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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVOLUTION OF SOME COMPLEXES OF N-(4-(BENZYLOXY)PHENYL)-3 – (4 METHOXYPHENYL) ACRYLAMIDE

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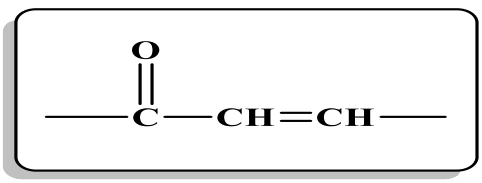
Abstract

Co (II), Ni (II) and Cu (II) complexes are prepared, the ligand chalcones are α,β-unsaturated carbonyl ligands and were obtained from the reaction of paracetamol with different aldehydes. Paracetamol and other aldehydes were reacted in ethanol to give α,β-unsaturated carbonyl ligands which were treated with Co, Ni and Cu salt's to obtain the complexes. Antibacterial activity was tested for the prepared compounds which shows a good effect.

Keywords: α,β-Unsaturated Carbonyl, Complexes, Organic Ligands, Paracetamol.

Introduction

A molecule that has *α,β*-unsaturated carbonyl compounds possesses traits that are unique to both functional groups [1]. Such compounds are crucial intermediate in the organic synthesis for many chemical and life science products [2]. α,β-unsaturated carbonyl is a general term for substances that have both a carbon-carbon double bond and a carbon-oxygen double bond[3].



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α,β-Unsaturated carbonyl molecules have been made utilizing many methods, For example, Claisen-Schmidt aldol condensation, Wittig reaction, and Friedel-Crafts acylation[4]. The pharmacological effects of α,β-unsaturated carbonyl are contributed by aromatic rings and unsaturation [5]. α,β-unsaturated carbonyl, both natural and synthetic, have a broad spectrum of biological activity, including anticancer effects [6-8]. Inhibiting glycogen synthase kinase-3 (GSK-3) inhibition and antimicrobials [9], Anti-Human Immunodeficiency Virus (anti-HIV) [10], and antimalarial [11]. This study aims to synthesize α,β-unsaturated carbonyl compounds and coordinate with different metals and investigate their antibacterial activity.

MATERIAL & METHODS

Paracetamol, benzyl chloride, ethanol, methanol, DMF, Sodium chloride, potassium bicarbonate, 4-methoxy benzaldehyde, Chromium(III) Nitrate, Cobalt(II) Nitrate Hexahydrate, Nickel(II) Nitrate Hexahydrate and Copper(II) nitrate trihydrate, Staphylococcus aureus, Blood agar, Mannitol salt agar. Escherichia coli isolates, MacConky agar, Eosin Methylene blue. They were of analytical grade and were used without further purification. Melting points were determined in open capillary tubes and were uncorrected. FT-IR data were acquired with a Shimadzu8400S FT-IR spectrophotometer in the frequency range of 4000–400 cm^{-1}. The ^{1}HNMR spectra were recorded on a Bruker Ultershield 400MHz NMR spectrometer, Co., Germany, using DMSO-d^{6} as a solvent, with tetramethylsilane as the internal standard.

Synthesis of N-(4-(benzyloxy)phenyl)acetamide (H1)

A 6.6 mmol equimolar solution of paracetamol and K_2CO_3 was add to a round bottom flask that contain 25 mL of DMF, and stirred for 15 minutes. Followed by the addition of 6.6 mmol benzoyl chloride, the mixture refluxed for 4 hours. Then, the reaction mixture was cooled using ice bath, the product was filtered and recrystallized from ethanol to give compound H1, chemical formula ($C_{15}H_{15}NO_2$), solid white, yield 82%, m.p. 140-142 C^{o}.

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Synthesis of N-(4-(benzyloxy)phenyl)-3-(4-methoxyphenyl) acrylamide (H2)

N-(4-(Benzyloxy)phenyl)acetamide H**1** (1.2 mmol) and 4-methoxybenzaldehyde (1.2 mmol) were added to a round-bottom flask contain 25 mL of methanol and thoroughly mixed at room temperature. Then (1.2 mmol) of NaOH dissolved in distilled water and was added dropwise to the mixture, the reaction mixture was stirred at room temperature for overnight. Acidified with dilute hydrochloric acid solution. The yield was filtered, recrystallized from methanol to give compound H**2**. The Chemical Formula ($\mathbf{C_{23}H_{21}NO_3}$), solid yellow, yield 78%, m.p. 132-134 C°.

