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Synthesis, Docking, and Biological Activity of Chalcone and Metal Complexes

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Abstract: This study investigates the synthesis and characterization of chalcone derivatives and their metal complexes, focusing on their potential pharmacological activities and antibacterial effects. Specifically, the research explores the preparation of 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (R5) chalcone and its complexes with Ni(II), Co(II), and Cd(II). Various physical and spectral techniques were employed for characterization, including FT-IR, UV, and NMR spectroscopy. The antibacterial activity of the synthesized compounds was evaluated against antibiotic-resistant bacterial strains, revealing notable inhibitory effects. Molecular docking studies were conducted to assess the compounds' interactions with the active sites of *Pseudomonas aeruginosa* protein. Results suggest that the prepared compounds and complexes exhibit promising antibacterial properties and have the potential for further medicinal chemistry applications. This research fills a knowledge gap regarding the synthesis, characterization, and biological activities of chalcone derivatives and their metal complexes, providing insights for future drug discovery efforts in combating bacterial infections.

Keywords: Chalcones, Complexes, hydroxyacetophenone , Molecular docking, Bioactivity, Complexes Co(II), (Ni(II), And Cd(II).

1. Introduction

Chalcones are defined as organic aromatic ketones of important biological compounds such as flavonoids, the general formula has two aromatic rings linked through the α - β -carbonyl unsaturated system, and is also known as styrene phenylketone [1,2]. It is one of the most prominent α - β -carbonyl compounds unsaturated, and it is one of the most prevalent organic compounds because it has two important functional groups, the carbon-carbon double bond (C=C) and the oxygen-carbon double bond (C=O) (carbonyl group) [3]. These compounds are among the most prominent sources for the formation of new organic compounds derived from them, such as the preparation of several heterocyclic compounds [4] and chalcone complexes[5] It is used in coordination chemistry in the preparation of chalcone complexes as they occupy a large area in the preparation of new compounds[6], and chalcone are yellow crystalline compounds that do not dissolve in water but dissolve in organic solvents[7]. The reaction in the basal medium is one of the most important methods for the preparation of chalcones [8] where

aromatic aldehydes interact with aromatic ketones in the presence of a dilute strong base (hydroxyl ion or koccide) and the result is ketone containing unsaturated alpha-beta

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sites. The synthesis of chalcone and its derivatives contributed to the development of new bioactive substances and derivatives of great importance for medicinal chemistry and have received great attention due to their diverse pharmacological activities, including the manufacture of drugs[9] including anticancers[10].

chalcone complexes: I have attended several complexes in which chalcone ligand is used with multiple metal abundances of transition and non-transition elements. These complexes have been used in a wide range of fields in medicine[11], industry, agriculture, and pollution.[12] chalcones complexes have an important role in the development of coordination chemistry because chalcones can form complexes with antioxidant and antimicrobial effects [13], as they have many biological activities, including antibacterial and anti-cancer effectiveness[14].

2. Materials and Methods

2.1 MaterialsXEmployed: AllXchemicals utilizedXwere procured fromXFluka, Aldrich Companies

2.2 Used Instruments

Infrared spectra for the produced compounds were recorded using an FTIR-8400S instrument from SHIMADZU at the Chemistry Department of the University of Tikrit's College of Sciences. KBr pellets were used to record the spectra, which fell between 400 and 4000 cm^{-1} (IH, ^{13}C -NMR) at the University of Basra in Iraq, nuclear magnetic resonance spectra were recorded using a Bruker Spectrometer (500 MHz), in d_6 -DMSO solvent. The melting points of synthetic substances were ascertained using an Automatic Melting Point device (model SMP10) from the British business STUART Magnetic susceptibility measurements of specific solid metal complexes were performed at laboratory temperature using a Sherwood Scientific device. These measurements were made using the Faraday method. The electron spectra of the prepared compounds were measured using a Jasco UV-vis Spectrometer (V-530) and using a solvent (DMSO) at a concentration of ($M 10^{-3}$) in the Central Laboratory - University of Tikrit.

