Synthesis of Some New pyrazoline Compounds Derived from chalcones Compounds and Study Their biological activity

تحضير عدد من مركبات البايرازولين المشتقة من مركبات الفا-بيتا-غير المشبعة وتقييم فعاليتها الحيوية

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Abstract:

In this work, α- β- unsaturated compounds (w_{1-9}) have been prepared from the reaction of acetophenone derivatives with appropriate aromatic aldehydes in presence of NaOH(10%),The research included synthesis of pyrazoline from the reaction of semicrbazid with chalcones yieldedscompounds(W_{10-18})3.3-di-p.toly-4,5dihydro-1Hpyrazole-1-Carboxamide). All thesesy ntheized compounds were characterized on the basis of their(IRand H^1NMR) . The study is showed biological activity for chemical compounds, at three concentration 0.01,0.001,0.0001)mg/ml The minimum inhibitory concentration [MIC] have been determined with the reference of stander drugs the results showed that the pyrazoline derivatives are better than growth of both types of bacteria (gram- positive and garm–negative compared to drug.

Key word: pyrazoline, chalcones, biological activity, α,β-unsaturated compounds.

الخلاصة:

يتضمن البحث تحضير مركبات الفا- بيتاغير المشبعة (W_{1-8}) من تفاعل مشتقات الاسيتوفينون مع الالديهايدات الاروماتية بوجود (10%NaOH). تفاعل سيميكاربازايد مع الجالكونات يعطي مركبات (W_{9-16}). 5-(اريل)-3-(4-معوضات-فنيل)4-5-ثنائي هايدرو-H1-بايرازول-كارباثاياميد. تم التأكد من صحة التراكيب بأستعمال الطرق الطيفية ب ^{1}H NMR,IR. وتم اختبار الفعالية الحيوية للمركبات المحضرة ضد البكتريا السالبة والموجبة لصبغة كرام. والتركيز المثبط الادنى (MIC) تم اختباره مع ادوية قياسية اظهرت النتائج بأن المركبات المحضرة تمتلك فعالية تثبيط على نمو كلا النوعين السالبة (*E.coli*) والموجبة(*Proteus*) لصبغة كرام مقارنة مع الدواء لمستعملة كمحلول قياسي.

INTRODUCTION:

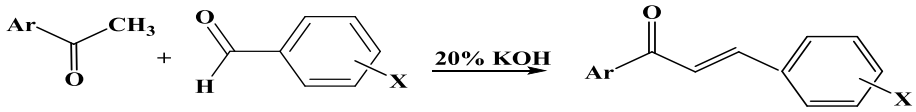
The α,β-unsaturated ketones (chalcones) are considered to be precursors of flavonoids and is flavonoids and found as naturally-occurring compounds, but it could be considered that their true importance is extended in two branches. The biological activity associated with them, including anti-inflammatory[1], antitubercular, cytotoxic, anti-HIV[2] antioxidant, analgesic, antiviral and antimicrobial [3], analgesic[4], anti-tuberculosis[5], anti-funga[6], anti-malarial[7],11, anti-tumor, and and antioxidant[8] properties; as well as their recognized synthetic utility in the preparation of pharmacologically-interesting heterocyclic systems like pyrazolines .

Pyarzoline are an important an class of five- membered heterocyclic compounds and were found to have potential, anti- inflammatory [9], anti-pyretic [10], anti-depressant [11], anti-bacterial[12], anti-tranquillizing[13], anti-cancer[14], anti-convulsat, insecticidal[15], fungicidal, antiviral[16] and antiparasitic [17]

Experimental: -

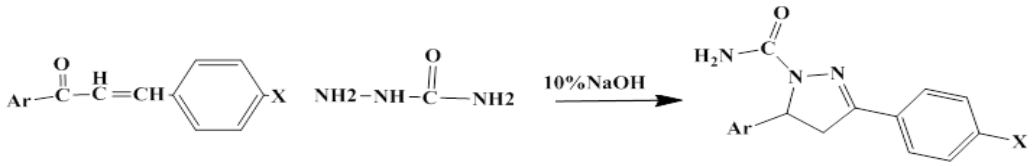
All the chemicals and solvents used were of Aldrich and Fluka products and were used without further purification**.** Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infrared spectra have been recorded on a Shimadzo FTIR-8100 spectrophotometer using KBr discs–and ^{1}H NMR Spectra have been measured on a MH_Z spectrometer using (DMSO-d_6) as solvent. reaction monitoring and verification of the purity of the compounds was done by TLC on silica gel-percolated alumni sheets (type 60 F254 Merck, Darmstadt, Germany).