General procedure for the synthesis of Complexes ($H_{3\text{-}5}$)

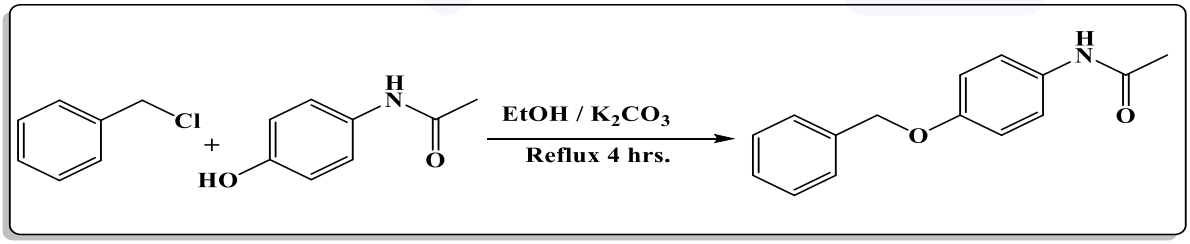
The complexes 3,4 and 5 was prepared by dissolving (0.1 g, 0.24 mmol) of ligand H**2** in (10 mL) of ethanol. Then (0.02 g, 0.12 mmol) of the Co, Cu and Ni salts in ethanol 5 mL was added gradually, the reaction was left overnight under stirrer at room temperature. Table (1) shows the Molecular Formula and some Physical Properties of obtained Complexes.

Table (1): The physical properties of compounds ($H_{3\text{-}5}$)

Comp.	Formula	Yield %	M.P. C°	Colour	Cond.Λm (Ω^{-1} cm^2 mol^{-1})	μ eff(B.M)
H3	$C_{46}H_{46}CoN_4O_{14}$	66	190-192	Brown	2.7	3.39
H4	$C_{46}H_{46}CuN_4O_{14}$	62	160-162	Plumbic	7.5	1.77
H5	$C_{46}H_{46}Ni\ N_4O_{14}$	58	140-142	light Plumbic	8.5	4.7

Results and Discussion

The protection of hydroxyl group was carried out to give ether, see scheme 1. However, paracetamol was reacted with benzyl chloride in the presence of K_2CO_3 as catalyst in DMF as a solvent as following [10].



Scheme-1: Prepare Compounds H1

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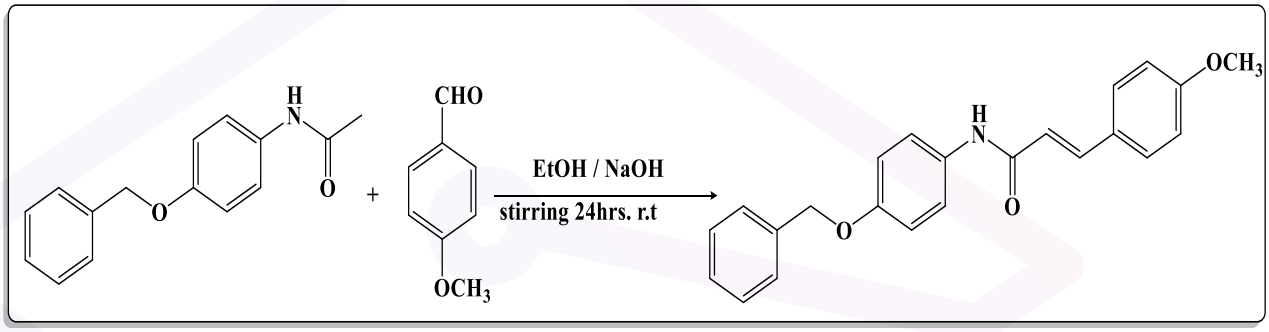
FT-IR spectra confirmed the structure of the synthesized ether. FT-IR spectra showed the disappear of the characteristic absorption frequencies of (OH) at (3676-3584) cm^{-1}, In addition to the stretching absorption of the other groups, C=O at (1658) cm^{-1} and C-O–C in (1242-1010) cm^{-1} [11-12].

