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Synthesis of New Pyrazoline Derivatives from 2-Furylmethanethiol and Study Their Biological Activity

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Abstract

A series of pyrazoline derivatives were synthesized by reaction furan-2-yl methyl (sulfanyl) acetic acid hydrazide with chalcone dibromides. The later was synthesized by grinding the different aldehydes with different ketones without using any solvent after that addition of bromine to produce the desired in the presence of sodium hydroxide. all compounds were confirmed by FT-IR, H-NMR and ^{13}C-NMR.All these pyrazoline compounds were tested for antibacterial and antifungal activities. Some compounds show very antibacterial activity and antifungal activity.

Key word: pyrazoline, chalcone, antibacterial, antifungal.

1.1 INTRODUCTION

The frame work 1,3-diaryl prop-2-en-1-one [1] is well known by the generic term "chalcone", A name coined by kostanecki and Tambor [2] . It is also known as benzal acetophenone and benzylidene acetophenone. Chalcones belong to the flavonoid family[3-4]. These open-chain flavonoids have two aromatic rings that are linked by an aliphatic three-carbon chain[5]. The versatile molecule chalcone is an Alpha-Beta-Unsaturated ketone that contain the reactive keto-ethylenic group (-CO-CH=CH-)[6]. A chromophore responsible for the color in chalcone compounds[7], Depending on the presence of other auxochromes[8]. Chalcones are characterized by an oily texture most of the time[9], And the final predominant color is yellowish-brown[10]. The increase in the state of the resonance of the compound increases the concentration of color in the chalcone[11], such as azo dyes. As for the amount of chalcone produced, it is increased by increasing deactivating groups such as NO2, Br, especially if the compensation is in the location of para, unlike activating groups that reduce the amount of chalcone produced[12].

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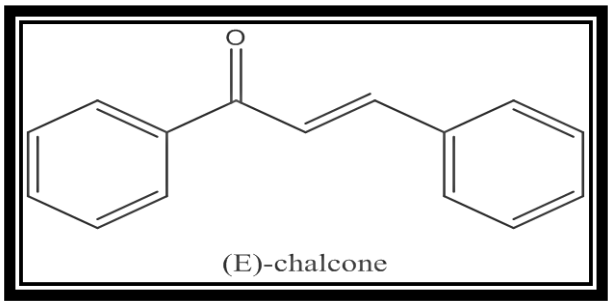

Fig. (1)

2.1 Experimental

All using materials supplied from merck and BDH chemical company. Melting points used electrothermal melting point apparatus, UK. FTIR spectra used on SHIMADZU FT.IR-8400S infrared, Baghdad University. 1H-NMR spectroscopy, operate at 300 MHZ with tetramethyl silane as internal standard, measurements were made on chemistry department, AL-Al-Bayt University, Jordan.

Compound **A1** was prepared according to the published procedure [13]; compound A2 was prepared according to the published procedure [14] and compound A3 was prepared according to the published procedure [15]

Preparation of Chalcones (A4-A7)

A mixture 0.5 g of sodium hydroxide and 12.5m moles of acetophenone was grinded well for (1 h). Then 12.5 mmoles of suitable aromatic aldehydes was added gradually to mixture and grinded for an hour. The grinding product was leaved overnight, the formed precipitate was washed with water to get rid of the base and then the product was recrystallized from acetone.

1-(4-nitrophenyl)-3-phenylprop-2-en-1-one(A4): -

. Yield (91%), light yellow crystals, m.p. 162-166°C (acetone + ether). IR (KBr) in cm^{-1}, 1658 (C=O), (1639 and 1608 C=C), (1336 and 1515) (NO_2)

1-(4-bromophenyl)-3-phenylprop-2-en-1-one (A5): -

Yield (93%), light yellow crystals, mp **152-148**°C (acetone + ether). IR (KBr) in, cm–1: 1658 (C=O), 1639 and 1608 (C=C), 532 (C-Br).

1,3-di(furan-2-yl) prop-2-en-1-one (A6): -

. Yield (79%), yellow crystals, mp 64-66°C (extraction by ether). IR (KBr) in, cm^{-1}: 1660 (C=O), 1639 and 1604 (C=C).

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3-(furan-2-yl)-1-(4-nitrophenyl) prop-2-en-1-one (A7): -

Yield (83%), yellow crystals, mp 120-124°C (acetone + ether). IR (KBr) in, cm–1: 1654 (C=O), 1614 and 1595 (C=C) ,1342 and 1517 (NO_2).