Synthesis of chalcones (w_1-w_8) [18]



A mixture of appropriate acetophenone (0.01mol) and aromatic benzaldehyde (0.01mol) have been added to a solution of (10%) sodium hydroxide (5mL), and (3mL) of ethanol. The mixture was stirred for (2-3) hr. at (20-40) ° C and kept in a refrigerator for (12) hr. Then it was diluted with ice-cold distilled water (30mL), filtered washed with cold water, dried and recrystallized from ethanol. The physical properties are shown in Table (1)

Synthesis of pyrazolines (W_{9-18}) [19]



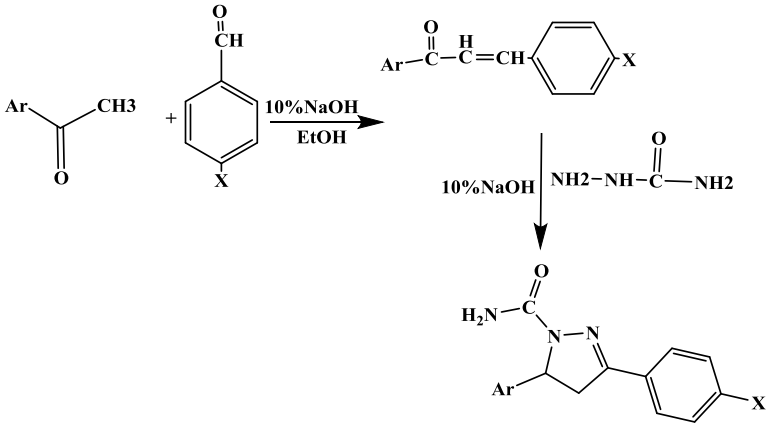
A mixture of (0.01 mol) of semicrbazid, (0.01 mol) of chalcones, in dioxan (10ml) containing glacial acetic acid (1mL) was refluxed for 2h. The mass reaction have been concentrated to one- third volume under vacuum. The product hav been poured in to ice-cold and filtered water. The separated products hav been recrystallized from ethanol. The physical properties are shown in Table (2)

Evaluation of biological activity

The biological activity has been estimated by using the propagation method whereas the biological activity has been estimated by the Kirby Bauer movement, where 0.1 ml of bacterial suspension has spread to the ager Muller Hinton dishes and left for 5 minutes to absorb the suspension. After that, holes were prepared for each dish using a Cork Porer and a diameter of (5) mm per hole (0. 1 mL) of the prepared solutions of the fourth hole using(DMSO) as acontrol
sample and incubated the dishes for(24) hours at 37℃ [20,21]. The inhibition zone diameters around each holes has been measured in milmeter, depending on the method of Prescott. (22).

Result and Discussion:

The synthesis of chalcones and pyrazoline derivatives were performed as Shown in scheme (1). The reaction of acetophenon with aromatic aldehydes yielded the compounds (W_1-$_8$) , the IR spectra of compounds (W_1-$_8$) showed characteristic (C=O) stretching at (1668-1655 cm^{-1}) and (C=C) stretching frequencies at (1604-1592 cm^{-1}), band at (1572-1446 cm^{-1}) for**(C=C)** group band at (3073-3004 cm^{-1}) for (Ar-H) group figure(1). ^{1}H NMR Spectrum of compound (W_2) , (Figure 2),Showed the following signals : a singlet signal at δ 2.66ppm due to a proton of (6H-CH_3) group , sharp signal at δ 2.66 ppm due to a proton of phenyl, signal at (7. 67 to 8.05 ppm) for (HC=CH)) figure(2).The structure of the pyrazoline derivatives(W_9-$_{18}$) .The The IR spectral data of these compounds showed band at (1541-1517 cm^{-1}) due to stretching (**(C=C)**) group. a band at (1573-1631 cm^{-1}) for (C=N) group. band at (2169-2185) for (HC≡N) group. a band at (3012-3068) for (Ar-H) group. aband at (3212-3244 cm^{-1}) for (NH) group and other bands. The IR data showed in the Figure (3) Table (4) . H^1 NMR spectrum of compound (W_{10}) ,(Figure 4), showed the following signals : a sharp singlet singl at (2.50 ppm) due to (DMSO) , sharp signals at (3.37 ppm) could be attributed to two protons of ($2CH_3$) group , sharp signals at(3.37ppm) could be attributed to two protons of (CH_2) group-pyrazoline, signal at (6.5) for (NH_2), many signals (aromatic protons) appeared in the region (7.35to 7.97ppm) .