α,β-Unsaturated carbonyl was synthesized by the reaction of N-(4-(benzyloxy) phenyl) acetamide **1** and 4-methoxybenzaldehde as in scheme 2.



Scheme-2: Prepare Compound H2

The functional groups of the prepared α,β-unsaturated carbonyl **H2** was determined by FT-IR and confirmed by NMR spectroscopy. The FT-IR spectrum showed disappear of the distinctive (Carbonyl group) absorption band at 1720-1740 cm^{-1}, and the stretching absorption band of the N-H groups appeared at 3278 cm^{-1} , C=O of α,β-unsaturated carbonyl at 1658 cm^{-1} .

^{1}HNMR spectra confirmed the structures of the synthesized compound peak at 9.81 ppm represent N-H, and the range 7.30-7.50 ppm for13 proton represent the protons of aromatic rings, peaks at 6.93 and at 6.96 ppm as doublets represent for 2 protons of CH=CH olefin, and peak at 5.05 ppm for 2 protons belong to OCH_2 and peak at 2.00 ppm of 3 protons as singlet represent the OCH_3 see figure 1.

^{13}CNMR spectrum of compound H2 168.22 ppm represent C=O, δ 137.69 ppm represent β-unsaturated carbonyl, peak at 120.92 ppm represent α-unsaturated carbonyl, peak at 69.97 ppm belong to C-O of methylene, peak at 69.77 ppm represent C-O of methoxy, and other chemical shifts represent aromatic rings, see figure 2.

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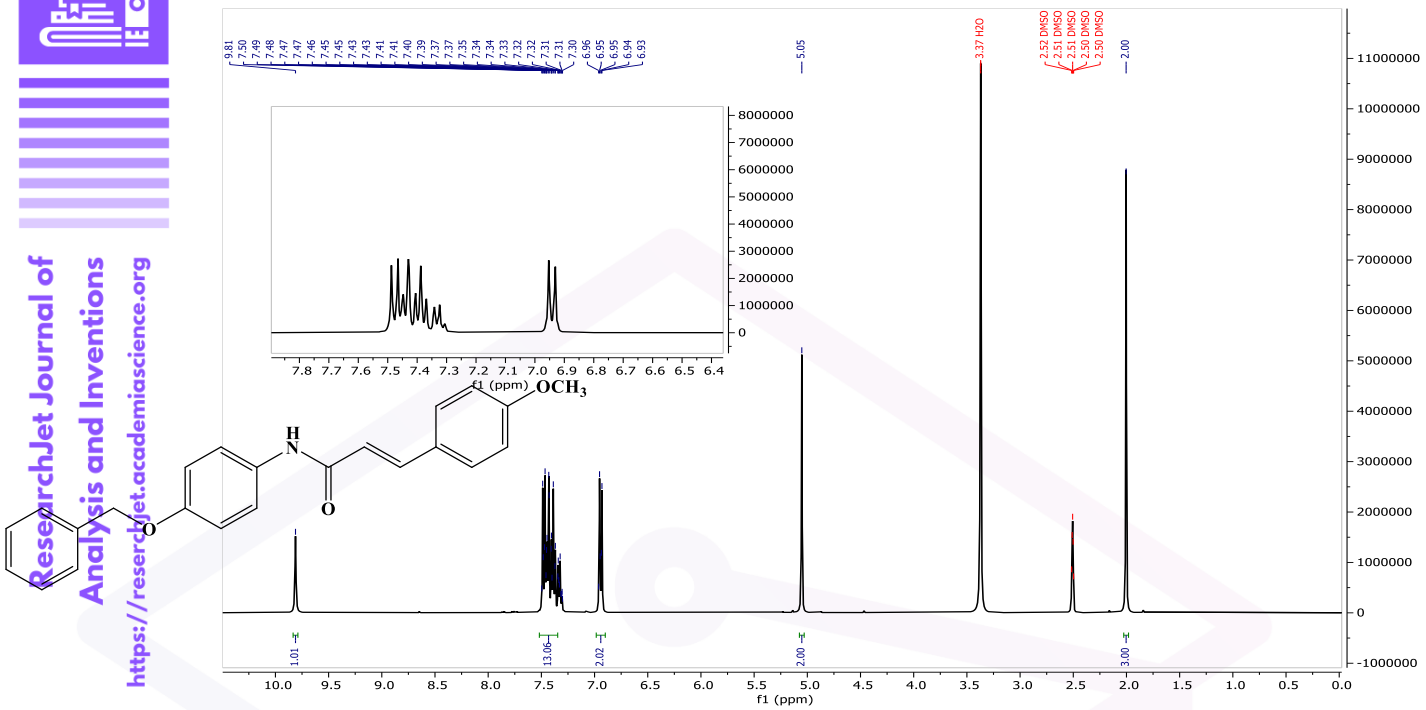