2.3 Preparation of Chalcone (R5) in the following way[15]:-

The compound Chalcone (R5) was prepared by dissolving equal moles (0.005mole) 4'-hydroxyacetophenone in (10ml) of ethanol and added (5ml) of (10% NaOH) solution. alcohol with stirring in a conical flask, and in an ice bath, leave the mixture to stir for (15) minutes until the ketone has reacted with the base and then add 4-naitro benzaldyad dissolved in (10 ml) of ethanol, and the same number of moles (0.005mole) to the reaction flask, close the flask tightly and fix the temperature at (42-45 $^{\circ}\text{C}$) using a mercury thermometer, leave the reaction on stirring for 4-5 hr) and leave in the refrigerator for 24hr Then it was added to the ice crushed and then the medium was equalized using dilute HCl, the precipitate was collected, filtered and dried, the product was recrystallized, melting point measured, the percentage was calculated, and color was set, where the reaction was tracked by TLC and Table (2) physical properties of R5 as shown in scheme (1).

2.4 Preparation of Chalcone complexes.

Added to the Chalcone solution (R2) (0.00056mol) dissolved in absolute ethanol (10mL) Metallic brine ($\text{MCl} \cdot n\text{H}_2\text{O}$) (0.00056 mol) dissolved in absolute ethanol (10mL), Stir the mixture for (3 hours) at room temperature, then ascend for two hours, evaporate the

solvent, and then recrystallize it into absolute ethanol, as in diagram (2) and table (1) shows some of the physical properties of the prepared complexes.

Table 1. Some physical properties, connectivity and magnetic measurements of complexes (R5,R39,R40,R41

No.	Complexes	Color	M.P C ^o	Yield %	Cond. $\Delta m (\Omega^{-1} \cdot cm^2 \cdot mol^{-1})$	μ_{eff} (BM)	C.H.N. Calculated\ (Found)			Stru Cture
R5	C ₁₅ H ₁₁ NO ₄	Yellow	220- 221	58	-	-	C	H	N	-
R39	[Co (R5) (H ₂ O) ₂ Cl ₂]	Light yellow	278- 279	77	18	4.01	51.16 50.97	3.72 3.69	3.98 4.01	Oh
R40	[Cd(R5)Cl ₂]	Yellow	256- 257	81	8.6	0	49.92 49.78	3.07 2.98	3.88 3.80	S.p
R41	[Ni (R5) (H ₂ O) ₂ Cl ₂]	Light Green	271- 272	76	5.7	2.97	51.17	3.72	3.98	Oh

2.5 MeasurementXof BiologicalXActivity

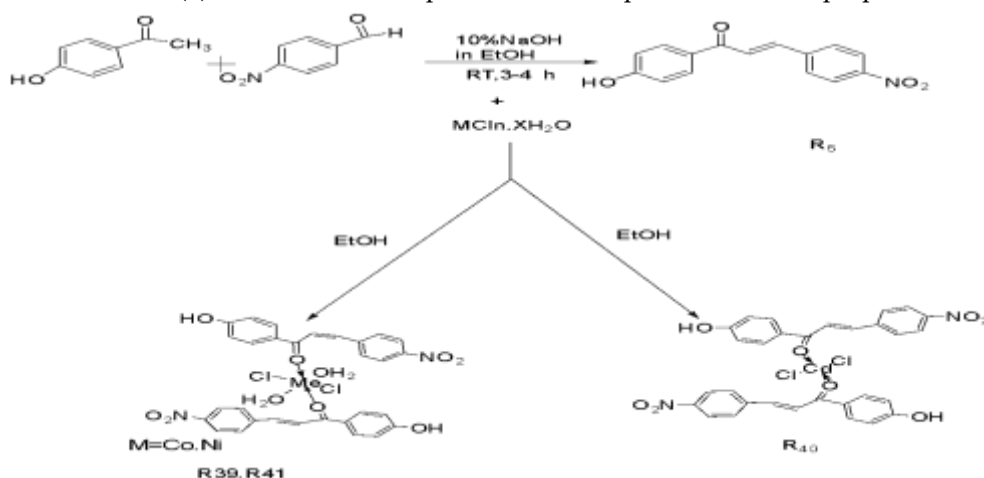
The Agar-well diffusion method was used to assess biological activity. This necessitated inoculating the bacterial cultures throughout the entire growing medium with a cotton swab. Subsequently, sterile 6 mm diameter piercing tools were used to create wells in the agar medium [16, 17]. Subsequently, 100 microliters of every medication were introduced into these wells situated on distinct culture plates, every one housing a distinct strain of bacteria[18]. With consideration for the specific bacterial strains and concentrations under investigation, this process was carried out once more for every solution that was produced. The antibacterial activity was assessed against three distinct strains of bacteria: *Pseudomonas aeruginosa*, gram-negative *Escherichia coli*, and gram-positive *Staphylococcus*. Both bacterial species were first re-cultivated and then incubated for 18-24 hours at 37°C in a controlled laboratory setting to guarantee the test's efficacy[19,20].