Scheme 1. Synthesis of title compound (W_1-$_{16}$)

Evaluation of biological activity :

The antimicrobial activities of the synthesized compounds were determined in vitro against several pathogenic representative microorganism (*Escherichia coli* and *Proteus spp)* , using Agar well-diffusion method[22]. Ciprofloxacin were used as standard drugs for studying the potential activities of these compounds, All the compounds were tested at different concentration level (0.01, 0.001, 0.0001 mg / ml), DMSO was used as solvent and as control. showed high activity against all the microorganisms employed in contrast with the ciprofloxacin derivatives. The maximum activity (MIC = 12.5 μg/mL) was indicated for compounds. he results are summarized in Table 5[23].

Table (1): The physical properties of compounds (w_1-w_8)

Comp. No.	X	Ar	Molecular formula	M.P (C)°	Yield (%)	Color
W_1	CH_3	-C_6H_5	$C_{16}H_{14}O$	45-48	85	White
W_2	CH_3	4-CH_3-C_6H_5	$C_{17}H_{16}O$	110-112	92	White
W_3	CH_3	-(CH=CH)-C_6H_5	$C_{18}H_{16}O$	73-75	88	White
W_4	Cl	-C_6H_5	$C_{15}H_{11}O$ Cl	83-86	83	Yellow
W_5	Cl	4-CH_3-C_6H_5-	$C_{16}H_{13}O$ Cl	118-120	94	White
W_6	Cl	-(CH=CH)-C_6H_5	$C_{17}H_{13}O$ Cl	102-105	79	Yellow
W_7	F	-C_6H_5	$C_{15}H_{11}OF$	73-75	84	Yellow
W_8	F	4-CH_3-C_6H_5-	$C_{16}H_{13}OF$	108-110	92	White

Table No. (1) : Physical properties of synthesized compounds (w_9-w_{16})

