Synthesis and Biological Activity of Novel Complexes of α, β-Unsaturated Carbonyl ligands Derived from Paracetamol

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Abstract
Cobalt, Nickel and Copper complexes derived from α, β-Unsaturated carbonyl Ligands that obtained from the reaction of paracetamol with different aldehydes. Hydroxyl group on paracetamol was protected using benzyl chloride and the resulted compound was treated with different aldehydes to produce the required chalcone. Then, nitrate salts of Cobalt, Nickel and copper was reacted with the chalcone to obtain the complexes. FT-IR, 1HNMR, and 13CNMR spectroscopy were used to determine the new compounds.

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

1. Introduction

The same chemical substance has two official names—N-acetyl-para-aminophenol and Nacetyl-para-aminophenol and used under the international term the paracetamol in Europe and acetaminophen in the USA. As is common with important discoveries, this antibiotic was discovered by accident and has a long history. After doctors immediately announced their finding in 1886, acetanilide was initially utilized in medicine under the name antifebrin [1]. Although acetanilide could be produced at a very cheap cost, it soon became clear that it was too toxic to be utilized as an antipyretic, with methemoglobinemia being the most concerning side effect. [2] Actually, acetaminophen/paracetamol gained popularity in 1948, Half a year after Bernard Brodie and Julius Axelrod established that methemoglobinemia was caused by phenylhydroxylamine, a different active metabolite of acetanilide and phenacetin, and that paracetamol was their main active metabolite responsible for their analgesic and antipyretic effect.[3] Similar to NSAIDs, it possesses analgesic and antipyretic characteristics, but unlike them, it lacks anti-inflammatory action. [4] In pharmacological textbooks, paracetamol has not been classified as an NSAID since it lacks an anti-inflammatory component. [5] Only probable allergic skin responses have been reported as major side effects, although following higher dosages or longer periods of drug use, certain adverse effects, particularly in the liver, may develop. [6] This study aims to synthesis Chalcone compounds and coordination with different metals and investigate this compound.

2. Material and Methods

Paracetamol, Benzyl chloride, ethanol, methanol, DMF, Sodium chloride, potassium bicarbonate, 4-bromobenzaldehyde, Co $(NO_3)_2.6H_2O$, Cu $(NO_3)_2.4H_2O$, Ni $(NO_3)_2.6H_2O$, Staphylococcus aureus, Blood agar, Mannitol salt agar. Escherichia coli isolates, MacConky agar, Eosin Methylene blue. The uncorrected melting points were recorded in open capillary tubes. FT-IR data were acquired with a Shimadzu8400S FT-IR in the frequency range of 4000–400 cm^{-1}. And using DMSO as the solvent and TMS as the internal standard, 1HNMR and 13C NMR spectra were recorded using a (Bruker 500) MHz equipment.

Preparation 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 contained 25 mL of DMf. 15 minutes were stirring the mixture. Following the addition of benzoyl chloride, a same equimolar, the mixture refluxed for 4 hours. Then, in an ice bath, the reaction mixture was cooled, and filtering and recrystallizing a product from ethanol, compound H1 was produced. The chemical formula $(C_{15}H_{15}NO_2)$, white colour, 82% yield, 140-142.

synthesis of N-(4-(benzyloxy) phenyl)-3-(4-bromophenyl) acrylamide H2

N-(4-(Benzyloxy) phenyl) acetamide H1 (1.2 mmol) and 4-Bromobenzaldehde (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 was added dropwise to the mixture, the reaction mixture was stirred at room temperature overnight, acidified by dilute hydrochloric acid solution. The yield was filtered, recrystallized from methanol to give compound H2. The Chemical Formula $(C_{22}H_{18}BrNO_2)$, 78% yield, melting point 120-122 and color light yellow.

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General procedure for the synthesis of Complexes

The complexes 3,4 and 5 was prepared by dissolving (0.1g, 0.24 mmol) of Ligand H2 in (10 mL) of ethanol. Then (0.02 g, 0.12 mmol) of the salt in ethanol 5 mL was added gradually, the reaction was left overnight under stirrer at room temperature.

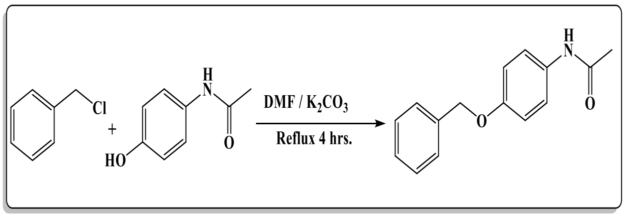
Table (1) shows the Molecular Formula and some Physical Properties of obtained Complexes.

