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Synthesis, Characterization, and Biological Activity Evaluation of Chalcones and Pyrazole Derivatives Derived from Indole

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Abstract:
This work ten compounds were prepared including chalcones derivatives (Z1-Z5) are made by reacting Benzaldehyde substitutes with indole in methanol solvent. Then the preparation of pyrazole derivatives (Z6-Z10) from the reaction of chalcone derivatives (Z1-Z5) with aqueous hydrazine in ethanol solvent. Characterization by using spectroscopic techniques Uv-vis, FT-IR, ^{1}H-NMR, ^{13}C-NMR of some the prepared compounds using DMSO-d^{6} a solvent. Antibacterial behaviors were investigated against a variety of bacteria, including *E. coli* Gram (-) ve, and *S. aureus* Gram (+) ve.**Keywords:** Indole, Chalcone, Pyrazole, Antibacterial, Escherichia coli, Staphylococcus aureus.

1. Introduction

Indole is one of the heterocyclic aromatic compounds, it has a bicyclic structure consisting of a hexagonal ring of benzene combined with a pentagonal ring containing a nitrogen atom (pyrrole ring), and the indole ring enters the structure of many natural products [1]. The indole compound is a colorless, shiny solid powder with weak basicity but does not form many salts with acids [2]. Indole is also prepared in the laboratory by the Fischer method [3]. Since the pyrrole ring in indole is the most active part so nucleophilic substitution (nucleophilic substitution) of the benzyl ring [4] will occur only when a substitution process occurs at sites N-1, C-2, and C-3, and as in the oxidation of indole [5]. Alpha–Beta-unsaturated ketone compounds are an important type of carbonyl compound [6], and the carbonyl group is the most important and widespread functional group in organic chemistry, especially Conjugated with double actin, where its importance increases as a source for the preparation of other organic compounds such as heterocyclic compounds [7], due to the spread of electron charge on the four common atoms in the successive system (occurrence of the resonance State) [8], so these compounds undergo addition reactions on the Group (C=C) of the type of Michael addition (1,4-addition), as well as the addition on the carbonyl group (C=O) addition Classes-Schmidt condensation (1,2-addition) and in both additions, when the reactant has more than one reaction site, then peri coronation of the resulting substance may occur. Compounds containing a carbonyl group and a double acylation in the alpha-beta position are gluconates [9], or benzylidene compensators [10]. balconies can exist in the form of two isomers (Z or E), and it turns out that the most stable form is isomer E, so most of them are in their form [11]. The importance of gluconates comes from their similarity with the structures and effectiveness of some important natural substances in the plant kingdom, such as flavonoids and anthocyanidins [12]. Pyrazole compounds are pentacyclic heterocyclic compounds containing two nitrogen atoms at positions 1 and 2. The Scientist Knorr discovered in 1884 [13]. the pyrazole compound has a pentacycloaromatic structure consisting of three carbon atoms and two adjacent nitrogen atoms at Position (2). pyrazole derivatives are formed when the 1,3,4,5 positions of the ring are substituted [14]. Pyrazoles have shown different biological and industrial efficacy, and pyrazole compensators can be used as inhibitors, anticancer, antiviral or antimicrobial, anti-inflammatory, or

antifungal substances [15]. Pyrazole was first prepared in (1890) from the condensation of epichlorohydrin with hydrazine [16]. Therefore, our goal in this study was to prepare, diagnose and study the biological effectiveness of gluconate and pyrazole derivatives.

2. Experimental

2.1. Material: All chemicals were used through this work purchased from Fluka, Aldrich, BDH Companies.

2.2. Devices used: Melting points were recorded using a measuring device melting point type: Automatic melting point\SMP40 and were uncorrected. Thin layer chromatography (TLC) was carried out using sheet polygram silica- gel as stationary phase, the spots were enhanced using Iodine. Infrared spectra were recorded using FT-IR-600 Fourier- Transform infrared Spectrophotometer by KBr disc and with a scale of (400-4000) cm^{-1}. The nuclear magnetic resonance (^{1}H,^{13}C-NMR) spectra were measured for the compounds prepared in the laboratories of Sannati Sharif University - Iran, using MS5973 Agilent Technology, Germany Bruker 500 MHz, at 500 MHz, and using (DMSO-d^{6}) as a solvent.

2.3. Preparation of chalcone derivatives (Z1-Z5) [17, 18]:

(0.012 mol, 2 g) of 3-acetyl indole was dissolved in 30 ml of methanol in a round flask with a capacity of 100 ml, then 20 ml of an alcoholic solution of 20% NaOH was added to it, stirred for 30 minutes, then 0.012 mol of various benzaldehyde substitutes were added (P-Diphenylamine benzaldehyde, P-chloro benzaldehyde, P-bromo benzaldehyde, P-Nitro benzaldehyde, P-methoxy benzaldehyde). The stirring continued for two hours at room temperature, after which the mixture was added to crushed ice. The completion of the reaction was confirmed by using thin-layer chromatography. The precipitate was filtered and washed three times using cold distilled water. The residue was dried and recrystallized with absolute ethanol. The physical properties are shown in Table (1).