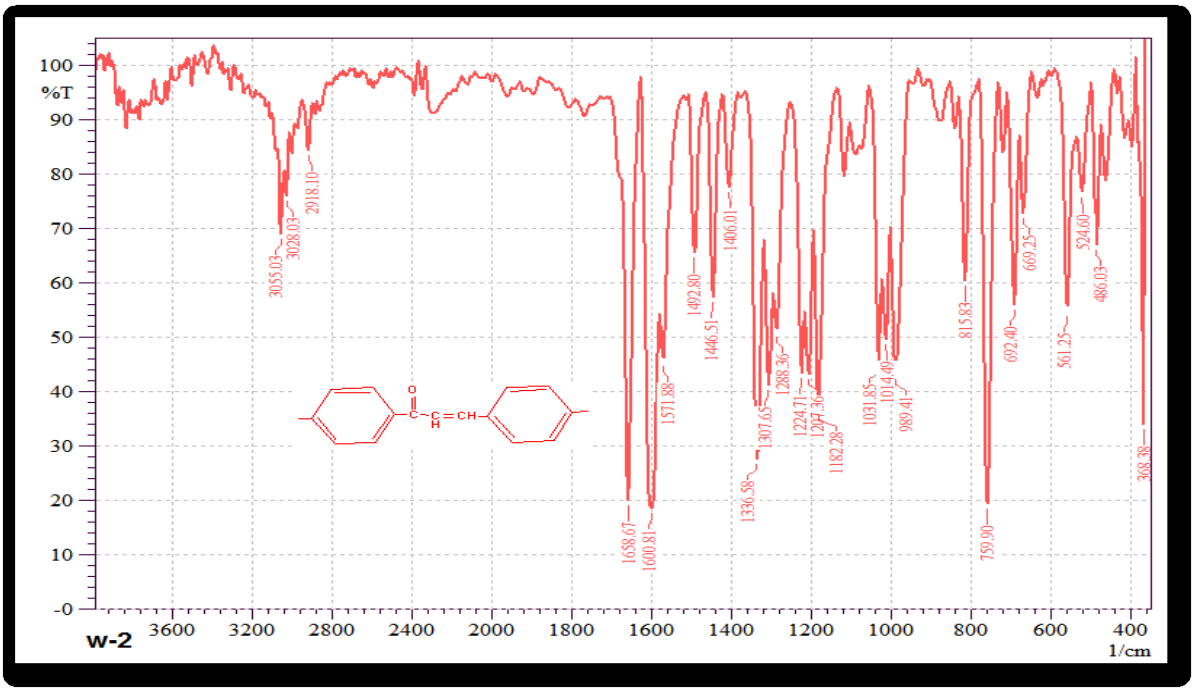
Comp. No.	X	Ar	Molecular formula	M.P. (C)	Yield (C)°	Rf	Physical State
W_9	CH_3	-C_6H_5	$C_{17}H_{17}N_3O$	160-163	93	0.74	Yellow Crystals
W_{10}	CH_3	4-CH_3-C_6H_5	$C_{18}H_{19}N_3O$	168-170	81	0.79	Dark Yellow Crystals
W_{11}	CH_3	-(CH=CH)-C_6H_5	$C_{19}H_{18}N_3O$	137-139	93	0.67	Pale Yellow Crystals
W_{12}	Cl	-C_6H_5	$C_{16}H_{14}N_3OCl$	143-145	95	0.81	Yellow Crystals
W_{13}	Cl	4-CH_3-C_6H_5-	$C_{17}H_{16}N_3OCl$	157-160	74	0.83	Brown Crystals
W_{14}	Cl	-(CH=CH)-C_6H_5	$C_{18}H_{16}N_3OCl$	122-125	72	0.71	Pale Yellow Crysta
W_{15}	F	-C_6H_5	$C_{16}H_{14}N_3OCl$	134-137	78	0.76	Dark Yellow Crystal
W_{16}	F	4-CH_3-C_6H_5-	$C_{17}H_{16}N_3OF$	152-155	84	0.67	Pale White Crystals

Table (3): IR –spectral data of compounds (w_1-w_8)

Comp .No	X	Ar	FT-IR cm^{-1} (KBr)				
			-C=O	υ (Ar-H)	υ (C=C) olefin	υ(C----C)	Others cm^{-1}
W_1	CH_3	$-C_6H_5$	1655	3057	1602	1446	2921asy,2878sy υ(CH_3)
W_2	CH_3	4-CH_3-C_6H_5	1658	3055	1600	1571	2918asy,2884sy υ(CH_3)
W_3	CH_3	-(CH=CH)-C_6H_5	1644	3062	1595	1574	2937asy,2891sy υ(CH_3)
W_4	Cl	$-C_6H_5$	1660	3004	1604	1487	υ (C-Cl) 730
W_5	Cl	4-CH_3-C_6H_5	1654	3031	1603	1509	υ (C-Cl)773
W_6	Cl	-(CH=CH)-C_6H_5	1650	3078	1593	1508	υ (C-Cl) 821
W_7	F	$-C_6H_5$	1658	3061	1602	1568	υ (C-Br)810
W_8	F	4-CH_3-C_6H_5-	1689	3048	1592	1581	υ (C-Br)861

Table (4) Spectral data of compounds (w_9-w_{16})

Comp .No	X	Ar	FT-IR cm^{-1} (KBr)				
			υ -(C=O)	υ (Ar-H)	υ (C=N)	υ(C----C)	Others cm^{-1}
W_9	CH_3	$-C_6H_5$	1632	3032	1604	1519	υ(NH) 3212
W_{10}	CH_3	4-CH_3-C_6H_5	1676	3033	1596	1537	υ(NH) 3296
W_{11}	CH_3	-(CH=CH)-C_6H_5	1643	3012	1543	1450	υ(NH) 3227
W_{12}	Cl	$-C_6H_5$	1621	3017	1573	1523	υ (NH) 3166
W_{13}	Cl	4-CH_3-C_6H_5	1614	3026	1563	1514	υ (NH) 3244
W_{14}	Cl	-(CH=CH)-C_6H_5	1619	3076	1567	1517	υ (NH) 3278
W_{15}	F	$-C_6H_5$	1637	3043	1583	1531	υ (NH)3216
W_{16}	F	4-CH_3-C_6H_5	1657	3013	1600	1530	υ (NH) 3282