Preparation of (2,3-dibromo-3,1-diphenylpropan-1-one) (A8-A11): -

To a mixture of (0.63225 g, 12.5 mmoles) from 3,1-diparylprop-2-en-1-one in 10 ml of chloroform, 12.5m. moles of dissolved bromine in chloroform was added and then the mixture was mixed for 24 hours. The product was deposited by evaporation of the solvent and the result was purified by recrystallization from ethanol and ether.

2,3-dibromo-1-(4-nitrophenyl)-3-phenylpropan-1-oneI(A8): -

Yield (83%), yellow crystals, mp 182-186°C (Recrystallization by Ethyl acetate + Ether). IR (KBr) in, cm^{-1}: 1683 (C=O), 1602 (C=C arom), 1346 and 1523(NO_2), 540(C-Br)

2,3-dibromo-1-(4-bromophenyl)-3-phenylpropan-1-one(A9): -

Yield (91%), Off white crystals, mp °C (Recrystallization by acetone + Ether). IR (KBr) in, cm^{-1}: 1679 (C=O), 1591 (C=C arom), 528(C-Br).

2,3-dibromo-1,3-di(furan-2-yl) propan-1-one(A10): -

Yield (73%), light brown crystals, mp °C (Recrystallization by acetone + Ether). IR (KBr) in, cm^{-1}: 1654 (C=O), 1604(C=C arom), 592(C-Br).

2,3-dibromo-3-(furan-2-yl)-1-(4-nitrophenyl) propan-1-one(A11): -

Yield (85%), brown crystals, mp °C (Recrystallization by acetone + Ether). IR (KBr) in, cm^{-1}: 1666 (C=O), 1600(C=C arom), 592(C-Br).

Prepare of 2-((furan-2-ylmethyl) thio)-1-(3-hydroxy-3,5-diphenyl-2,3-dihydro-1H-pyrazol-1-yl) ethan-1-one dravites (A12-A15): -

To a mixture of 12.5 mmol from 2,3-dibromo-3,1-diphenylpropan-1-one in 40 ml of absolute ethanol,12.5 mmol from 2 - ((furan-2- ylmethyl (thio) acetohydrazide, with 10 mL of Et_3N was added. The reaction mixture was heated under reflex condensation for (14 hours) in a water bath. The ingredients were reduced, cooled and deposited on the broken ice, and left-over night. The product was then collected by filtering, then purified with ethanol with drops of water.

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2-((furan-2-ylmethyl) thio)-1-(3-hydroxy-5-(4-nitrophenyl)-3-phenyl-2,3-dihydro-1H-pyrazol-1-yl) ethan-1-one(A12): -

Yield (60%), yellow crystals, mp °C (Recrystallization by Acetone). IR (KBr) in, cm^{-1}: 3548(OH), 3415 (N-H), 1660 (C=O), 1608(C=C arom), 1338-1515(NO_2).

^{1}H-NMR (DMSO-d6) (in ppm) 2.7 and 3.2 (dd, 2H, CH_2 pyrazoline ring), 3.19 (s,2H, S-CH_2-CO), 3.43 (s,2H, furan-CH_2), 5.10 (broad, OH) 6.19-831(CH aromatic). ^{13}C-NMR (DMSO-d6) (in ppm) 167.91 C=O, 150.26-107.76 aromatic, 49.28 CH_2 pyrazoline ring, 39.07 S-CH_2-CO, 28 furan-CH_2, 83(C-OH).

1-(5-(4-bromophenyl)-3-hydroxy-3-phenyl-2,3-dihydro-1H-pyrazol-1-yl)-2-((furan-2-ylmethyl) thio) ethan-1-one(A13)

Yield (48%), dark orange, oily, (Recrystallization by CCl_4 / ether). IR (KBr) in, cm^{-1}: 3433(OH), 3249 (N-H), 1668 (C=O), 1595(C=C arom), 597 (C-Br).

^{1}H-NMR (DMSO-d6) (in ppm) 2.1 and 3.2 (dd, 2H, CH_2 pyrazoline ring), 3.18 (s,2H, S-CH_2-CO), 3.90 (s,2H, furan-CH_2), 4.93 (broad, OH) 6.30-8.09 (CH aromatic). ^{13}C-NMR (DMSO-d6) (in ppm) 170.78 C=O, 142.81-107.90 (C aromatic), 40.01 CH_2 pyrazoline ring, 28 S-CH_2-CO, 32 furan-CH_2.

