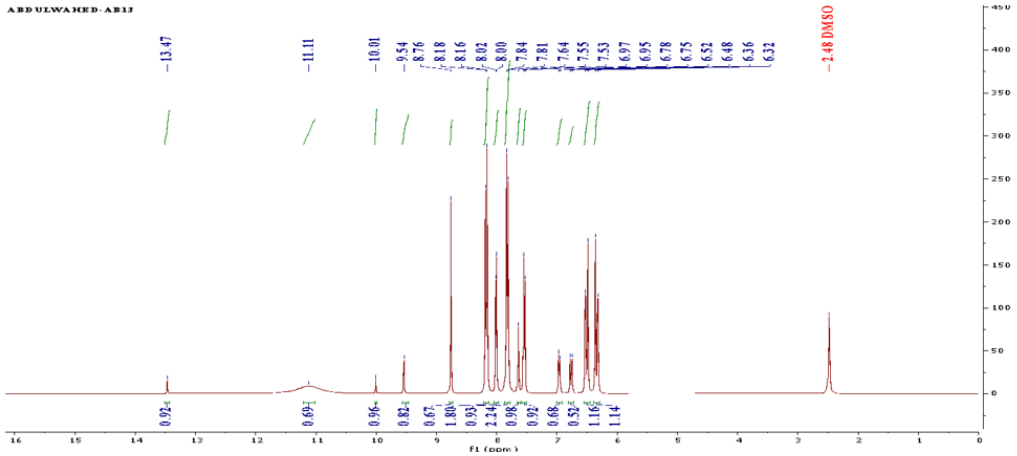


Figure 3. 1-H NMR spectra of the substance (AB13)

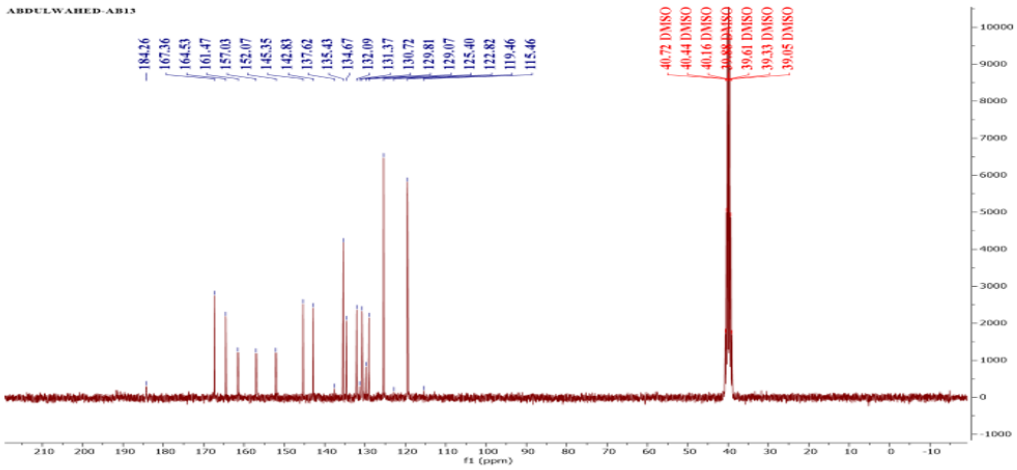


Figure 4. 13C-NMR spectrum of the compound (AB13)

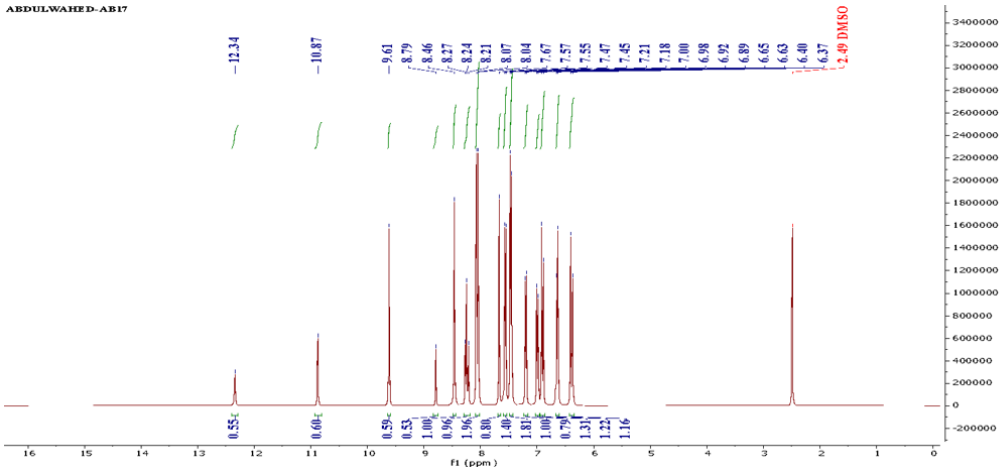


Figure 5. 1H-NMR spectra of the substance (AB17)