Table (1): The physical properties of compounds H3, H4 and H5

Comp	Formula	Yield%	M.P. O C	Color	Cond.Λm (Ω-1 cm2 mol-1)	μ eff (B.M)
H3	$C_{44}H_{40}Br_2CoN_4O_{12}$	66	190-192	Brown	2.7	3.39
H4	$C_{44}H_{40}Br_2NiN_4O_{12}$	58	140-142	Plumbic light	8.5	4.7
H5	$C_{44}H_{40}Br_2CuN_4O_{12}$	62	160-162	Plumbic	7.5	1.77

3. Results and Discussion

The protection of hydroxyl group was carried out to produce ether see scheme 1, 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 Preparation of compound H1

The functional groups of the prepared compound H1 were determined by FT-IR spectroscopy. FT-IR spectrum showed disappeared of the characteristic absorption frequencies of (hydeoxyl group) at (3676-3584) cm-1, the stretching absorption bands of amine group at 3278 cm-1 was appeared instead, in addition stretching absorption for the other groups, like C=O was at 1658 cm-1 and C-O–C in 1242-1010 cm-1 [11-13], see figure 1.

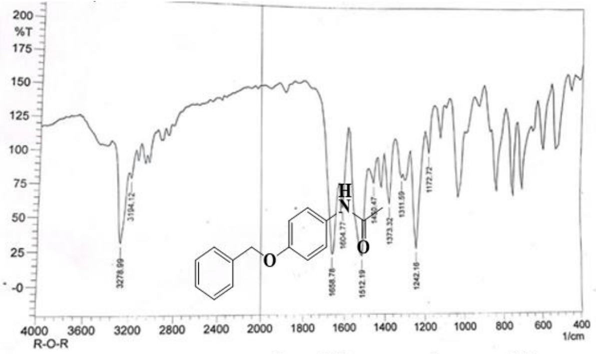
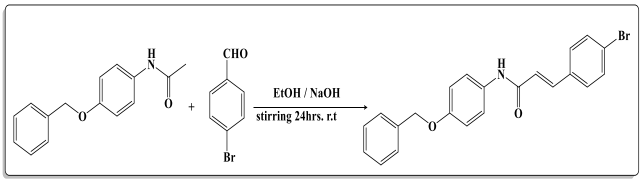


Figure 1: IR spectrum of compound H1

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



Scheme 2 Preparation of compound H2

The functional groups of the prepared α, β-unsaturated carbonyl was determined FT-IR and confirmed by NMR spectroscopy. The FT-IR spectrum showed disappear of the the bromo aldehyde's 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 and C-Br at 694 cm-1.

1H-NMR spectrum confirms the structure of synthesized compound H2, peak at 9.81 ppm (1H s) represent for N-H, 6.93-7.50 ppm (15H m) represent the protons of Olefin and aromatic rings and peak at 5.05 ppm (2H s) represent to OCH2 figure 2.

13CNMR spectrum of compound H2 168.2 ppm represent for C=O, δ 137.67 ppm represent β-unsaturated carbonyl, δ 120.93 ppm represent α-unsaturated carbonyl, δ 69.78 ppm represent C-O methoxy and other chemical shift represent aromatic rings. figure 3.

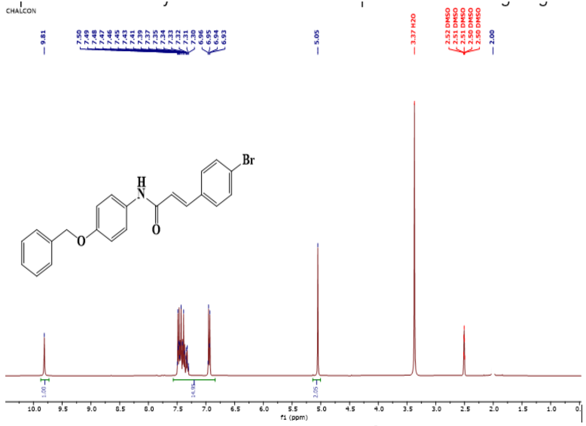


Figure 2: ^1H NMR spectrum of compound H2

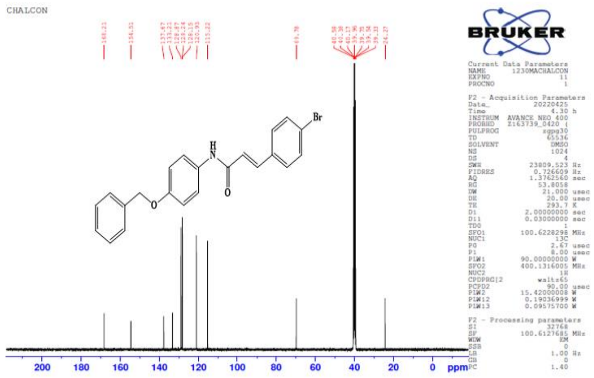
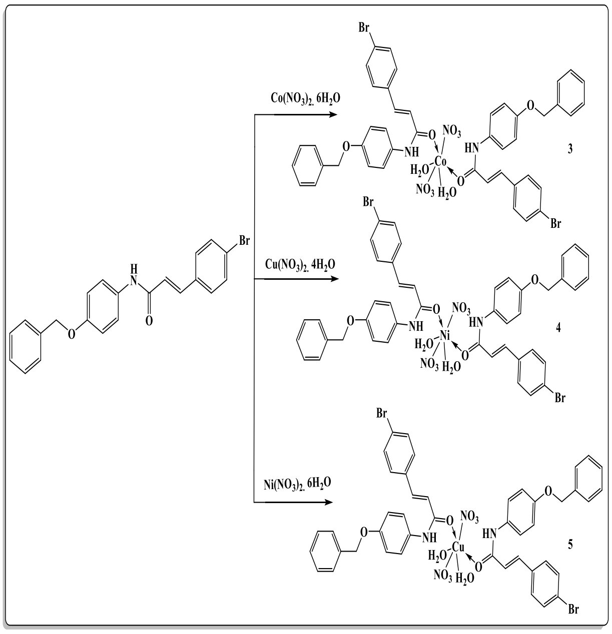