1-(3,5-di(furan-2-yl)-3-hydroxy-2,3-dihydro-1H-pyrazol-1-yl)-2-((furan-2-ylmethyl) thio) ethan-1-one (A14): -

Yield (77%), yellowish brown, m.p. 98-102^{o}C., (ether). IR (KBr) in, cm^{-1}: 3442 (OH), 3400 (N-H), 1676 (C=O), 1560 (C=C arom). ^{1}H-NMR (DMSO-d6) (in ppm) 2.19 and 2.50 (dd, 2H, CH_2 pyrazoline ring), 3.34 (s,2H, S-CH_2-CO), 3.89 (s,2H, furan-CH_2), 5.93 (broad, OH) 6.03-7.70 (aromatic). ^{13}C-NMR (DMSO-d6) (in ppm) 166.88 C=O, 149.52-105.70 (C aromatic), 40.22 CH_2 pyrazoline ring, 39.84 S-CH_2-CO, 29.33 furan-CH_2.

1-(3-(furan-2-yl)-3-hydroxy-5-(4-nitrophenyl)-2,3-dihydro-1H-pyrazol-1-yl)-2-((furan-2-ylmethyl) thio) ethan-1-one(A15): -

Yield (88%), Dark brown, m.p. 120-126C^o., (Recrystallization by ethanol/H_2O + ether). IR (KBr) in, $cm^{-1:}$ 3564 (OH), 3415 (N-H), 1668 (C=O), 1602 (C=C arom), 1344-1519(NO_2). ^{1}H-NMR (DMSO-d6) (in ppm) 2.46 and 2.50 (dd, 2H, CH_2 pyrazoline ring), 3.30 (s,2H, S-CH_2-CO), 3.42 (s,2H, furan-CH_2), 5.42 (broad, OH) 6.05-8.57 (aromatic). ^{13}C-NMR (DMSO-d6) (in ppm) 170.23 C=O, 158.70 C=N, 145.18-103.26 aromatic, 52.85 C-C-C pyrazoline ring, 39.86 S-CH_2-CO, 26.80 furan-CH_2

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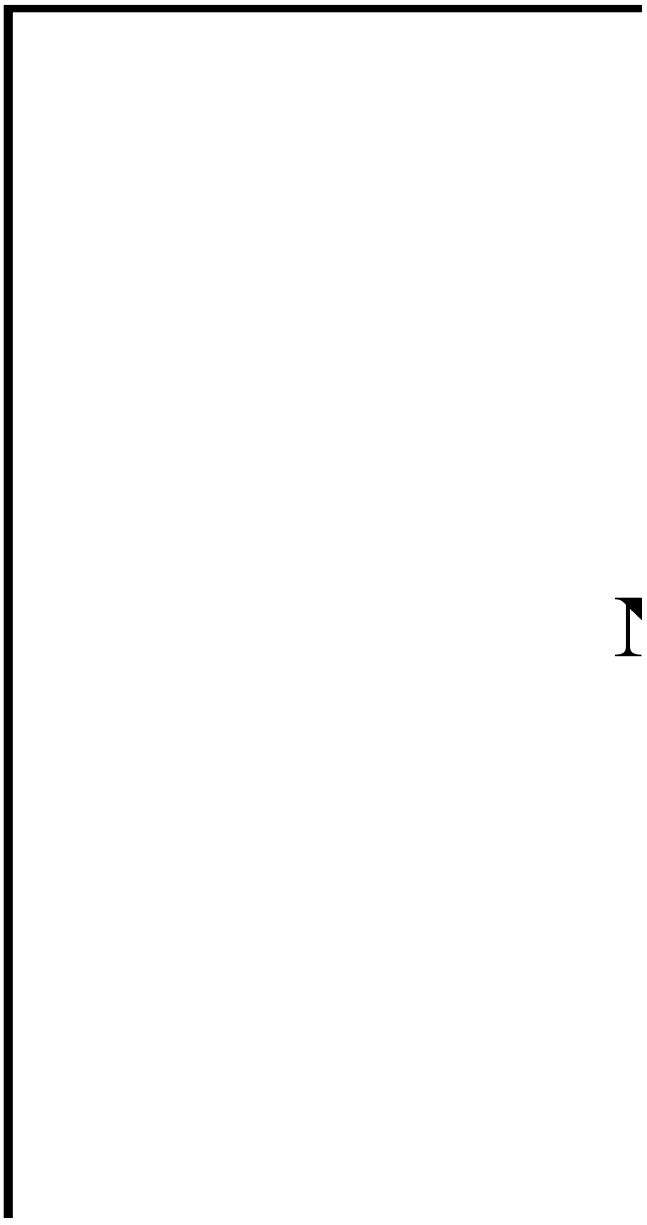
Results and discussion: -

