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Quinoline Derivatives with Different Functional Groups: Evaluation of Their Catecholase Activity

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Abstract: In this work, we are interested in finding new catalysts for catecholase, whose principle is based on the oxidation reaction of catechol to *o*-quinone. In this context, we have studied a series of seven quinoline-based compounds. The present work indicates that the complexes formed between seven selected quinoline compounds and the copper salts viz. $Cu(OAc)_2$, $CuSO_4$, $Cu(NO_3)_2$, and $CuCl_2$ elicit catalytic activities for the oxidation of catechol to *o*-quinone. The complexes formed with the $Cu(OAc)_2$ salt show a much higher catalytic activity than the others, whereas the $Cu(NO_3)_2$ and $CuCl_2$ salts formed complexes with low catalytic activity. This study also shows that the oxidation rate depends on two factors, namely the chemical structure of the ligands and the nature of the ions coordinated with the copper.

Keywords: catalytic activity; quinoline; catechol oxidase; *o*-quinone

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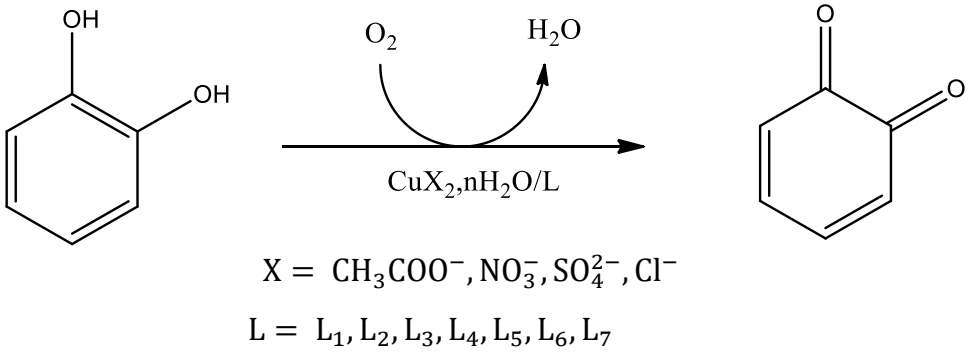
1. Introduction

Copper is among the important metals in many catalytic processes and is characterized by its ability to combine with organic ligands to catalyze several diverse biological processes [1]. For example, catechol oxidase is a copper-based moiety that catalyzes the oxidation of phenols to quinones in the presence of oxygen. It is found for example in plants, wherein it plays an essential role in catalyzing the oxidation of catechol to *o*-quinone to produce after polymerization melanin, which gives a dark brown color to damaged fruits [2]. Dopamine is an important neurotransmitter, which after oxidation and polymerization gives polydopamine, an adhesive agent with many industrial applications. The oxidation of phenols to corresponding quinones is a very interesting process that has various applications in many fields [3].

Quinoline derivatives are among the compounds with great pharmacological powers [4], such as antimicrobial [5], anticancer [6–8], antifungal [9,10], antiviral [11], anti-inflammatory [12], antioxidants [13,14], antitumor [15], anti-SARS-CoV-2 [16], corrosion inhibitors [17,18], and antimalarial [19]. On the other hand, copper–quinoline complexes are similar systems that can catalyze many biological processes. For this reason, we are interested in this work to better understand this compelling mechanism and to discover the efficiency of quinoline derivatives in the oxidation of catechol.