Figure 3: ^{13}C NMR spectrum of compound H2

Complexes H3, H4 and H5 were synthesized by the reaction of α,β-unsaturated carbonyl compound 2 and deference metals salt see Scheme 3.



*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 3278–3286 cm-1, as well as those of the C=O and M–O groups at 1651–1652 cm-1 and 504-511 cm-1, respectively.

Table (2): IR characteristic absorption of compound (H3, H4 and H5)

Comp.	v N-H	vC=O	vC=C	vC-O-C		vC-Br	M-O
				Asym.	Sym.		
H3	3278	1652	1512	1242	1010	694	504
H4	3286	1651	1512	1242	1010	694	509
H5	3278	1651	1519	1243	1010	696	511

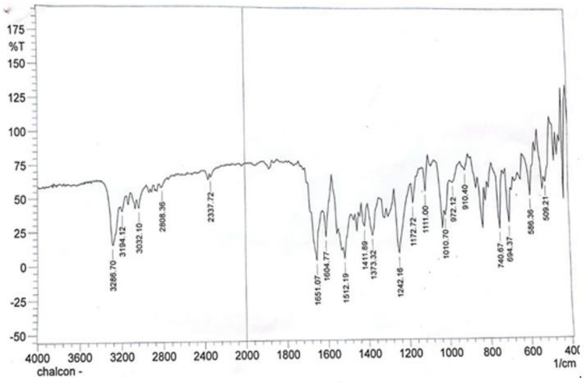


Figure 4: IR spectrum of compound H4

Determination the Antimicrobial activity of compounds (H3, H4 and H5) by agar well diffusion method

Several bacteria colonies were transported by loop to prepare the suspended bacteria and put it in tubes contain 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. 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.

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 strong activity.

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

Microorganism	E. coli			S. aureus		
Tested materials	100	75	50	100	75	50
H3	16mm	13mm	R	16mm	13mm	12mm
H4	R	R	R	R	R	R
AM	R	R	R	R	R	R
DMSO	0	0	0	0	0	0

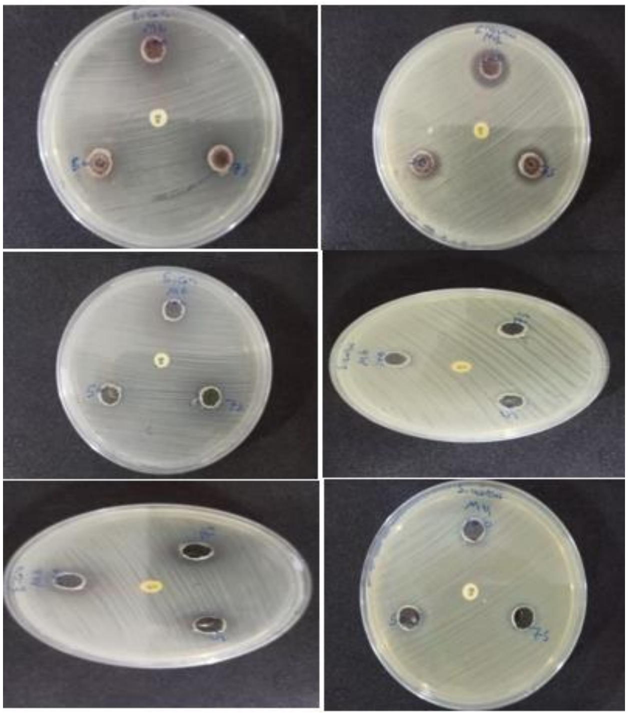


Figure (5) The inhibitory activity of Complexes against (S. aureus, and E. coli)

4. Conclusion

Depending on the results of the spectroscopic diagnosis, the H2 α, β-unsaturated carbonyl compound act as one-toothed of a group (C=O), with the complexes. All results indicates that the proposed shape is octahedral complexes, except for the Ligand complex H4, which is octahedral distorted. These complexes showed significant inhibitory activity against the tested bacteria.

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