2.4. Preparation of 5-phenyl-3-indole pyrazole derivatives (Z6-Z10) [19, 20]:

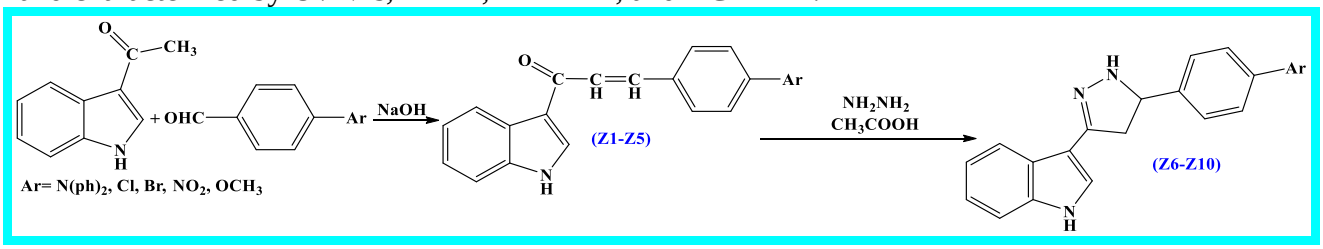
(0.005 mol) of chalcone derivatives (Z1-Z5) were dissolved in 30 ml of absolute ethanol in a round flask with a capacity of 100 ml, then (4-5) drops of glacial acetic acid were added to it with constant stirring, then (0.005 mol, 0.25 ml) was added) mole of aqueous hydrazine, and the mixture was elevated for (10-12) hours, after which the solution was concentrated and then added to ice with stirring for 24 hours until it precipitated, filtered and dried, and the completion of the reaction was confirmed using the thin layer chromatography (TLC) technique. It was repeatedly crystallized with acetone. The physical properties are shown in Table (1).

2.4. Antibacterial activity for prepared compounds (Z1-Z10) [21, 22]:

The antibacterial function of compounds (Z1-Z10) were evaluated using the disk diffusion system against two bacteria: ***Escherichia coli*** and Gram (-) ve, ***Staphylococcus aureus***, Gram (+) ve. The disks were then immersed in DMSO and dried in an incubator before being used in bacteria cultures. DMSO was used as a pessimistic monitor. The plates were incubated for two days at 37°C. For of test microorganism form, the maximum inhibition zone diameter (IZD) was observed and calculated. At one dose, ***ampicillin***, was used as monitoring samples [23].

3. Results and Discussion

In this work, ten compounds were prepared including chalcones derivatives (Z1-Z5) are made by reacting Benzaldehyde substitutes with indole in methanol solvent. Then the preparation of pyrazole derivatives (Z6-Z10) from the reaction of chalcone derivatives (Z1-Z5) with aqueous hydrazine in ethanol solvent, and characterized by Uv-Vis, FT-IR, ^{1}H-NMR, and ^{13}C-NMR.



Scheme 1. Route of prepared compounds (Z1-Z10)

3.1. Characterization of chalcones derivatives (Z1-Z5)

When studying the ultraviolet-visible (Vis-UV) spectrum of the prepared compounds [Z6-Z10] using ethanol (95%) as a solvent and a concentration ranging between (10^{-4}-10^{-5}) molar for the prepared compounds, short wavelengths ($\lambda_1$max) appeared at (215-240) nm due to ($\pi \rightarrow \pi^*$) transitions, noting the appearance of long wavelengths ($\lambda_2$max) at the range (288-364) nm belonging to electronic transitions of

the type (n→π*) [24, 25], as in Table (2).When studying the infrared spectrum of chalcone derivatives [Z1-Z5], it was observed that an absorption beam appeared at the range (3140-3196) cm^{-1} due to the stretching of the (NH) bond, the appearance of an absorption beam at the range (3039-3087) cm^{-1} due to the stretching bond (CH) aromatics, with a clear decrease in the frequency of the carbonyl group (C=O) ketones to appear at the range (1670-1698) cm^{-1} due to the succession between the carbonyl group and the double bond, which leads to a decrease in the value of the strength constant of the double bond, which reduces its frequency, the appearance of an absorption band at the range (1602-1621) cm^{-1} due to the stretching of the (C=C) olefin bond, as well as the emergence of two absorption bands at the range (1575-1595 & 1488-1491) cm^{-1} dating back to the stretching the aromatic bond (C=C) [26, 27], as shown in Table (2) and Figures (1, 2).When studying the ^{1}H-NMR spectrum of the compound [Z2], it was observed that a single signal appeared at (7.89) ppm due to the proton of the (NH) group in the indole ring, and a multiple signal appeared at (7.45-7.84) ppm due to the protons of the rings. Aromatics, the appearance of a mono signal at the chemical shift= (7.43) ppm attributed to the proton of the (C=CH) group in the indole ring, and the appearance of a binary signal at the chemical shift= (7.39 and 7.36) ppm attributed to the proton of the (HC=C) group adjacent to the benzene ring, and the appearance of A binary signal at the chemical shift= (6.85 and 6.38) ppm is attributed to the proton of the (HC = C) group adjacent to the carbonyl group, the appearance of a mono signal at the chemical shift= (3.36) ppm is attributed to water (HDO), and the appearance of a single signal at the chemical shift= (2.51) ppm is attributed to The protons of the solvent (DMSO-d^{6}) [28, 29], as in Figure (3).When studying the ^{13}C-NMR nuclear magnetic resonance spectrum of the compound [Z2] using a solvent (DMSO-d^{6}), it was observed that a signal appeared at the chemical shift= (188.90) ppm due to the carbonyl group (C=O), and a signal appeared at the chemical shift= (168.91) ppm due to the carbon of the (HC=C) group adjacent to the benzene ring. The appearance of a signal at the chemical shift= (142.00) ppm attributed to the carbon of the (HC=C) group of the benzene ring, and the emergence of multiple signals at (120.92-138.75) ppm due to the carbons of the aromatic ring, and the emergence of two signals at the chemical shift= (126.71 and 120.92) ppm attributed to the carbons of the group (C=C) of the indole ring, and the emergence of signals at the chemical shift= (39.48-40.48) ppm attributed to the carbon of the solvent (DMSO-d^{6}) [30]. The spectrum is shown in Figures (4).When studying the ^{1}H-NMR spectrum of the compound [Z3], it was observed that a single signal appeared at (8.72) ppm due to the proton of the (NH) group in the indole ring, and a multiple signal appeared at (7.69-8.44) ppm due to the protons of the rings. Aromatics, the appearance of a mono signal at the chemical shift= (7.67) ppm attributed to the proton of the (C = CH) group in the indole ring, the appearance of a binary signal at the chemical shift= (7.65 and 7.66) ppm due to the proton of the group (HC = C) adjacent to the benzene ring, and the appearance of A binary signal at (7.64 and 7.63) ppm is attributed to the proton of the (HC=C) group adjacent to the carbonyl group, a mono signal at (3.35) ppm is attributed to water (HDO), and a single signal is at (2.50-2.52) ppm. Attributable to the protons of the solvent (DMSO-d^{6}) [31, 32], as in Figure (5).