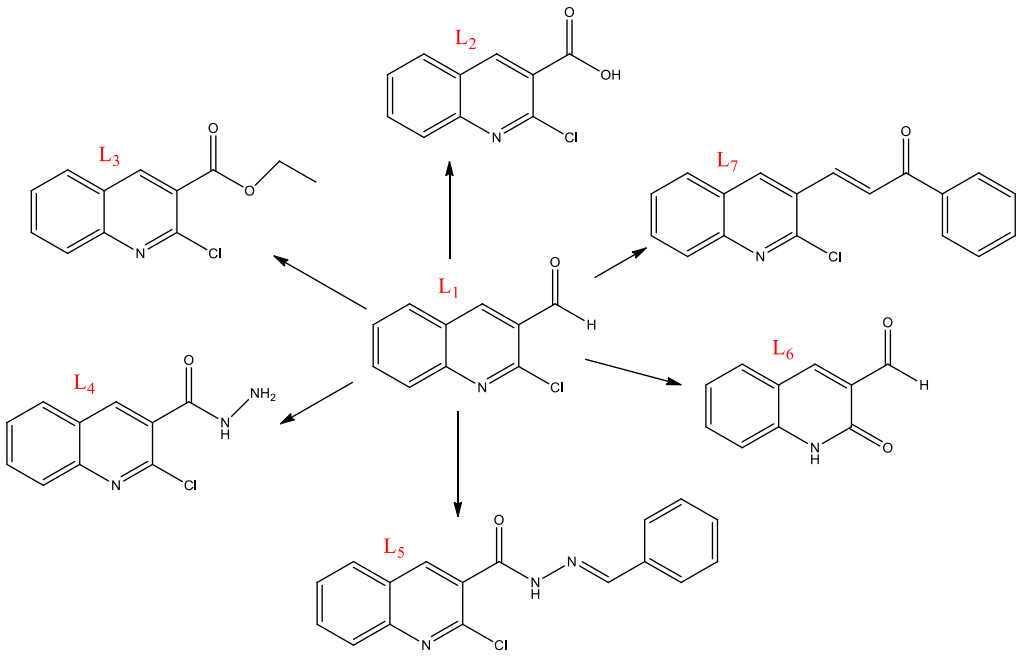
This work aims to study the effect of ligands–copper(II) complexes on the oxidation of catechol to *o*-quinone in the presence of O_2 (Scheme 1). In this respect, the reaction was first performed without catalysts, then using the copper salts $Cu(OAc)_2$, $CuSO_4$, $Cu(NO_3)_2$, and $CuCl_2$, then using the synthesized ligands (L_1, L_2, L_3, L_4, L_5, L_6, and L_7—Scheme 2), and finally, the reaction was catalyzed by the ligands–copper (II) complexes. In order to be able to compare and discuss the obtained results, the oxidation rate for each catechol transformation was calculated.



$$X = CH_3COO^-, NO_3^-, SO_4^{2-}, Cl^-$$

$$L = L_1, L_2, L_3, L_4, L_5, L_6, L_7$$

Scheme 1. The oxidation reaction of catechol to *o*-quinone.



Scheme 2. Chemical structure of the studied quinoline ligands.

2. Results and Discussions

The results of this study are represented in Figures 1 and 2, which give the absorbance as a function of time for the different cases. Figure 1a presents the oxidation of catechol without any catalyst, while Figure 1b represents the reaction catalyzed by the synthesized ligands. In Figure 1c, the reaction is catalyzed by the metal salts and finally, Figure 2 provides the obtained results using the complexes formed between the synthesized ligands and the metal salts. Table 1 represents the oxidation rate for the different cases.