2.6 StudyXof MolecularXDocking of someXprepared compounds[21].

The Molecular Docking of some prepared compounds (R5, R39, R40, R41) was studied to discover the possibility of these compounds to Molecular Docking with the active sites of the target protein representing a single line (*Pseudomonas aeruginosa* (PDB (ID: 6R3X), using MOE software. (2014), where the energy reduction process for the vehicles under study was completed to obtain the most stable vacuum form (the least disabled energy), then the composition of *Pseudomonas aeruginosa* bacteria was downloaded from the protein data bank website, and a personal PC calculator was used, which required calculations in all their stages at a somewhat appropriate time.

4. Results and Discussion

Scheme (2) below shows compounds and complexes that were prepared in this study.



Scheme 1. Route of prepared compounds R5 and complexes (R39,R40,R41)

4.1 Characterization of Compounds R2,R30,R31,R32 by FT-IR Spectroscopy[22]

During the study of the FT-IR spectrum of chalcone compounds (R5), a difference was observed between the spectrum of the resulting compounds and the primary materials. The (C-H) aldehyde group band, which has a range between (2780-2700 cm⁻¹), disappeared. In its place, a band belonging to the (C=C) olefin bond appeared at the frequency. (1598 cm⁻¹). Additionally, there was a decrease in the frequency of the (C=O) carbonyl group, which appeared between the frequency of (1650 cm⁻¹). The infrared spectrum showed clear bands of the (ArC-H) group at the frequency of (3014 cm⁻¹), and bands appeared at the frequency (1510 cm⁻¹) dating back to the stretching of the double bond (C=C) of the aromatic ring. Table (3) displays the absorption values of infrared frequencies for chalcone (R5), while Figure (1) shows the spectrum.

The results of the study on the infrared spectrum of chocolate complexes (R39, R40, R41) are remarkable. The carbonyl group (C=O) in the chalcone showed a significant shift in its band, which was observed within the range of (1645-1666 cm⁻¹). Additionally, a new absorption band appeared within the range of (3150-3417 cm⁻¹), indicating the stretch of the band (M-OH₂). The appearance of another new absorption band within the range of (447-509 cm⁻¹), indicating the stretch of the sphincter (νM-O), is equally noteworthy. These findings suggest that the chocolate complexes have a unique composition that deserves further exploration. The original ranges of the rest of the ligand's bands have been retained, as shown in Table 3 and Figure(2).