Addition bromine to chalcone derivatives which were prepared by grading method was very effective method to make cyclization of hydrazide with di bromo chalcones was more easily to produce pyrazoline derivatives than usually method (scheme 1). The final produce was confirmed by FTIR;^{13}CNMR and ^{1}HNMR.



Scheme 1

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Synthesis of Chalcones (A4-A7): -

Chalcone was prepared by claisen-schimidt condensation starting by reaction aromatic aldehyde with ketone using grinding method in the presence of sodium hydroxide to synthesize chalcone derivative.

to produce (A4-A7), synthetic of the sequence of these compounds was shown below equation 1. The compounds were characterized by their melting points, FTIR test and TLC

Equation 1

The mechanism was involved the abstraction alpha Proton by base of alpha to a carbonyl group that the carbanions attacks the carbonyl group of aldehyde compound that no has α-H as shown to produce α-β-unsaturated ketone as shown in scheme 2.

Scheme 2

The FTIR spectrum of compound (A4-A7) appearance of absorption bands for ν(C=O) of the ketone at (1654-1660) cm^{-1} respectively showed

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synthesis of (2,3-dibromo-3,1-diphenylpropan-1-one) (A8-A11): -

The halogenation of compound (A4-A7) using bromine in chloroform solution at room temperature gave 2,3-dibromo-3-(4-nitro-phenyl)-1-phenyl-propan-1-one (A8-A11). Equation 2

Equation 2

, FTIR spectrum of the title compounds (A8-A11) showed the appearance of absorption bands for ν(C=O) of the ketone at (1654-1683) cm^{-1}. An increase in the carbonyl group value was observed due to the induction effect of bromine, which saturated the double bond through its interaction with bromine.

synthesis of 2-((furan-2-ylmethyl) thio)-1-(3-hydroxy-3,5-diphenyl-2,3-dihydro-1H-pyrazol-1-yl) ethan-1-one dravites (A12-A15): -

The reaction of compounds (A8-A11) of chalcone dibromides with aryloxy acid hydrazides in absolute ethanol as a solvent as equation 3

Equation 3

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The mechanism of the reaction was proceeded by dehalogenation (-HBr) triple bond then in presence of (-NH_2) electron donating group attack Beta-position of chalcone, cleavage containing double bond, rearrangement leading to closing ring gives chalcone derivative (A12-A15), as shown in scheme 3

The FTIR spectrum of compounds (A12-A15) showed the appearance of characteristic absorption bands at (1660-1676) cm^{-1} for ν (C=O) group, and the shift in the frequency to lower value could be explained on the basis of the mesmeric shift and intra molecular hydrogen bonding and appearance of characteristic absorption bands at (3433-3564) cm^{-1} for (OH) group.

The ^{1}H-NMR spectrum of compound A 12 showed doublet signals at 5.1 ppm for hydroxyl group, singlet at 3.3ppm for tow protons of (S-CH_2-CO), singlet 3.4 for tow protons of (CH2-furan ring), singlet signal at 6.1ppm for one proton of tautomerism structure (CH=C-NH) group and multi signals at (6.19-8.31ppm) for C-H aromatic. While ^{13}C-NMR spectrum for the same compound showed at 24 ppm for methylene group of (S-CH_2-CO), signal at 28.7 for methylene group of (furan-CH_2), signal at 83 ppm for carbon of (C-OH) and at167 for carbon of carbonyl group.