Figure 1: ^{1}H NMR spectrum of compound H2

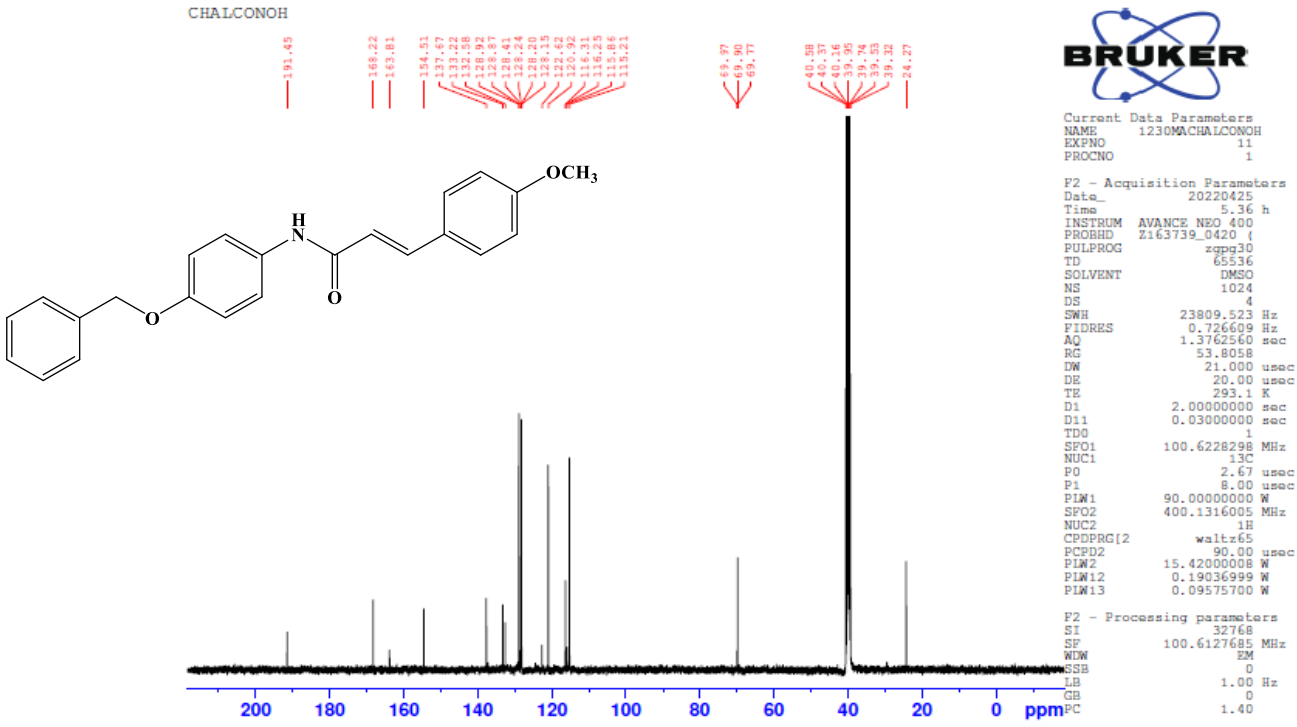

Figure 2: ^{13}C NMR spectrum of compound H2

Complexes H3-H5 were synthesized by reaction of α,β-Unsaturated Carbonyl Compound H2 and deference metals as the following (**Scheme-3).**