Table 3. Infrared absorption results (cm⁻¹) for chalcone and its complexes (R2, R30, R31, R32)

No.	Complexes	IR (KBr) cm ⁻¹					Others
		ν (Ar-H)	ν C=O	ν (C=C) ν (C-C)	(M-O)	(M-O OH ₂)	
R5	C ₁₅ H ₁₁ NO ₄	3014	1650	1598 1507	-	-	3326 ν (OH) asy 1434,sym 1340 (NO ₂)
R39	[Co(R5)(H ₂ O) ₂ Cl ₂]	3083	1645	1519 1465	455	1417	3221 ν (OH) 1346 ν (NO ₂)
R40	[Cd(R5)Cl ₂]	3001	1644	1609 1519	442	-	3453 ν (OH) ,1346 ν (NO ₂)
R41	[Ni(R5) (H ₂ O) ₂ Cl ₂]	3076	1641	1519 1466	460	3433	3220 ν (OH) 1345 ν (NO ₂)

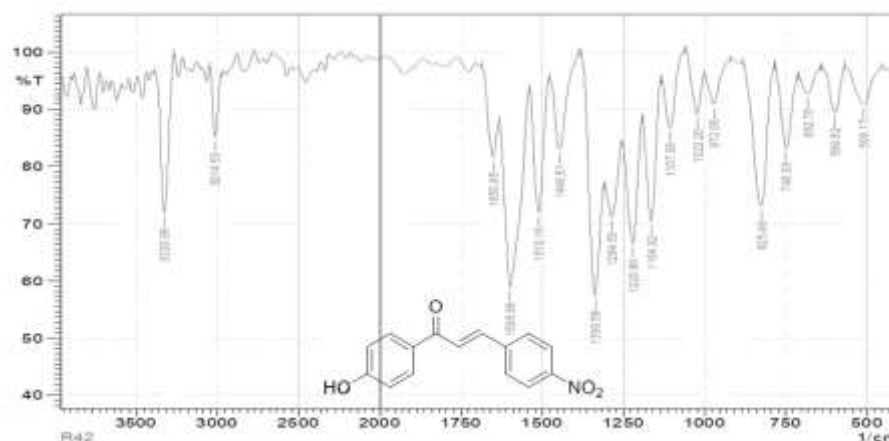


Figure 1. FTIR spectrum of the tested compounds (R5)

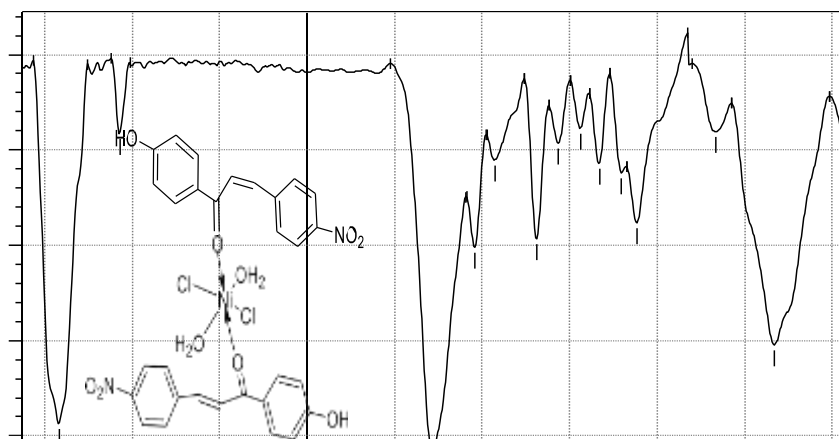


Figure 2. FTIR spectrum of the tested compounds (R30)

4.2 Characterization of Compound by ^1H , ^{13}C -NMR Spectroscopy

The ^1H -NMR spectrum of compound R5 showed various signals. There was a signal at $\delta = 2.50$ ppm, which belonged to DMSO protons, and another one at $\delta = 3.40$ ppm, which belonged to diluted water protons. There was a double signal in the range of $\delta = 7.6$ ppm, which referred to the proton of the unsaturated alpha-beta group ($\text{HC}=\text{CH}$) and a signal of $\delta = 7.90$ ppm, which referred to the second proton in the unsaturated alpha-beta group. Additionally, there were signals in the range of $\delta = 8.17$ - 6.84 ppm, which referred to the protons of the furan ring. Lastly, there was a signal in the range of $\delta = 8.39$ - 8.12 ppm, which referred to the protons of the benzene ring. When studying the ^{13}C -NMR spectrum of the prepared compound (R5), it was observed that a signal appeared at frequency ($\delta = 189$ ppm) belongs to the carbonyl carbon atom, and the signal at ($\delta = 128$ - 120 ppm) belongs to the carbon atoms ($\text{CH} = \text{CH}$), respectively, and the signals (101) ($\delta = 154$ - 120 ppm) belong to the carbon atoms of the furan ring and the benzene ring, and a signal appears at The chemical displacement ($\delta = 40$ - 38 ppm) is attributed to the carbon of the solvent (d6-DMSO), as in the following figures (3)(4).