The ^{1}H-NMR spectrum of compound A 13 showed doublet signals at 5.93 ppm for hydroxyl group, singlet at 3.4 ppm for tow protons of (S-CH_2-CO), singlet 3.9 for tow protons of (CH2-furan ring), singlet signal at 6.3ppm for one proton of tautomerism structure (CH=C-NH) group and multi signals at (6.32-8.09 ppm) for C-H aromatic. While ^{13}C-NMR spectrum for the same compound showed at 28 ppm for methylene group of (S-CH_2-CO), signal at 32 for methylene group of (furan-CH_2), signal at 81 ppm for carbon of (C-OH) and at170 for carbon of carbonyl group.

The ^{1}H-NMR spectrum of compound A 14 showed doublet signals at 5.3 ppm for hydroxyl group, singlet at 3.4 ppm for tow protons of (S-CH_2-CO), singlet 3.5 for tow protons of (CH2-furan ring), singlet signal at 6.1 ppm for one proton of tautomerism structure (CH=C-NH) group and multi signals at (6.2-8.5 ppm) for C-H aromatic. While ^{13}C-NMR spectrum for the same compound showed at 29.3 ppm for methylene group of (S-CH_2-CO), signal at 31 for methylene group of (furan-CH_2), signal at 83 ppm for carbon of (C-OH) and at166.8 for carbon of carbonyl group.

The ^{1}H-NMR spectrum of compound A 15 showed doublet signals at 5.19 ppm for hydroxyl group, singlet at 3.3 ppm for tow protons of (S-CH_2-CO), singlet 3.8 for tow protons of

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(CH2-furan ring), singlet signal at 6.05 ppm for one proton of tautomerism structure (CH=C-NH) group and multi signals at (6.22-8.57 ppm) for C-H aromatic. While ^{13}C-NMR spectrum for the same compound showed at 26.8 ppm for methylene group of (S-CH_2-CO), signal at 31.7 for methylene group of (furan-CH_2), signal at 89 ppm for carbon of (C-OH) and at170 for carbon of carbonyl group.

Biological activities: -

1- Anti-bacterial activity: -

The efficacy of some synthesized compounds were measured and compared with some medicines such as sproflexocin and amoxocillin against two types of bacteria, one positive for Gram stain (*Staphylococcus aurius*) and negative for Gram stain (*Klebsilla pneumoniae*)[16]. By using well diffusion method.

Table 1

Compound NO. *Conc.100(mg/ml)*	*Staphylococcus aurius Conc.100(mg/ml) Inhibition zone diameter (mm)*	*Klebsilla pneumoniae Conc. 100 (mg/ml) Inhibition zone diameter (mm)*
control	-	-
A12	17	19
A13	19	19
A14	17	20
A15	23	25
Amoxicillin 500 mg	15	32
Ciprofloxacin 500 mg	47	47

The results showed that the find compounds (A12-A15) was more active them Amoxicillin as stander drug against *Staphylococcus aurius* and less active against *Klebsilla pneumoniae* then Amoxicillin and ciprofloxacin as standard drugs, the results also showed that compound A15 which has nitro group with tow furan rings had the highest activity as shown in Table 1

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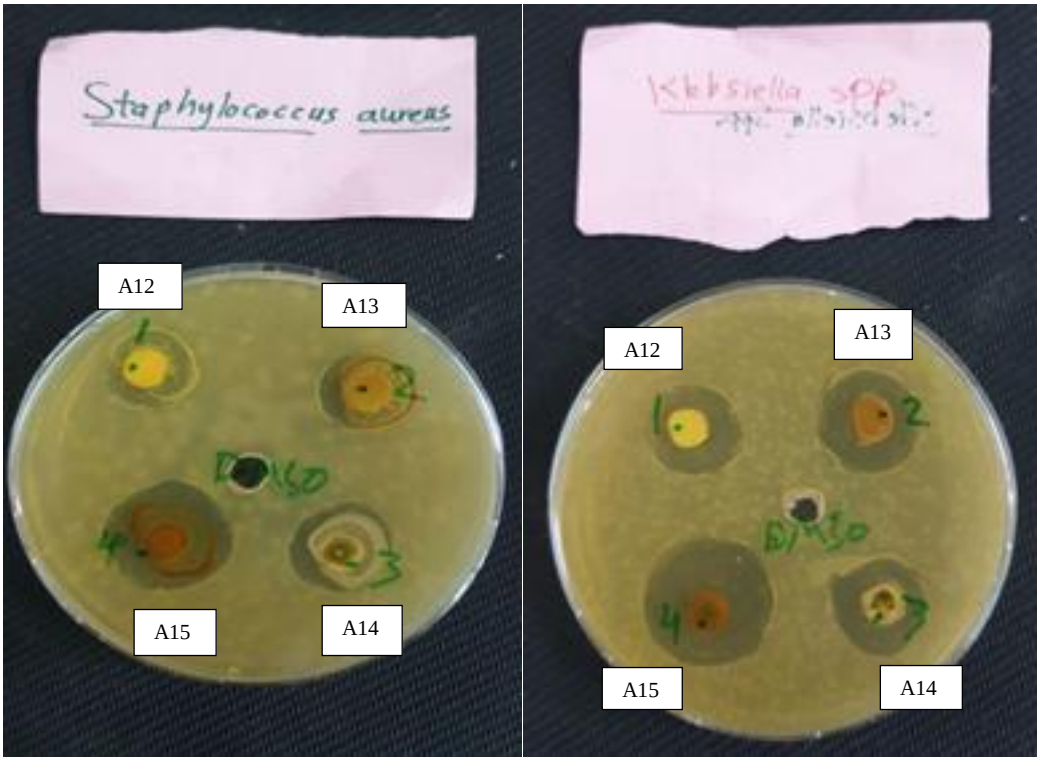