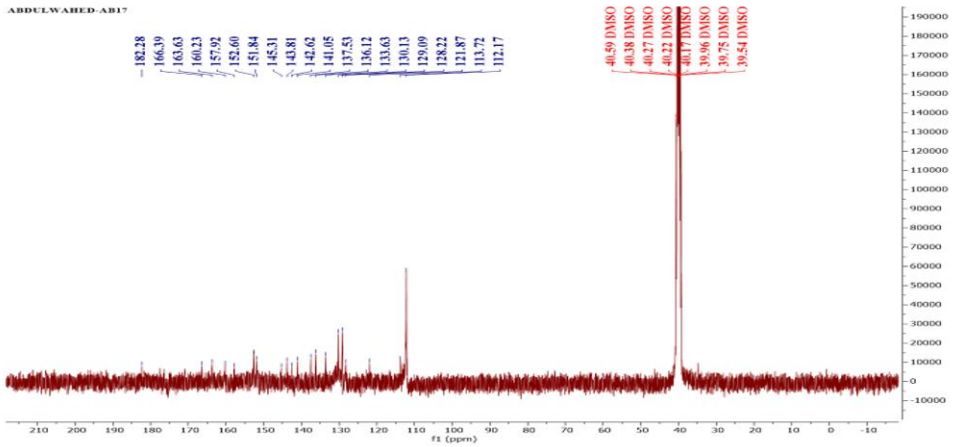


Figure 6. 13C-NMR spectrum of the compound (AB17)

Heterocyclic compounds have different biological activities against Gram-positive and Gram-negative bacteria, and the bioavailability of some of the prepared compounds (AB13, AB14, AB15, AB16, AB17) was evaluated. These bacteria were chosen for their medical importance, as they cause many diseases[19,20]. In addition, they differ in their resistance to antibiotics. The bioavailability of some of the prepared compounds was evaluated using the etching method and measuring the inhibition levels. The results showed that the prepared compounds can inhibit the growth of both Gram-positive and Gram-negative bacteria at different rates, and based on the following results, the antibiotic amoxicillin was used as a control sample[20,21]. Used in the laboratories of the Ministry of Health and based on the examinations of the World Health Organization, these antibiotics are widely classified, especially the two bacterial types studied, in addition to many types, these antibiotics also have a large inhibitory diameter because they have a very high inhibitory diameter[22-25].

To be selective in studying the susceptibility of bacteria to the prepared compounds, and because these antibiotics are used to treat many infections and diseases such as urinary tract infections, especially those caused by E. coli and Staphylococcus aureus, and they also treat uncomplicated infections, cystitis in women caused by E. coli and chronic prostatitis caused by E. coli and staphylococcus, as well as lower respiratory tract infections, sinusitis, arthritis, and bone infections. Compounds (AB14) have good inhibitory activity against E. coli with an inhibition rate of (19 mm), while compounds (AB13) also have good inhibitory activity against E. coli[26,27]. They showed good inhibitory activity against Staphylococcus aureus with inhibition rates of (17 mm), respectively. The remaining compounds showed moderate and good inhibition rates, and the concentration was positive with inhibition. The higher the concentration, the higher the inhibition rate, where the highest inhibition rate was reached at a concentration of 0.01 mg/ml[28-34].

Table 3. Bioogical efficacy of produced substances and control methods (measured in millimeters 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
AB13	**18**	**12**	**8**	**17**	**13**	**9**
AB14	**19**	**15**	**9**	**16**	**15**	**12**
AB15	**17**	**13**	**7**	**15**	**10**	**10**
AB16	**15**	**10**	**5**	**13**	**9**	**5**
AB17	**12**	**8**	**0**	**10**	**10**	**5**
Amoxicillin	**22**	**17**	**16**	**20**	**19**	**15**

Conclusion

The present research deals with the preparation of some new oxazepine derivatives from the group of ethyl-2-aminobenzothiazole-6-carboxylate. All the derivatives prepared in this way were analyzed by 1H&13C-NMR and infrared. Compared with the antibiotic, the prepared compounds showed good bioactivity against the used bacteria. This method of synthesis is accurate and gives high percent purity with a greater yield.

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