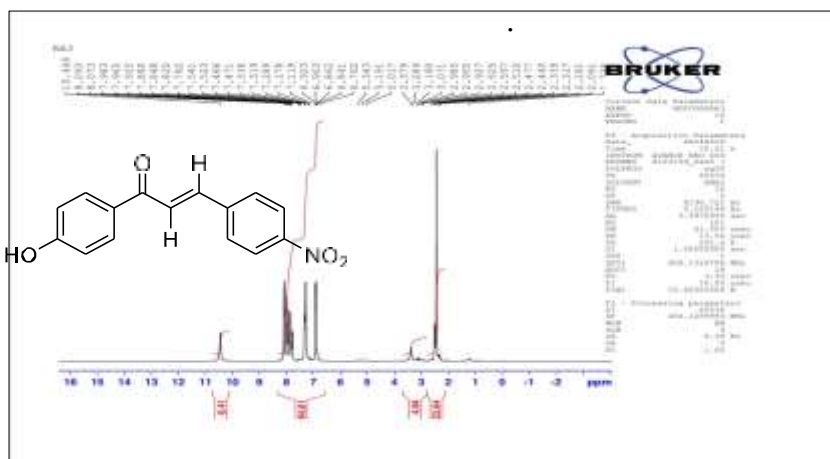


Figure 3. ^1H -NMR spectrum of the compound (R5)

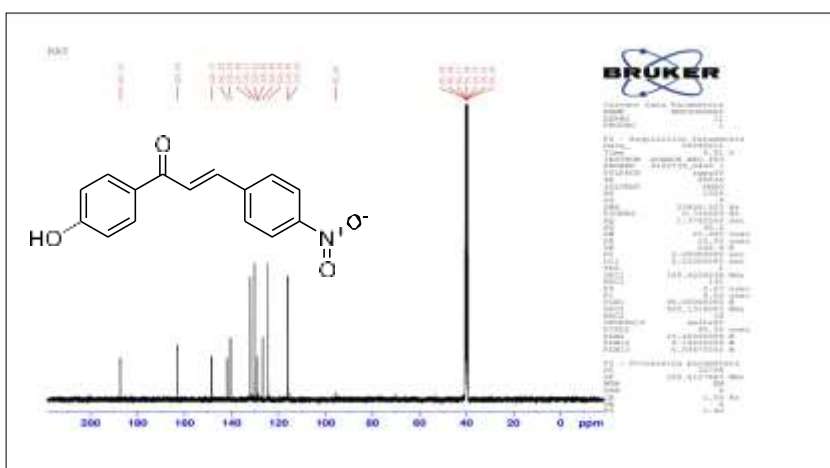


Figure 4. ^{13}C -NMR spectrum of compound (R5)

4.4 Measurement of electronic spectra

In measured the electronic spectra of the chalcone and the prepared complexes using a DMSO solvent with a molar concentration of (10^{-3} M). We used two cells with a diameter of (cm-1). The prepared chalcones (R2) showed main bands due to $n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$ transitions. In the spectra of the prepared complexes(R30,R31,R32) that we measured, we observed these bands shifting towards different frequencies. This shift indicates the occurrence of coordination between the chalcone and the metal in the prepared complexes. We also discussed the charge transfers of the complexes (C.T.). We calculated the wavenumber, which is the reciprocal of the wavelength in units of cm⁻¹. You can find the results of our study in Table (4) and Figures (5) and (6).