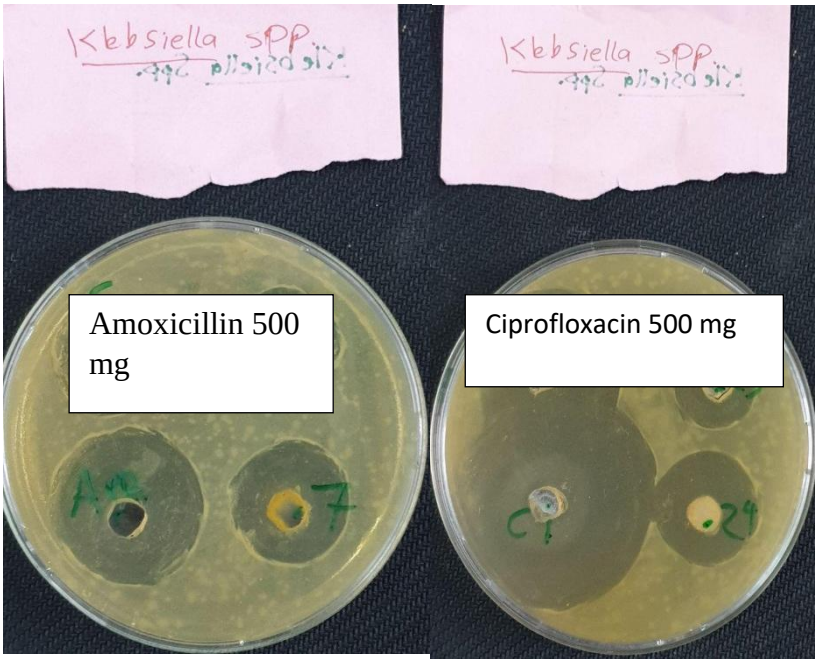

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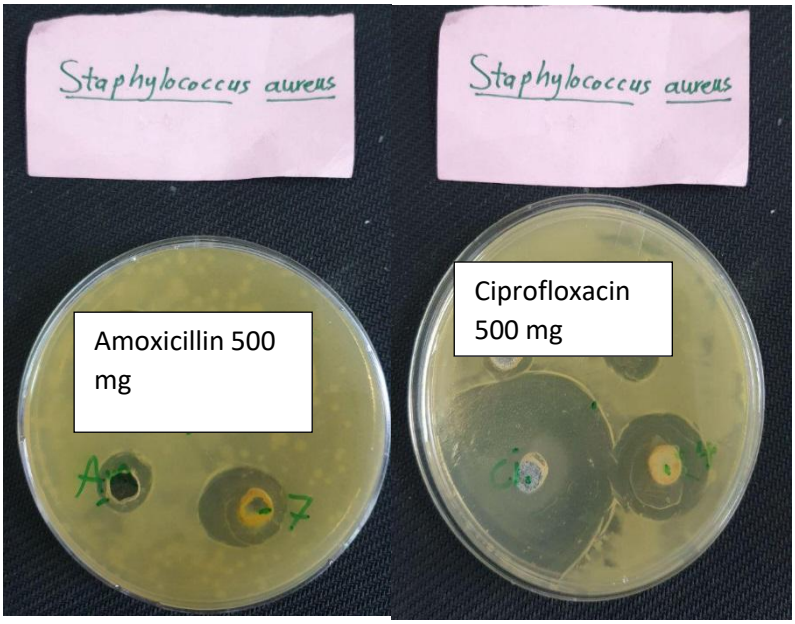