3.2. Characterization of pyrazole derivatives (Z6-Z10)

When studying the ultraviolet-visible (Vis-UV) spectrum of the prepared compounds [Z6-Z10] using ethanol (95%) as a solvent and a concentration ranging between (10^{-4}-10^{-5}) molar for the prepared compounds, short wavelengths ($\lambda_1$max) appeared at (210-262) nm due to (π→π*) transitions, noting the appearance of long wavelengths ($\lambda_2$max) at the range (305-375) nm belonging to electronic transitions of the type (n→π*) [33, 34], as in Table (2).When studying the infrared spectrum of the interaction of 5-phenyl-3-indolepyrazole derivatives [Z6-Z10], it was observed that an absorption band appeared at the range (3157-3199) cm^{-1} due to the (NH) bond of the indole ring, the appearance of an absorption band at the range (3120-3151) cm^{-1} refers to the stretching of the (NH) bond of the pyrazole ring, the appearance of an absorption band at the range (3032-3093) cm^{-1} refers to the stretching of the aromatic (CH) bond, and the appearance of two absorption bands at the range (2983-2924 and 2875-2812) cm^{-1} returns to the stretching of the aliphatic (CH) bond, with the emergence of a new band at the range (1612-1630) cm^{-1} that returns to the stretched (C=N) bond. It was noted that the carbonyl bond (C=O) and the (C=C) bond have disappeared olefins, as well as the emergence of two absorption bands at the range (1575-1600 and 1469-1493) cm^{-1} due to the expansion of the aromatic (C=C) bond [35, 36], as shown in Table (2), and Figures (6,7).When studying the ^{1}H-NMR spectrum of the compound [Z7] using a solvent (DMSO-d^{6}), it was observed that a single signal appeared at the chemical shift= (10.07) ppm due to the proton of the (NH) group in the pyrazole ring, and the appearance of a single signal at the chemical shift= (8.52).) ppm is attributed to the proton of

the (NH) group in the indole ring, the appearance of multiple signals at (7.33-7.61) ppm due to the protons of the aromatic rings, and the appearance of a single signal at chemical shift= (7.33) ppm due to the proton of the (C=CH) group in the indole ring, the appearance of a single signal at (3.41) ppm due to water (HDO), the appearance of a binary signal at (2.79 and 2.78) ppm due to the (CH_2) group proton, and the appearance of a triple signal at (2.75, 2.74 and 2.72) ppm is attributed to the proton of the (CH) group and the appearance of a signal at (2.52 and 2.51) ppm is attributed to the protons of the solvent (DMSO-d^6) [37, 38], as in Figure (8).When studying the 13C-NMR spectrum of the compound [Z7] using a solvent (DMSO-d6), it was observed that a signal appeared at the site (168.74) ppm due to the carbon group (C = N) in the pyrazole ring, and the emergence of multiple signals at (114.72-114.72). 166.71 ppm refers to the carbons of the aromatic ring, and the appearance of two signals at chemical shift= (113.94 and 110.39) ppm attributed to the carbon of the (C = C) group in the indole ring, and the appearance of a signal at the chemical shift= (102.73) ppm attributed to the carbon of the (CH) group in the ring pyrazole, and the appearance of signals at the chemical shift= (39.46-40.46) ppm attributed to the carbon of the solvent (DMSO-d6), and the appearance of a signal at the chemical shift= (24.47) ppm attributed to the carbon of the (CH2) group in the pyrazole ring [39, 40]. The spectrum is shown in Figures (9).

3.3. Evaluation of the biological activity of some prepared compounds:

Compounds with heterocyclic rings are characterized by different biological activity against Gram-positive and Gram-negative bacteria, so the biological activity of some compounds prepared in this thesis was evaluated on two types of bacteria, which are as follows: Escherichia coli and Staphylococcus aureus. Spreading on Petri dishes using Mueller Huntington medium for some compounds prepared at concentrations (0.01, 0.001, 0.0001 mg/ml) and the diameter of the inhibition zone was determined in millimeters [41]. The results were compared with a standard antibiotic. When comparing the effect of some of these compounds [42], it was noticed that some of the prepared compounds had a clear effect against the first type of bacteria compared to the other type [43]. Some of them had a clear effect against the second type of bacteria compared to the other type, which did not appear for any of the prepared compounds to affect them, as shown in tables (3) and Figures (10-15). From the table below, compounds with strong efficacy and inhibition can treat diseases caused by the aforementioned studied bacteria after conducting histological and anatomical studies of the prepared compounds [44]. And the antibiotic amoxicillin was used as a control sample, depending on what is used in the Ministry of Health laboratories and based on the World Health Organization examinations.Table (1): Some physical properties of the prepared compounds (Z1-Z10).