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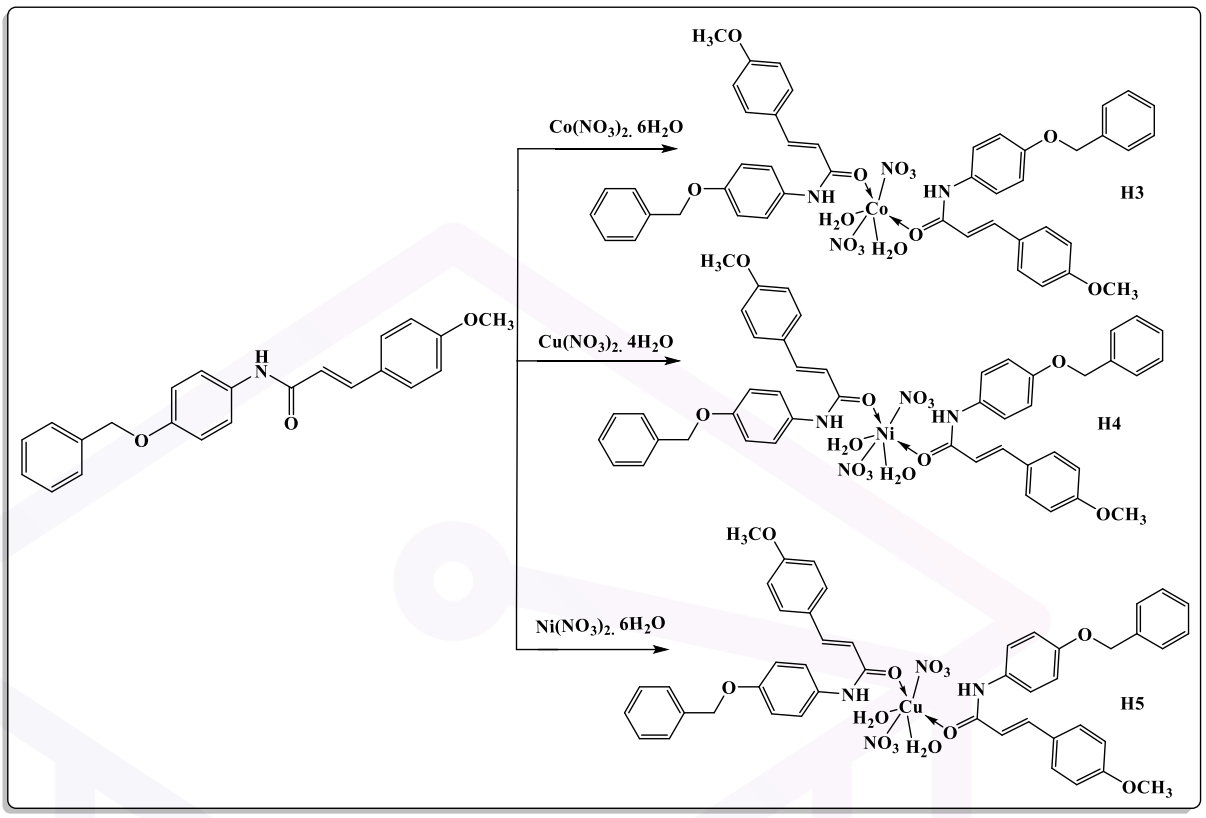

Scheme-3: Preparation of Complexes from α,β-Unsaturated Carbonyl Compounds

The structures of the synthesized compounds were confirmed by FT-IR spectroscopy see table 2 and figure 4. The characteristic absorption bands of the N-H group were seen in the FT-IR spectra at 3278cm^{-1}, as well as those of the C=O and M–O groups at 1658 cm^{-1} and 509 cm-1, respectively.