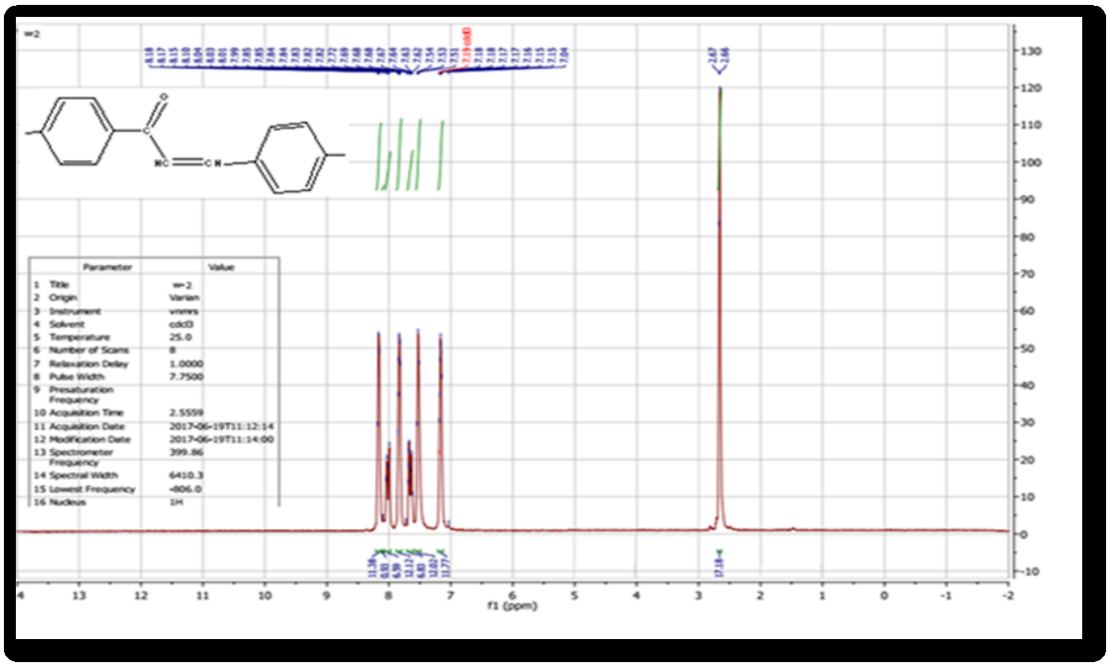


Figure (2) H^1 NMR spectrum of W_2

Figure (1) F-TIR spectrum of W_2

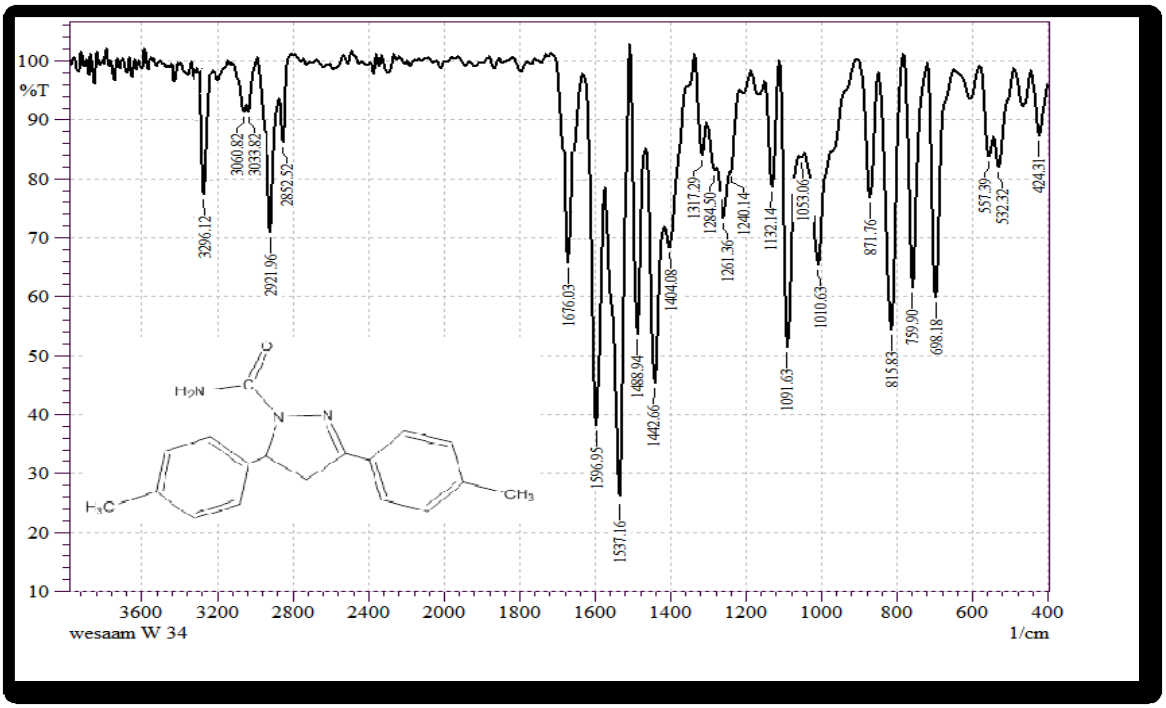


Figure (3) F-TIR spectrum of W_{10}