Comp. No.	Ar	Molecular Formula & M.wt	Y%	M.P. ^{O}C	Color	Time hr.	R.f (cm)
Z_1	$N(Ph)_2$	$C_{29}H_{22}N_2O$ / 414.51	79	130-132	White	10	0.79
Z_2	Cl	$C_{17}H_{12}NOCl$ / 281.74	82	105-107	White	9	0.94
Z_3	Br	$C_{17}H_{12}NOBr$ / 326.19	65	98-100	White	8	0.83
Z_4	NO_2	$C_{17}H_{12}N_2O_3$ / 292.29	82	153-154	White	10	0.80
Z_5	OCH_3	$C_{18}H_{15}NO_2$ / 277.32	55	116-117	White	8	0.88
Z_6	$N(Ph)_2$	$C_{29}H_{24}N_4$ / 428.54	57	212-214	Dark yellow	11	0.90
Z_7	Cl	$C_{17}H_{14}N_3Cl$ / 295.77	49	167-169	Dark yellow	10	0.77
Z_8	Br	$C_{17}H_{14}N_3Br$ / 340.22	56	184-186	Light yellow	11	0.85
Z_9	NO_2	$C_{17}H_{14}N_4O_2$ / 306.33	55	201-203	Light orange	12	0.83
Z_{10}	OCH_3	$C_{18}H_{17}N_3O$ / 291.35	49	186-188	White	10	0.92

Table (2): Uv-Vis (nm) and FT-IR (cm^{-1}) absorption results for compounds [Z1-Z10]

Comp. No.	Ar	Uv-Vis nm $_1\lambda max$ $_2\lambda max$	IR (KBr) cm^{-1} ν(NH)	ν(C-H) Arom.	νC=O	νC=C olefin	ν(C=C) Arom.	Others
Z_1	$N(Ph)_2$	231, 319	3196	3074	1670	1609	1589, 1490	-------
Z_2	Cl	224, 288	3159	3039	1685	1606	1583, 1491	ν (C-Cl) 754
Z_3	Br	240, 364	3171	3087	1698	1621	1575, 1488	ν (C-Br) 521
Z_4	NO_2	215, 323	3159	3043	1693	1614	1575, 1491	ν(NO_2) 1523, 1384
Z_5	OCH_3	228, 352	3140	3057	1692	1602	1595, 1490	ν (CH_3) 2963, 2881
Comp. No.	**Ar**	**$_1\lambda max$ $_2\lambda max$**	**ν(NH) ν(NH)**	**ν(C-H) Arom.**	**ν(C-H) Aliph.**	**νC=N**	**ν(C=C) Arom.**	**Others**
Z_6	$N(Ph)_2$	, 352٦٠2	3199, 3147	3032	2945, 2812	1630	1597, 1469	-------
Z_7	Cl	, 334٤٥2	3157, 3122	3047	2924, 2852	1616	1575, 1491	ν (C-Cl) 754

Z_8	Br	, 305٢٦٢	3167, 3151	3086	2963, 2844	1628	1600, 1477	ν (C-Br) 521
Z_9	NO_2	, 375٢١٠	3155, 3120	3043	2983, 2875	1612	1575, 1492	ν(NO_2) 1523, 1344
Z_{10}	OCH_3	, 366٣٧2	3172, 3142	3093	2960, 2814	1623	1581, 1493	-------

Table (3): Antibacterial effectiveness of the prepared compounds and control treatments (antibiotic) on the growth of several negative and positive bacteria (diameter of the inhibition circle measured in mm).

Comp. No.	*E. Coli*			*S. aureus*		
	0.0001	**0.001**	**0.01**	**0.0001**	**0.001**	**0.1**
Z_1	10	11	12	10	11	13
Z_3	10	12	14	12	13	15
Z_4	12	14	16	11	14	18
Z_6	11	12	14	10	13	15
Z_7	12	13	15	10	11	13
Z_9	10	12	13	12	13	15
Amoxicillin	10	16	24	10	20	20
Blank disk	٠	٠	٠	٠	٠	٠