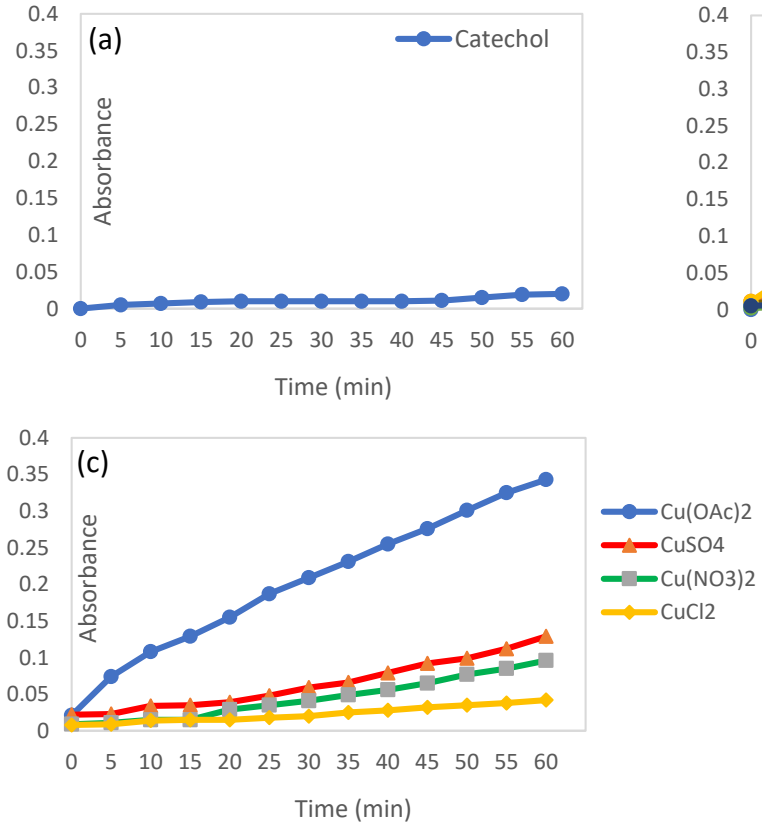


Figure 1. Oxidation of catechol to *o*-quinone in the absence of copper complexes: (**a**) Reaction without any catalyst, (**b**) reaction catalyzed by the synthesized ligands, and (**c**) reaction synthesized by the metal salts. Reaction conditions: methanol solutions, 0.15 mL metal salt at 2×10^{-3} mol/L, 0.15 mL ligand at 2×10^{-3} mol/L, 2 mL catechol at 10^{-1} mol/L are mixed, T = 25 °C, λ = 390 nm.

Table 1. Oxidation rate of catechol to *o*-quinone in (μmol L^{-1} s^{-1}).

	$Cu(OAc)_2$	$CuSO_4$	$Cu(NO_3)_2$	$CuCl_2$	Ligands Only
L_1	71.38	34.86	16.53	13.33	11.39
L_2	94.30	26.25	18.61	11.25	10.83
L_3	85.27	27.91	17.36	12.22	12.08
L_4	126.80	65.13	31.25	15.55	12.64
L_5	114.44	52.63	27.64	14.03	8.61
L_6	69.30	26.53	14.03	11.39	7.92
L_7	89.58	48.75	17.91	12.64	7.08
Salt only	47.63	17.91	13.33	5.83	
Without catalysis			2.78		

We notice from Figure 1a that the absorbance remains at almost zero over time and the oxidation rate is very low viz. 2.78 μmol L^{-1} s^{-1}. Figure 1b also shows a very low absorbance and conversion rate between 7.08 μmol L^{-1} s^{-1} and 12.64 μmol L^{-1} s^{-1}. From Figure 1c, we also notice that the absorbance and oxidation rate remain low for the metal salts $CuSO_4$, $Cu(NO_3)_2$, and $CuCl_2$; however, the salt $Cu(OAc)_2$ has a better oxidation rate of 47.22 μmol L^{-1} s^{-1}. Therefore, it can be deduced that the oxidation reaction cannot take place without a catalyst and that neither ligands nor salts alone can catalyze this reaction, except $Cu(OAc)_2$, which has a slightly greater catalytic effect compared to the others.