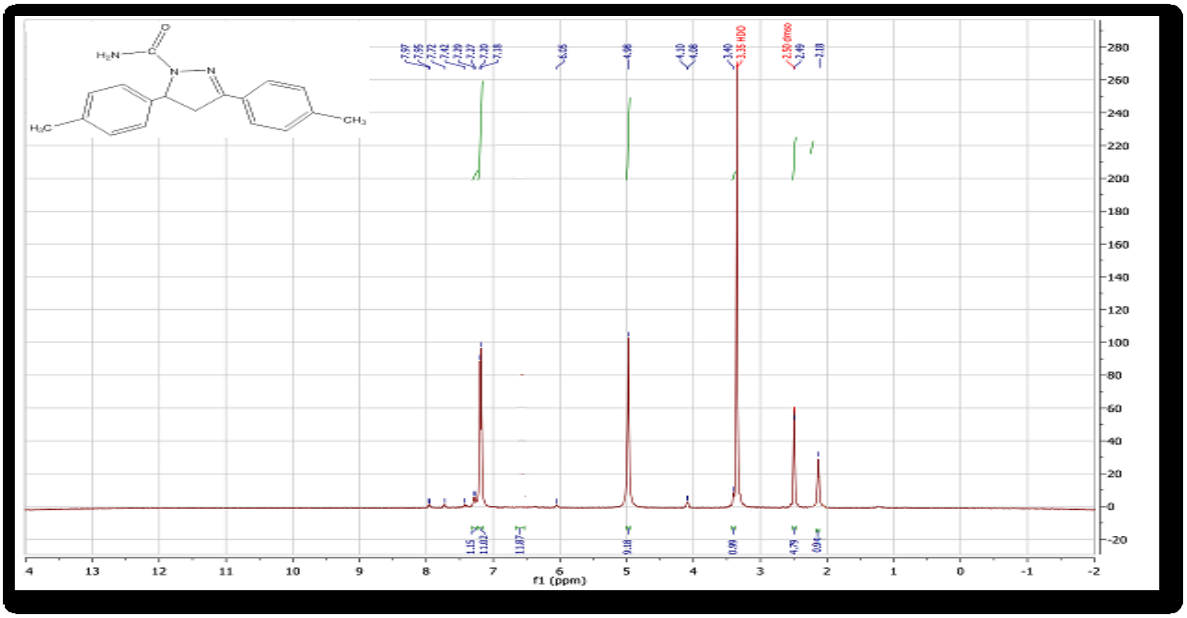


Figure (4) H^1 NMR spectrum of W_{10}

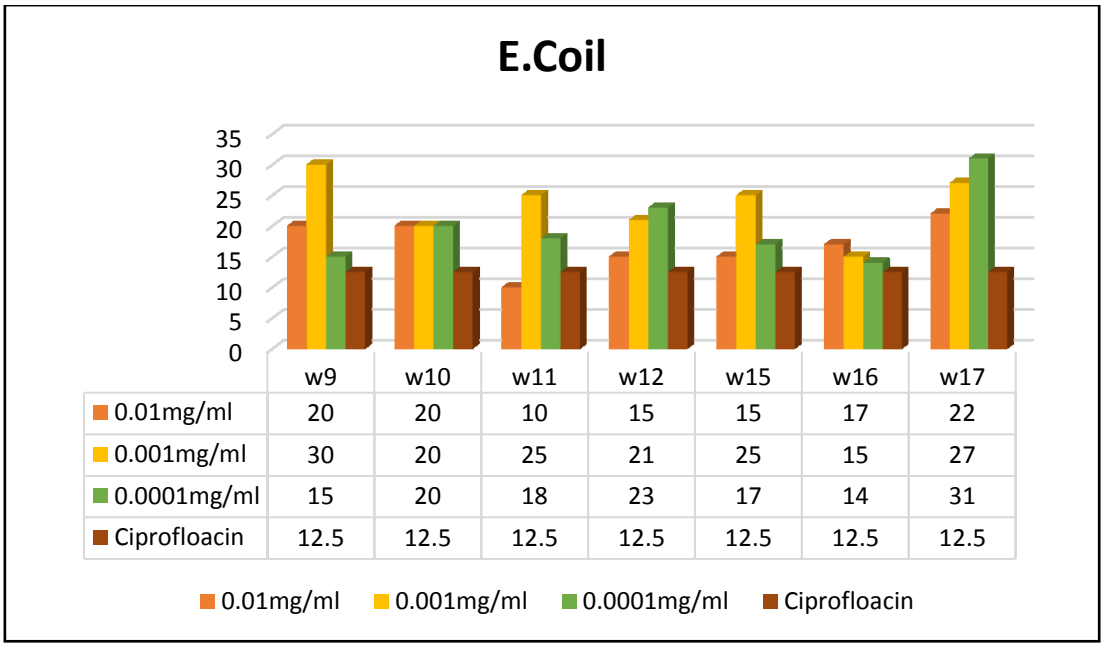


Figure (5) Differential effect and different concentrations of compounds(W_{9-16}) studied