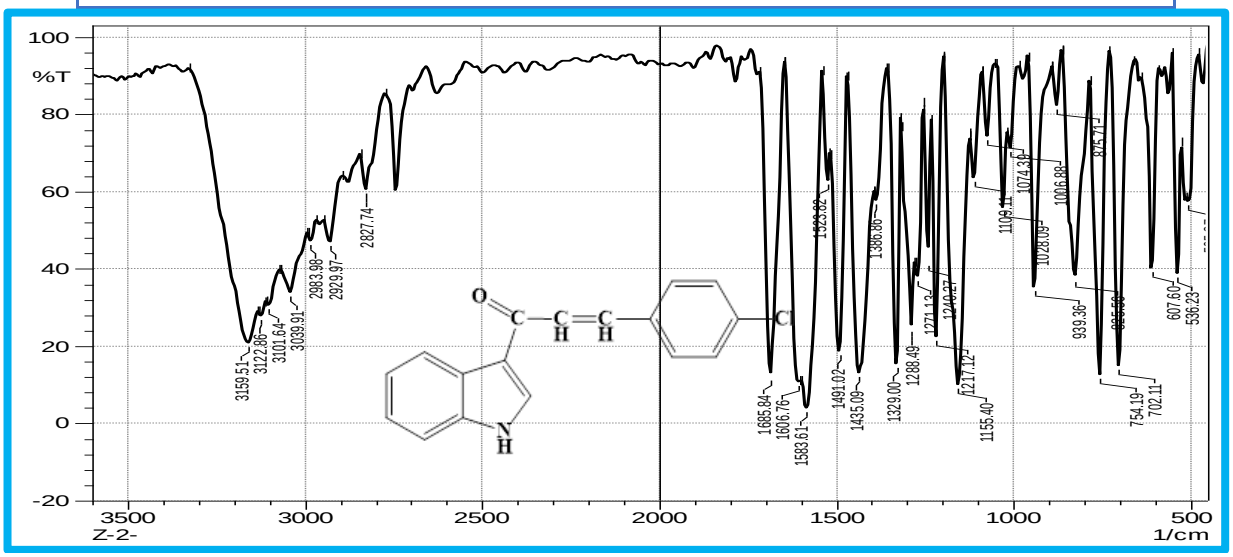


Figure (1): FT-IR spectrum of compound (Z2).

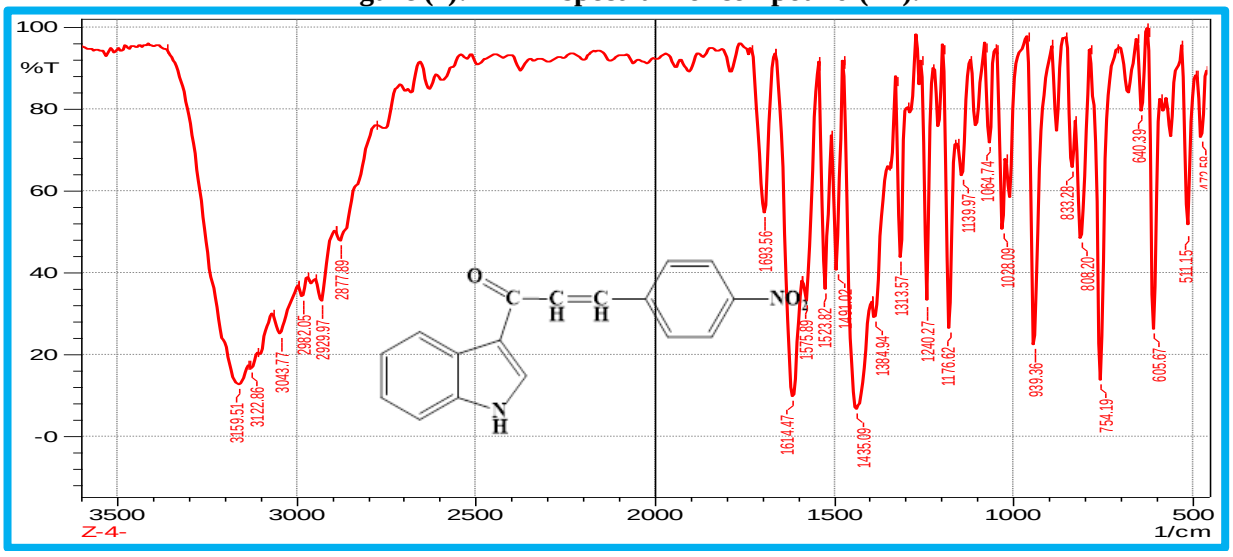


Figure (2): FT-IR spectrum of compound (Z4).

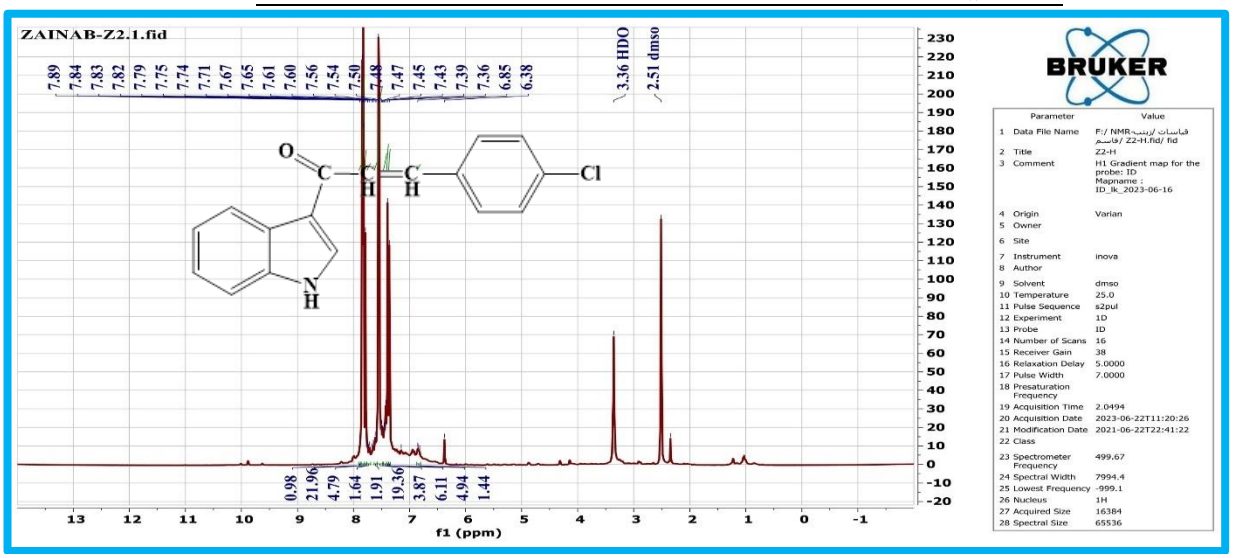


Figure (3): ^{1}H-NMR spectrum of compound (Z2).