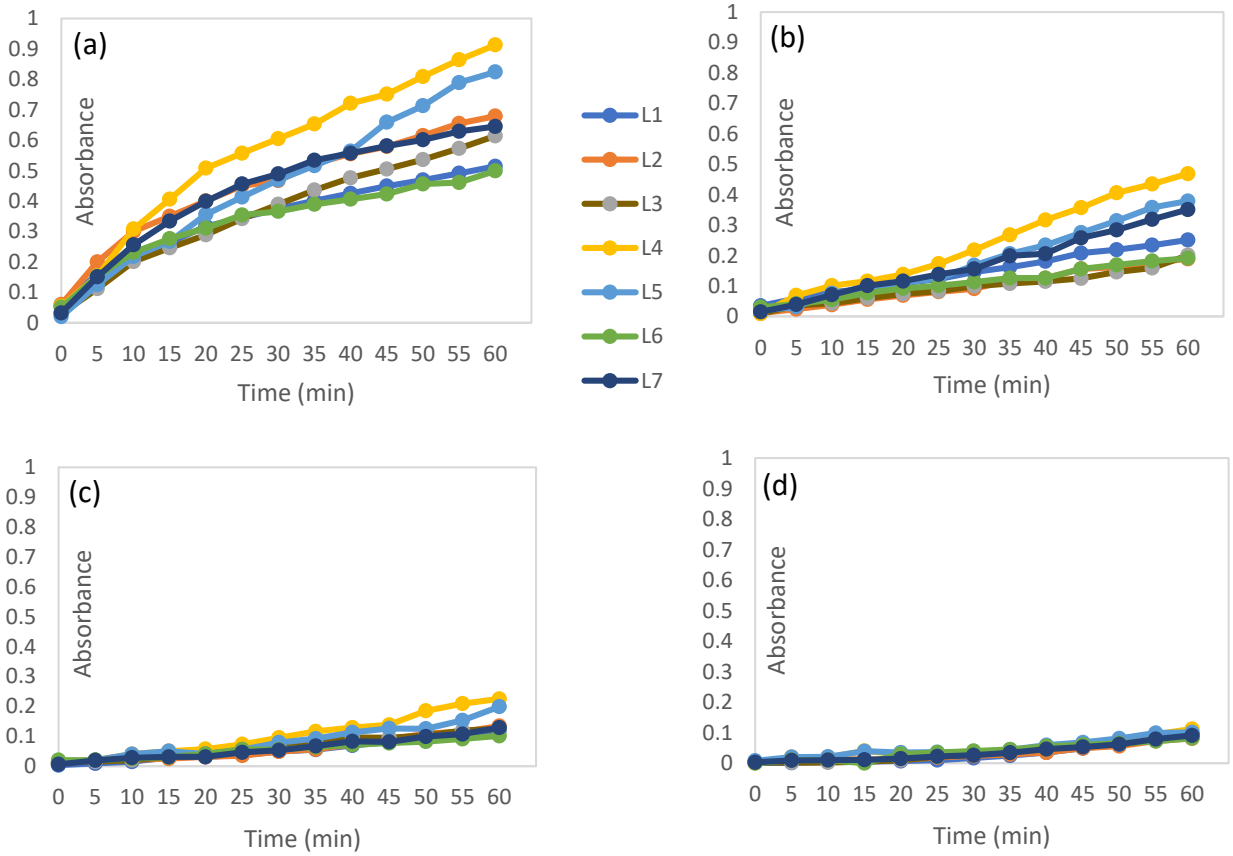


Figure 2. Oxidation of catechol to *o*-quinone in the presence of copper complexes: (**a**) Reaction in the presence of $Cu(OAc)_2$ and ligands, (**b**) reaction in the presence of $CuSO_4$ and ligands, (**c**) reaction in the presence of $Cu(NO)_3$ and ligands, and (**d**) reaction in the presence of $CuCl_2$ and ligands. Reaction conditions: methanol solutions, 0.15 mL metal salt at 2×10^{-3} mol/L, 0.15 mL ligand at 2×10^{-3} mol/L, 2 mL catechol at 10^{-1} mol/L are mixed, T = 25 °C, λ = 390 nm.

The results obtained in Figure 2 show that the complexes formed between the $Cu(OAc)_2$ salt and the ligands possess better catalytic activity for the oxidation of catechol, as the obtained oxidation rates are the highest (Figure 2a). The $L_4/Cu(OAc)_2$ complex shows an oxidation rate of 126.80 μmol L^{-1} s^{-1}, followed by the $L_5/Cu(OAc)_2$ complex (114.44 μmol L^{-1} s^{-1}), then the $L_2/Cu(OAc)_2$, $L_7/Cu(OAc)_2$, and $L_3/Cu(OAc)_2$ complexes with oxidation rates of 94.30, 89.58, and 85.27 μmol L^{-1} s^{-1}, respectively, and finally, $L_1/Cu(OAc)_2$ and $L_6/Cu(OAc)_2$, which give the lowest oxidation rates (71.38 and 69.30 μmol L^{-1} s^{-1}, respectively).

The complexes formed between the ligands and the $CuSO_4$ salt also give high oxidation rates but are generally lower than those obtained in the case of $Cu(OAc)_2$, as the highest oxidation rate is 65.13 μmol L^{-1} s^{-1} for $L_4/CuSO_4$, followed by $L_5/CuSO_4$ and $L_7/CuSO_4$, with oxidation rates of 52.63 and 48.75 μmol L^{-1} s^{-1}, respectively, and then the complexes formed between $CuSO_4$ and ligands L_1, L_3, L_6, and L_2 come last with oxidation rates of 34.86, 27.91, 26.53, and 26.25 μmol L^{-1} s^{-1}, respectively (Figure 2b).

The complexes formed between the ligands and $Cu(NO_3)_2$ also catalyze the oxidation reaction, but with slightly lower oxidation rates compared to the previous ones, as the $L_3/Cu(NO_3)_2$ complex gives the largest oxidation rate of 31.25 μmol L^{-1} s^{-1}, followed by the $L_5/Cu(NO_3)_2$ complex (27.64 μmol L^{-1} s^{-1}), and then the complexes formed between $Cu(NO_3)_2$ and the ligands L_2, L_7, L_3, L_1, and L_6, with oxidation rates of 18.61, 17.91, 17.36, 16.53, and 14.03 μmol L^{-1} s^{-1}, respectively (Figure 2c).