Table 4. Electronic transitions (cm⁻¹, nm) for some prepared compounds and complexes

No	Compound	wave length nm	Wave number cm ⁻¹	Transfer type
R5	C ₁₅ H ₁₁ NO ₄	363	27548.2	$n \rightarrow \pi^*$
		341	29325.5	$\pi \rightarrow \pi^*$
R39	[Co (R ₅) (H ₂ O) ₂ Cl ₂]	364	27472.5	$n \rightarrow \pi^*$
		341	29325.5	$\pi \rightarrow \pi^*$
		391	25575.4	C.T.
R41	[Ni (R ₅) (H ₂ O) ₂ Cl ₂]	350	28571.4	$n \rightarrow \pi^*$
R32	[Cd(R ₅)Cl ₂]	399	50251.2	$n \rightarrow \pi^*$
		348	28735.6	$\pi \rightarrow \pi^*$
		414	24154.5	C.T.



Figure 5. UV-visible spectrum of ligand (R5)

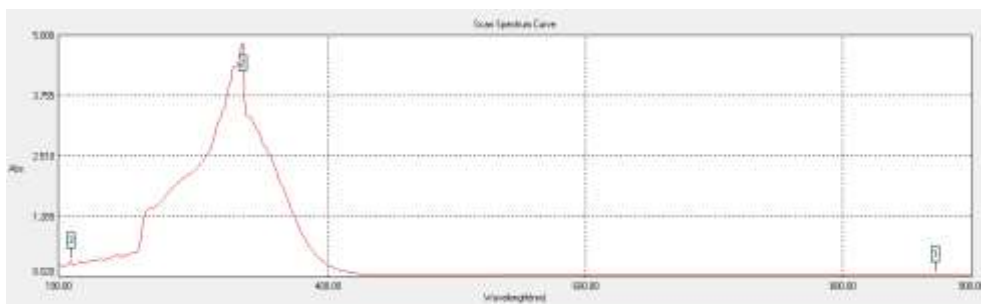


Figure 6. UV-visible spectrum of the complex $[\text{Ni} (\text{R5}) (\text{H}_2\text{O})_2\text{Cl}_2]$

4.5 Micro-analytical measurement of elements (C.H.N.)

The prepared complexes was carried out to ensure the correctness and accuracy of their composition, as the percentages obtained from the measurement were very close to the calculated percentage, and this confirms the correctness of their compositions, as shown in Table (1)

Molar conductivity: The results of the molar electrical conductivity measurements are displayed in Table (1). The measurements revealed that all of the prepared complexes gave values ranging between (5-18 $\text{ohm}^{-1}\cdot\text{cm}^2\cdot\text{mol}^{-1}$), which represents a non-electrolyte solution.

4.6 Magnetic Measurements of Prepared Complexes (R39-R40-R41)

At 25 degrees Celsius, the magnetic susceptibility of the cobalt, nickel, and cadmium complexes that were prepared was calculated. For the atoms making up the prepared complexes, Pascal's constants were used to adjust the diamagnetism (D) of the atoms in the organic molecules, metallic ions, and inorganic radicals. The magnetic moment (μ_{eff}) values were then computed. Magnetic Moment of EffectivenessAccording to magnetic measurements of the prepared cobalt (II) complexes (R39), the cobalt (II) ion is hexagonally coordinated and has a high octahedral shape. The values obtained are roughly (4.01) B.M. Values were obtained from magnetic measurements of the prepared nickel (II) complexes (R41). It is near (2.97) B.M., indicating that the nickel (II) ion has a high octahedral shape and is hexagonal in shape, and the cadmium (R40) complexes showed magnetic properties, as in the following table(1)