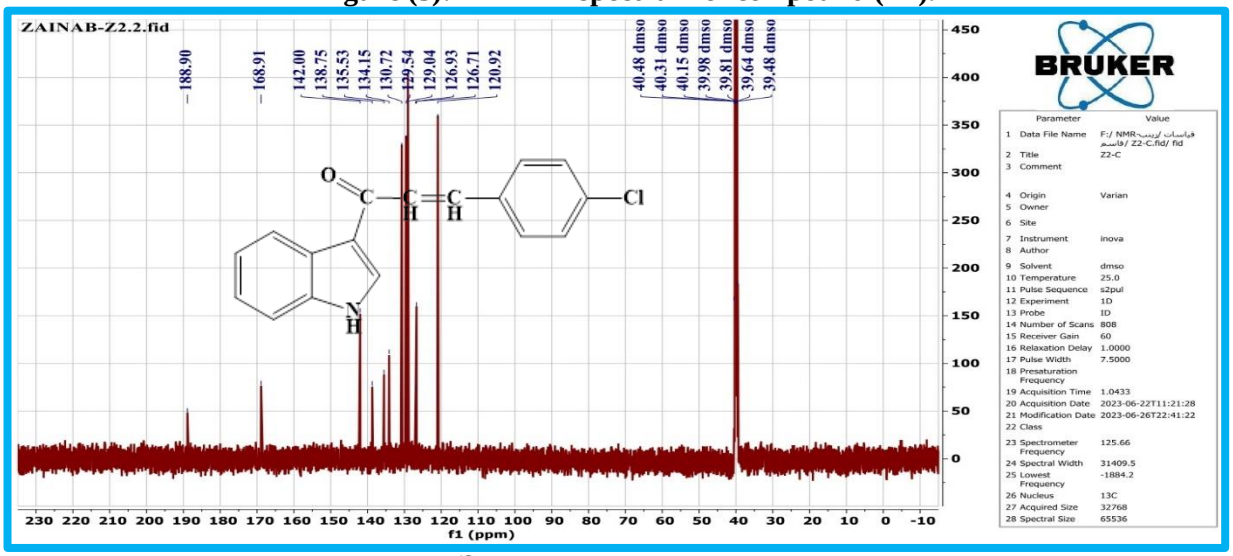


Figure (4): ^{13}C-NMR spectrum of compound (Z2).

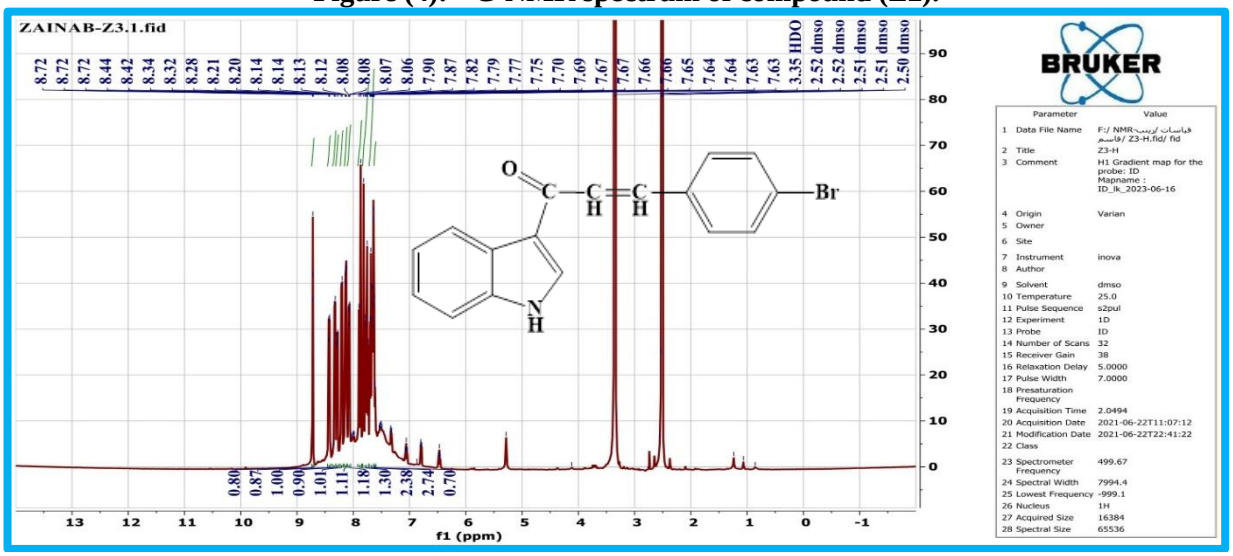


Figure (5): ^{1}H-NMR spectrum of compound (Z3).