The complexes formed between the ligands and $CuCl_2$ do not show a significant catalytic effect, as there is no significant increase in absorbance in all cases, and the oxidation

rate remains quite low, the largest conversion rate being 15.55 μmol L^{-1} s^{-1} for $L_4/CuCl_2$ and the smallest being 11.25 μmol L^{-1} s^{-1} for $L_2/CuCl_2$ (Figure 2d). We deduce from these results that the chemical structure of the ligands and the nature of the copper salts play an important role in the catalytic activity of the studied complexes.

It can be seen from this study that all the complexes formed between the ligands and $Cu(OAc)_2$ have very high catalytic activities compared to the complexes formed with the other salts, and this is due to the weak bonding between the OAc^- anions and the Cu^{2+} cations, which facilitates the coordination between the ligands and copper. On the other hand, the ligands L_4 and L_5 form complexes with a very high catalytic activity, because the presence of electron donor groups increases the electron density at the nitrogen atom, which favors the coordination with the metal and the formation of stable complexes. However, in the case of L_1 and L_6, the catalytic activity decreases due to the presence of electron-withdrawing groups (Cl and CO) that weaken the electron density at the oxygen atom and thus disfavor the formation of the copper–metal bond. In the case of complexes formed between the ligands and the metal salt $CuCl_2$, the absorbance remains low, and the catalytic activity decreases because the Cl^- anions are strongly bound to copper, and the coordination between the metal and the ligands thus becomes very difficult.

In summary, the catalytic activity of copper salts and quinoline ligands is very low, but their assembly results in complexes that efficiently catalyze the oxidation of catechol to *o*-quinone. The results show that the oxidation rate depends on two factors, namely the ions' nature, and the ligands' chemical structure. The ions strongly bound to copper reduce the coordination of the ligands, resulting in complexes of low catalytic activity, and the reverse is true for the ions weakly bound to copper, which facilitate the coordination of the ligands, giving stable complexes and high catalytic activities. On the other hand, the chemical structure of the ligands plays an essential role, and the presence of electron-donating groups enriches the coordination site in electron density, which increases the stability of the studied complex as well as its catalytic activity. However, the presence of electron-withdrawing groups decreases the electron density at the coordination site, which decreases the stability of the complex and its catalytic activity.