4.7 Evaluation of the antibacterial effectiveness of the chalcone compound and the preparation complexes:

Chalcones and their complexes are characterized by varying biological activity against bacteria. The biological effectiveness of some of the compounds and complexes prepared (R39, R40, and R5) was evaluated in this thesis on three types of bacteria, Streptococcus mutans, which are gram-positive, Pseudomonas aeruginosa, and Escherichia coil,[23] which are gram-negative. These bacteria were chosen due to their medical importance, as they cause many diseases. The results indicate that the prepared compounds and complexes can inhibit the growth of the bacteria used, both positive and negative, in varying proportions[24]. The antibiotic Amoxicillin was used as a control sample, and this antibiotic has a large inhibitory diameter, which gives high selectivity when studying the sensitivity of bacteria to the prepared compounds. The prepared compounds and complexes showed good inhibitory activity and the relationship of concentration with inhibition was a direct relationship. The higher concentration[25,26], the greater the inhibition. and the solvent DMSO is ineffective against bacteria[27], as in Table (4) and figures (7).

Table 4. Biological effectiveness of some prepared compounds and complexes and control parameters (in mm).

Comp. No.	<i>Streptococcus mutans</i>			<i>Pseudomonas aeruginosa</i>			<i>Escherichia coli</i>		
Conc. mg/ml	100	50	25	100	50	25	100	50	25
R ₅	13	11	9	14	12	10	14	10	9
R ₃₉	15	13	9	14	12	8	15	11	8
R ₄₀	14	11	8	13	11	8	14	11	7
Amoxicillin	24	20	11	23	20	10	25	18	12
Blank disk	0			0			0		



Figure 7. Inhibitory activity of compound (R39) against *Streptococcus mutans*, *Pseudomonas aeruginosa*, and *Escherichia coli* bacteria.

4.8 Results of the molecular docking study of some prepared compounds

The *Pseudomonas aeruginosa* bacteria was used as the model organism for the molecular docking study of several of the prepared compounds (R₅, R₃₉, and R₄₀). The MOE program (2014) was utilized to compute the binding energies of the compounds. The quantity and kinds of bonds that bind were discovered through an analysis of the molecular docking of the prepared organic derivatives. Through it, connections with Van der Waals forces, Pi-type bonds, and multiple hydrogen bonds were formed, preparing these derivatives with the amino acid residues found in the active site. It was also established how long the bonds (H.B.) were that connected the compound's linked amino acid residues. as shown in Table (5).

Table 5. Values of binding energy, lengths of hydrogen bonds, and the effect of amino acids between the prepared compounds and the receptor (6R3X) one line of *Pseudomonas aeruginosa* bacteria.

Compound	Docking Score	RMDS	Hydrogen bond			Other amino acids affected by Van der Waals forces and others	Number No acids Amino Affected
			B.H	Amino acids Associated	The length of the B.H		
R ₅	-6.632	4.17	3	Thr.168 Arg.273	1.96(A) 2.08(A)	Arg.127, Phe.167 Leu.276, Asp.169 Val.126,170,125,	9
R ₃₉	-7.025	1.64	3	Asp.428 Arg.200	2.35(A) 2.01(A)	Arg.199,Pro.49 ,Gly.201,Asp.198 ,Lys.87,Glu.121	8
R ₄₀	-8.566	4.87	3	Gln.458 Asp.428	2.45(A) 2.30(A)	Lys(255,432), Ser.455 Pro(451,516) Asp.51 Ala(426,513),Thr.551	11

The study showed that the compound (R5) interacts with amino acid residues present in the active site by forming two types of bonds, which are two hydrogen bonds. The first connects the amino acid residue, Arg.273 present in the active site with the electronic pair of the oxygen atom of the carbonyl group in the chalcone, and the second connects the amino acid residue Thr.168 located in the active site with the electron pair of the oxygen atom of the hydroxy group, and A Pi-Alkyl bond connects the amino acid residue Arg.127, which is located in active site, with the electronic pairs of the orumate ring. several Vanderwaals-type bonds with the following amino acid residues Phe167,Leu276,Asp169,Val126,Val125, As in Table (5) above. And Figure (8)