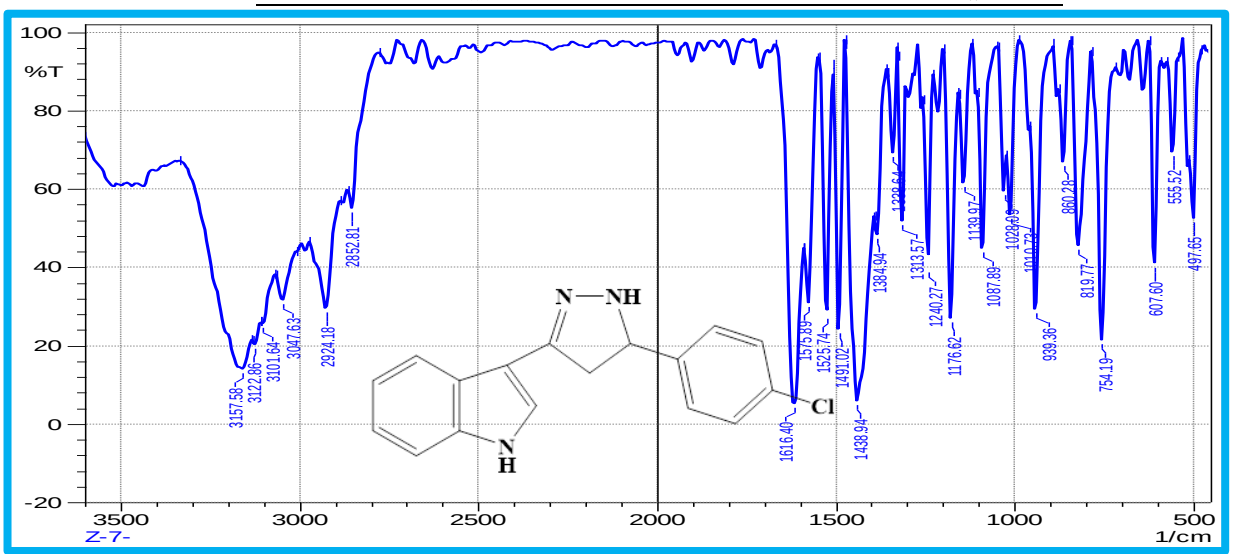


Figure (6): FT-IR spectrum of compound (Z7).

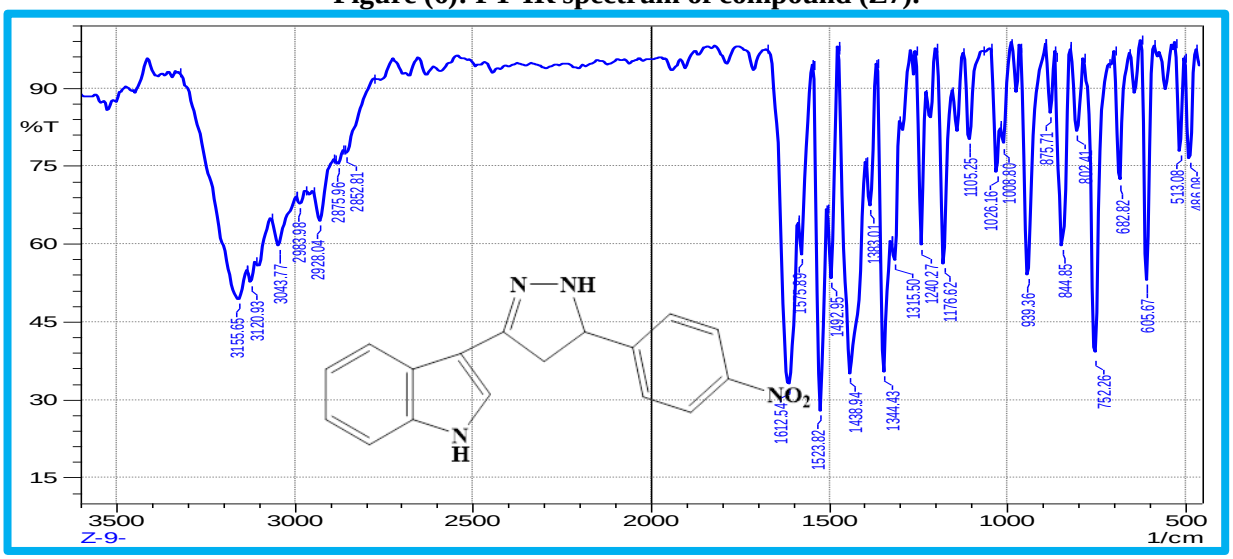


Figure (7): FT-IR spectrum of compound (Z9).

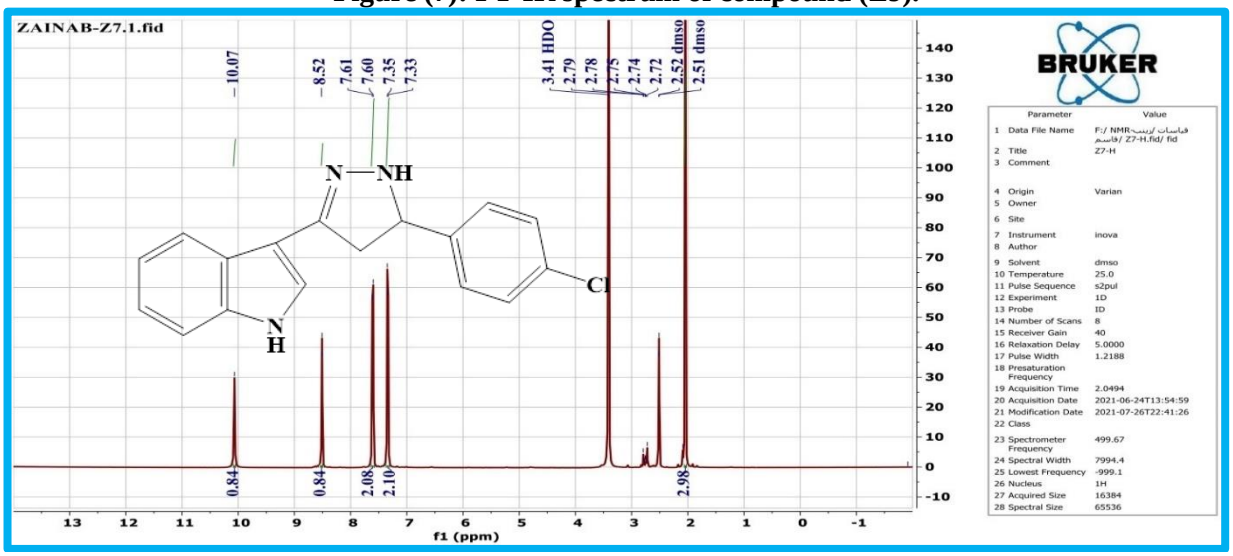


Figure (8): ^{1}H-NMR spectrum of compound (Z7).