2- Anti-fungal activity: -

The efficacy of some synthesized compounds were tested for anti-fungal and compared with Metronidazole 500 mg against *Rhizosporium Microsporus* by agar well diffusion method will diameter as 5 mm. Where it was noticed that the chemical composition is close to the chemical composition of the compounds whose effectiveness was measured, as the drug contains an amidazole ring as well as a hydroxyl group, while the prepared compounds contain a pyrazoline ring and also contains a hydroxyl group., and this effectiveness is shown in the table 2

Table 2

Compound NO.	*Rhizosporium* *Conc.100 (mg/ml)* *Inhibition zone diameter (mm)*
control	-
A12	32*
A13	37**
A14	38**
A15	32*
Metronidazole 500 mg	30

The synthesized compounds showed a very good activity against this fungal and much better than metronidazole stander drug.

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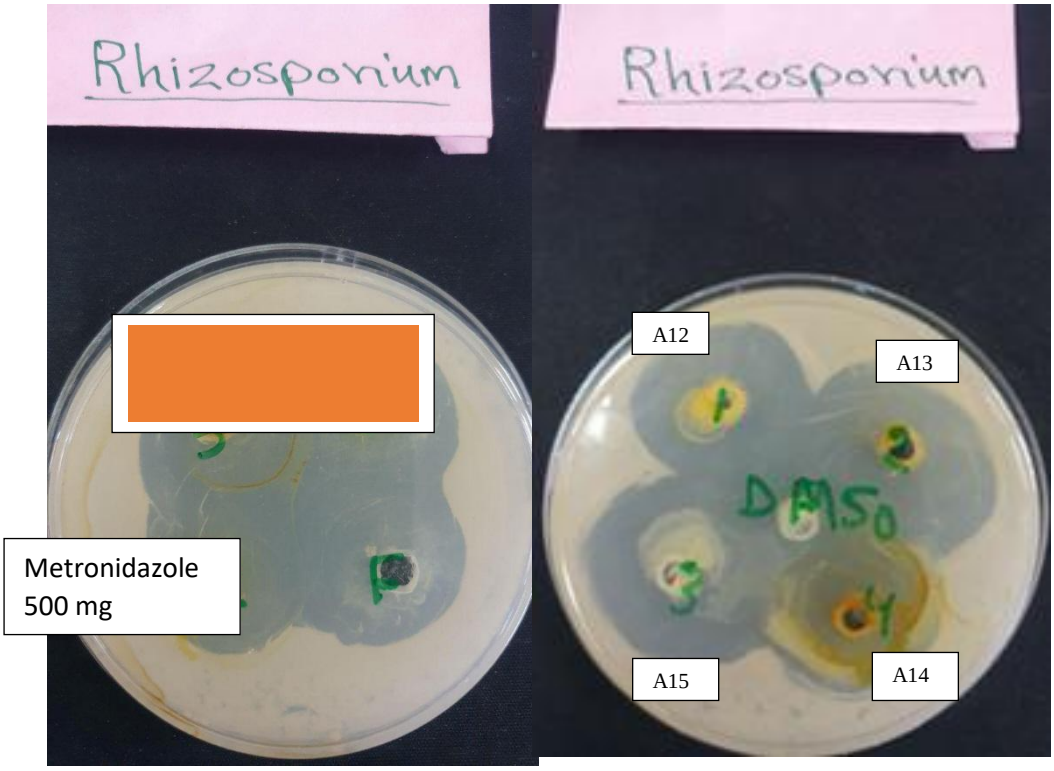

Conclusion

It was prepared from A1-A15. Where the chalcones was prepared by the method of grinding without solvent, and the biological activity of the compounds A12 - A15 was measured, as it gave a strong anti-fungal activity greater than the standard drug, and the activity against bacteria was less than ciprofloxacin in the two types of bacteria positive and negative for Gram stain Some compounds had comparable efficacy of amoxicillin in negatively of Gram stain, and their efficacy was greater than that of amoxicillin in positive effect of Gram stain.

Thanks for the University of Baghdad

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