Table (2): IR characteristic absorption of compound (H_{3-5})

Comp.	ν N-H	νC=O	νC=C	νC-O-C		M-O
				Asym.	Sym.	
H3	3278	1658	1519	1242	1018	509
H4	3278	1658	1519	1234	1018	509
H5	3278	1658	1519	1242	1018	509

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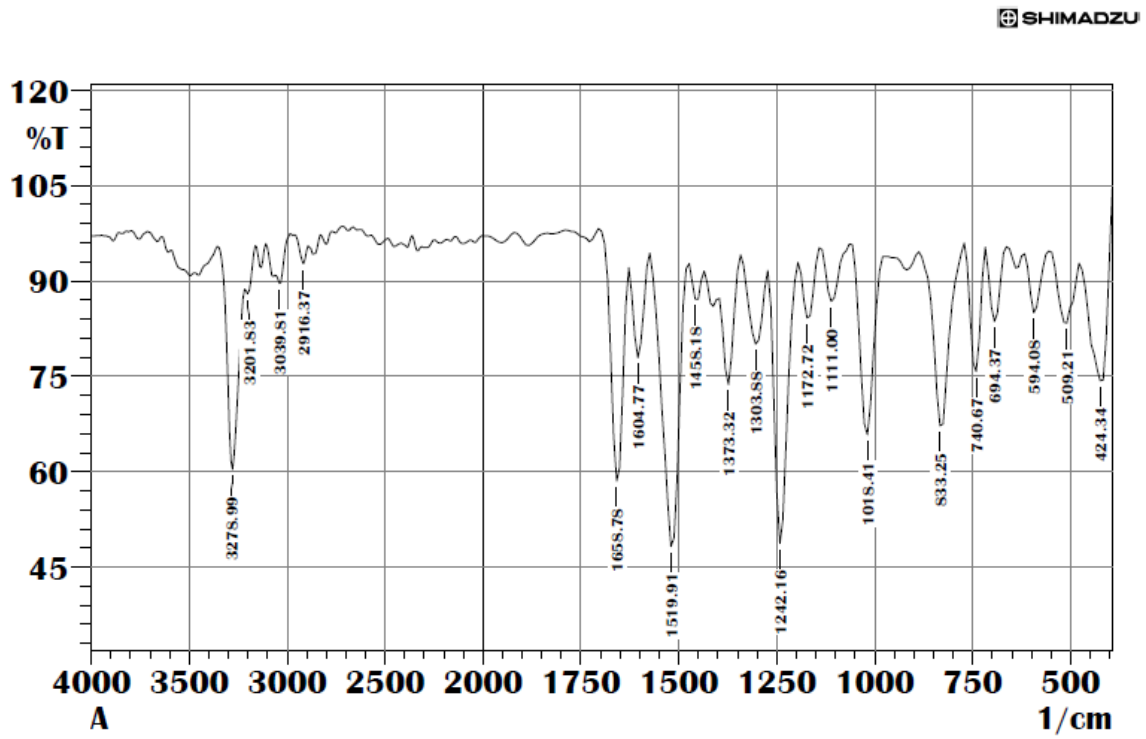

Figure 3: IR spectrum of compound H5

Determination of the Antimicrobial activity of compounds (H_{3-5}) by agar well diffusion method

A number of bacteria colonies were transported by a loop to prepare the suspended bacteria and put in tubes containing brain heart infusion broth to activate the bacteria. The tubes were incubated at 37 °C for (18–24) hours. The suspended bacterium was compared to the standard MacFarland solution (1.5 x 108) cells/ml. After that, the bacteria suspended was spread by Sterile Swab; it was spread on the plates containing Muller Hinton agar and then left the plate for a while to dry. A holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer. 100 µL of the material (concentration 100/75/50 mg/mL) were added to each hole individually by micropipette. After then, incubate the dishes at 37 °C for 24 h. Amoxicillin (25 µg) disk was added in the center of each plate. The diameter of the inhibition zone surrounding each hole was measured to assess the potency of each concentration.

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Biological Activity against Bacteria

The biological effect of the prepared complexes H3 and H4 against two pathogenic bacteria, Staphylococcus aureus and Escherichia coli, were studied. The results show intense activity.