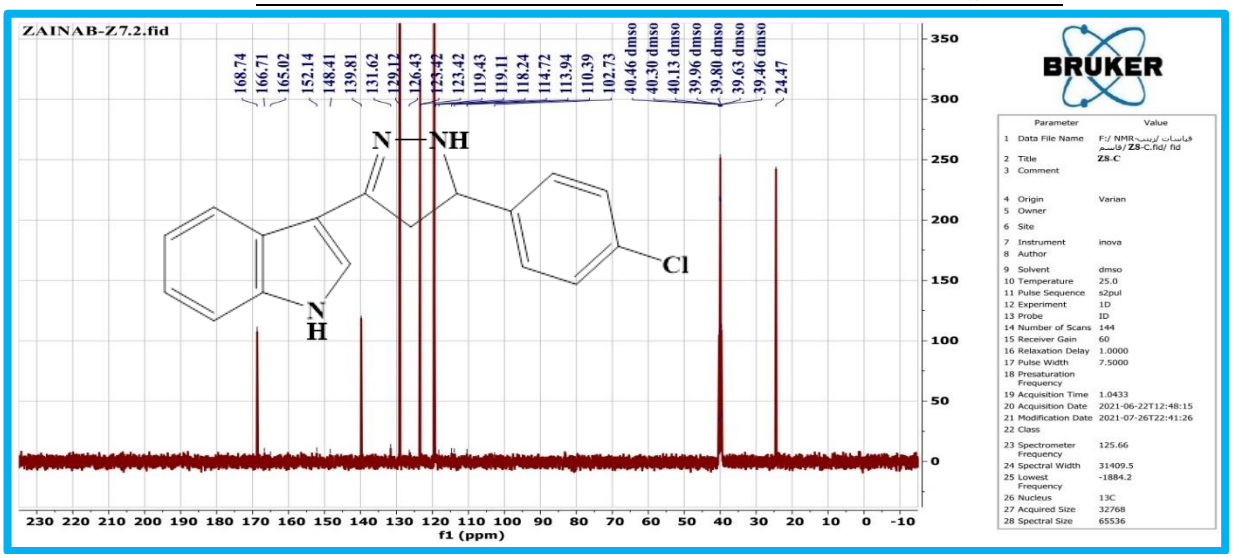


Figure (9): ^{13}C-NMR spectrum of compound (Z7).

Figure (10): Inhibitory effectiveness of compound (Z1) against *E. coli and S. aureus*

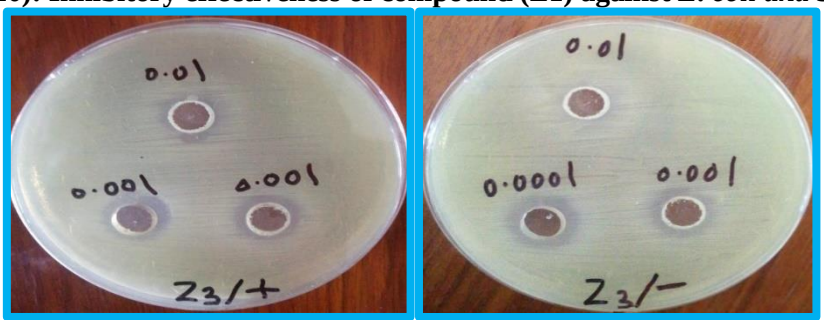


Figure (11): Inhibitory effectiveness of compound (Z3) against *E. coli and S. aureus*

Figure (12): Inhibitory effectiveness of compound (Z4) against *E. coli and S. aureus*

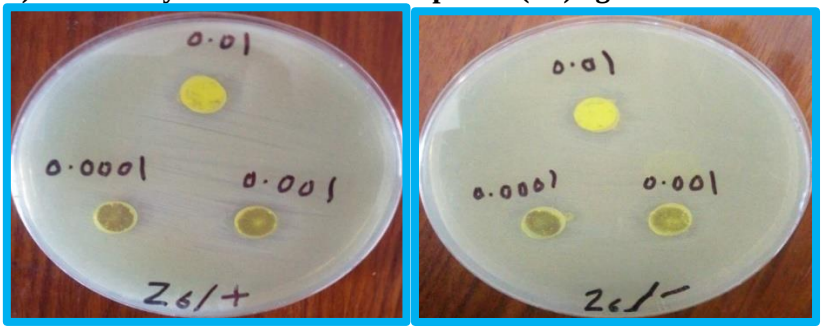


Figure (13): Inhibitory effectiveness of compound (Z6) against *E. coli and S. aureus*

Figure (14): Inhibitory effectiveness of compound (Z7) against *E. coli and S. aureus*

Figure (15): Inhibitory effectiveness of compound (Z9) against E. coli and S. aureus

4. Conclusions: The accuracy and validity of the prepared compounds were confirmed through spectral and physical measurements, where the infrared spectrum proved the presence of active aggregates accurately, and this confirmation increased the nuclear magnetic resonance spectrum of the proton and carbon, which accurately agreed on the validity of the structures of the prepared compounds. These compounds are stable at laboratory temperature and do not degrade or change color. The prepared compounds showed high and good inhibitory activity against Gram-positive and Gram-negative bacteria, and the results were compared with control samples, which are antibiotics.

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