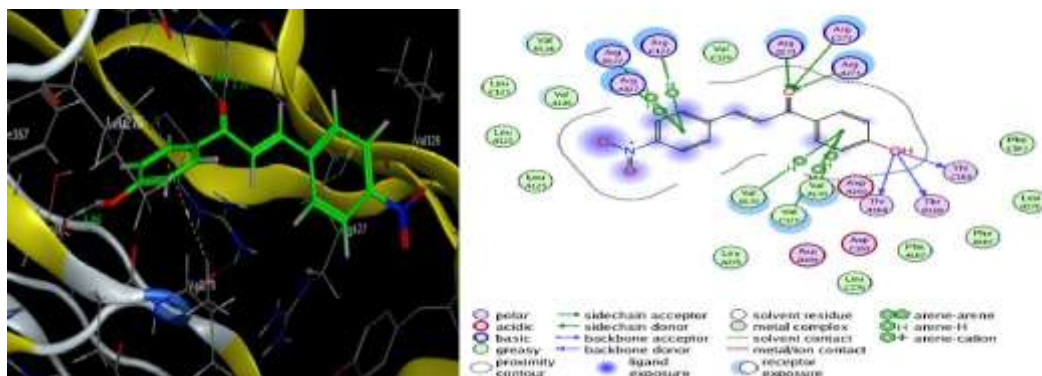


Figure 8. Interactions between the compound R5 and the receptor 6R3X) One line of *Pseudomonas aeruginosa* bacteria in 3D and 2D dimensions.

The study showed that the complex (R30) interacts with the amino acid residues that are present in the active site by forming two types of bonds, which are two hydrogen bonds linking the amino acid residues Aps.428 and Aps.200 present in the active site with the electronic pair of the oxygen atoms of attached to the metal. A Pi-Alkyl bond connects the amino acid residue Las.255, which is located in active site, with the electronic pairs of the orumaty ring. And several VanderWals type bonds with amino acid residues, as in Table (5) Figure (9).

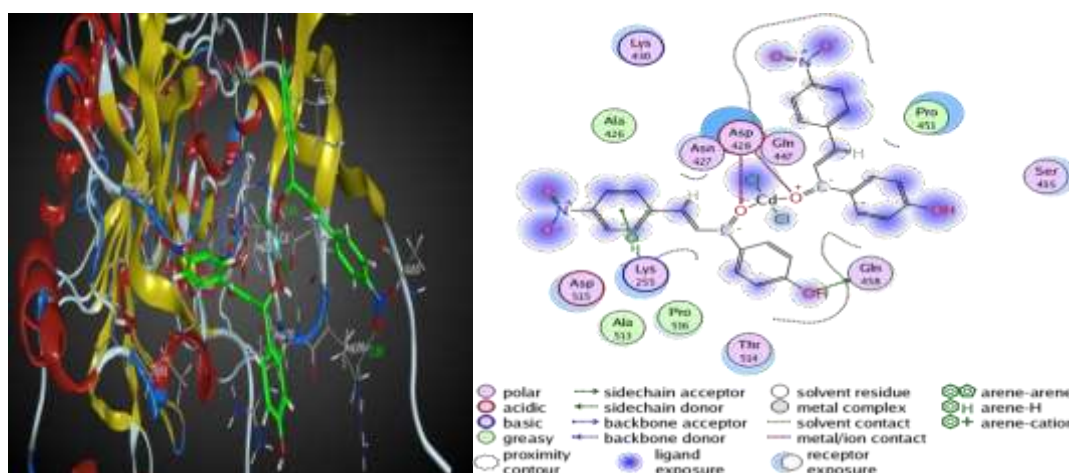


Figure 9. Interactions between the compound R40 and the receptor 6R3X) one line of *Pseudomonas aeruginosa* bacteria in 3D and 2D dimensions.

4. Conclusion

Compound (R5) easily forms complexes, particularly when combined with cadmium, nickel, and cobalt. High stability and strength were demonstrated by the prepared compounds and complexes, which kept their structure, color, and melting point under a range of laboratory temperatures from winter to summer. The majority of the prepared compounds and complexes have antibacterial activity and the capacity to stop bacterial growth, according to the biological study. Because it is similar to the outcomes of molecular docking, these compounds' higher biological efficacy when compared to their parent compounds is highly significant.

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