against bacteria(*E.Coli*)

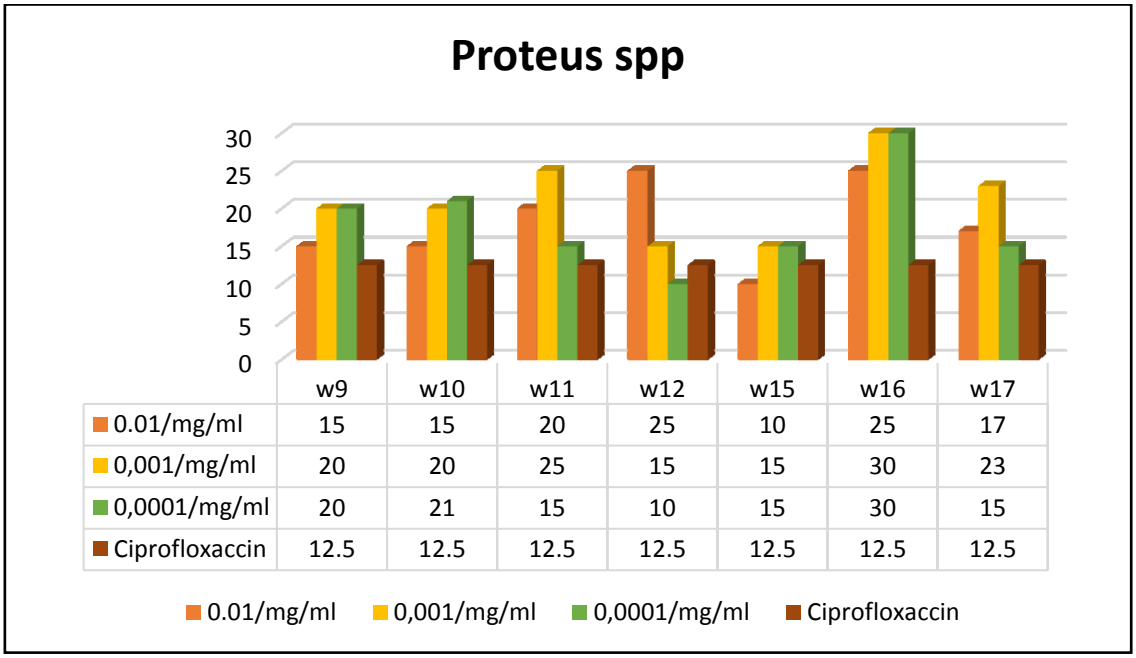


Figure (6) Differential effect and different concentrations of compounds(W_{9-16}) studied against bacteria(*protus sp*)