Table (3): Shows the inhibition rates diameters for complexes against (S. aureus and E. coli) Bacteria

Microorganism / Tested materials	*E. coli*				*S. aureus*			
	100	75	50	Am	100	75	50	Am
H3	14mm	R	R	R	11mm	R	R	R
H4	17mm	14mm	12mm	R	15mm	14mm	13mm	R
H5	R	R	R	R	11mm	R	R	R

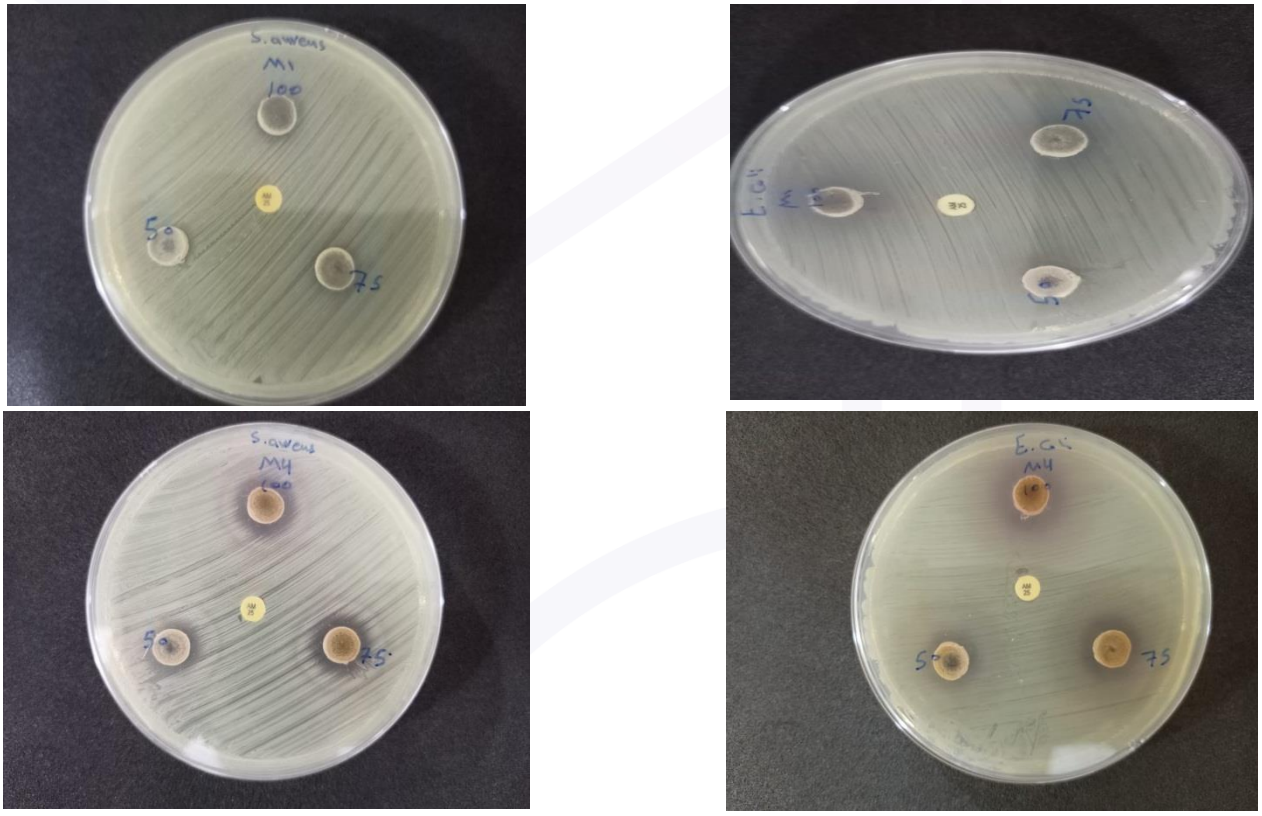

Figure (5)The inhibitory activity of Complexes against (S. aureus and E. coli)

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Conclusion

Depending on the results of the spectroscopic diagnosis, the (H2) α,β-Unsaturated Carbonyl Compound acts as one-toothed of a group (C=O) with the complexes. All results indicate that the proposed shape is of the octahedral complexes, except for the Ligand Complexe (H4), which are octahedrally distorted. These complexes showed significant inhibitory activity against the tested bacteria.

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