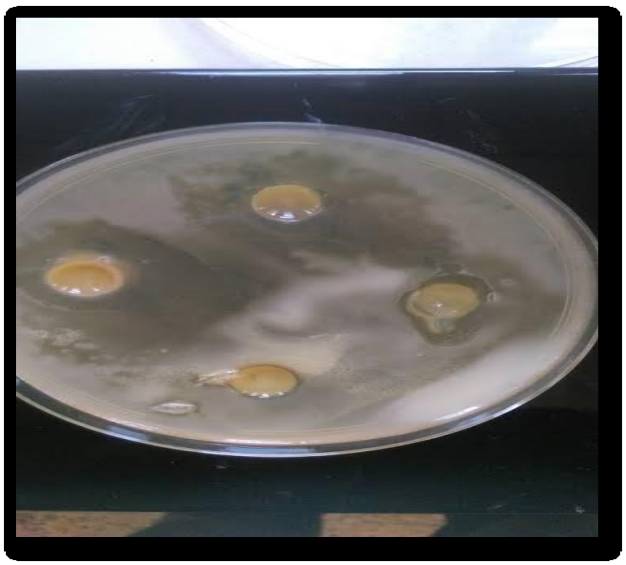


Figure (8) Compound (W_{10}) inhibits growth of bactera E.Coli

Figure (7): Compound (W_{16}) inhibits growth of bacteria E.coli

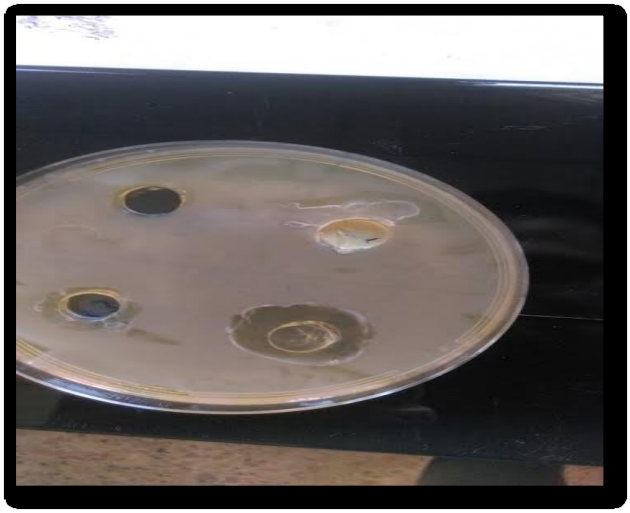


Figure (10): Compound (W_{10}) inhibits growth of bacteria growth bacteria Proteus Mirabil

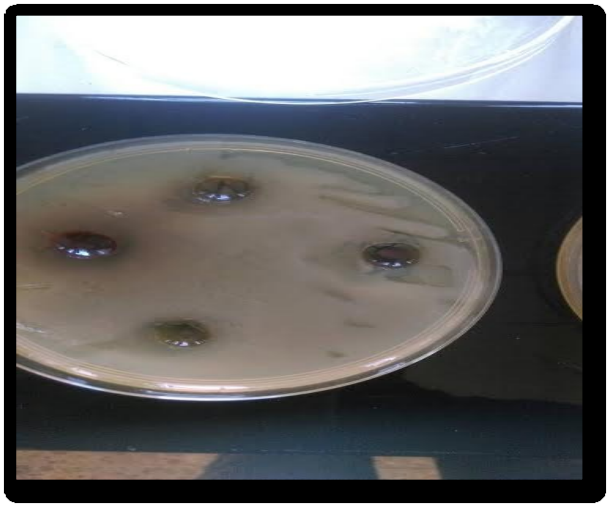


Figure (9): Compound (W16) inhibits growth bacteria Proteus Mirabilis

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