3. Materials and Methods

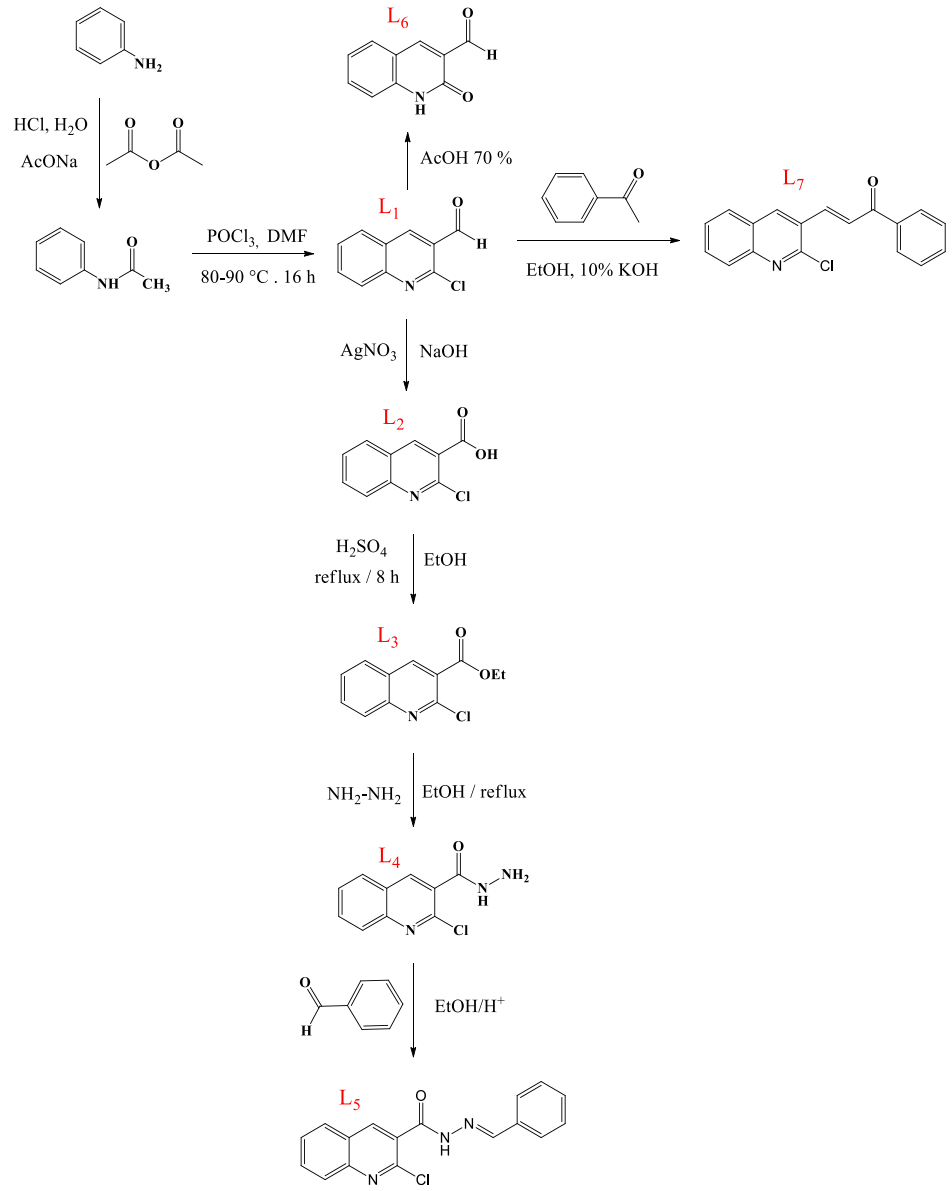
3.1. Reaction and Method

The reaction studied is schematized in Scheme 1, the kinetics of this reaction was followed by measuring the absorbance as a function of time by a UV–Vis spectrophotometer for one hour at 390 nm (absorption maximum of *o*-quinone), under the following conditions: T = 25 °C, ε = 1.6 L mol^{-1} cm^{-1}. The solutions are prepared by dissolving in methanol, and the complexes are synthesized in situ by mixing 0.15 mL of a solution (2×10^{-3} mol L^{-1}) of CuX_2, nH_2O, and 0.15 mL of a solution (2×10^{-3} mol L^{-1}) of the ligand, and then 2 mL of a solution of catechol at a concentration of 10^{-1} mol L^{-1} is added [20].

3.2. Synthesis of Ligands

The studied quinoline derivatives were synthesized according to the procedures described in the literature (Scheme 3):

Synthesis of 2-chloroquinoline-3-carbaldehyde (compound L_1): DMF (3 eq) and $POCl_3$ (4.5 eq) were stirred for 30 min at 0 °C, then acetanilide (1 eq) in $CHCl_3$ (15 mL) was added slowly, and after the addition, the reaction mixture was heated for 16 h (80–90 °C). When the reaction was complete, the mixture was poured into crushed ice and neutralized with saturated $NaHCO_3$ solution; the resulting precipitate was filtered, washed with water, and recrystallized in ethyl acetate [21].



Scheme 3. Protocol for the synthesis of quinoline derivatives.

Synthesis of 2-chloroquinoline-3-carboxylic acid (compound L_2): 89 mg of compound L_1 were dissolved in a minimum of ethanol, then an ethanolic solution of $AgNO_3$ (0.7 mmol) and NaOH (2.5 mmol) were added. The mixture was left under stirring at room temperature for 4 h; at the end of the reaction, the excess $AgNO_3$ was removed by filtration, then a few drops of concentrated sulfuric acid were added to neutralize the solution. The precipitate formed was filtered, washed with water, and dried to give a dark yellow product [22].

Synthesis of ethyl 2-chloroquinoline-3-carboxylate (compound L_3): In a minimum of ethanol, 100 mg of compound L_2 and 4 drops of concentrated sulfuric acid were added, and the mixture was refluxed for 8 h. After cooling, the solid formed was recovered by filtration, washed with water, dried, and recrystallized in ethanol [23].

Synthesis of 2-chloroquinoline-3-carbohydrazide (compound L_4): 0.5 mmol of compound L_3 and 0.5 mmol of hydrazine were heated at reflux for 4 h in a minimum of ethanol, and at the end of the reaction, 50 g of ice was added to the solution and the obtained precipitate was filtered, washed with water, dried, and recrystallized in ethanol [24].

Synthesis of N'-benzylidene-2-chloroquinoline-3-carbohydrazide (compound L_5): To 15 mL of ethanol, 56 mg of compound L_4 and 40 mg of benzaldehyde and a few drops of acetic acid were added and heated at reflux for 12 h. At the end of the reaction, the reaction mixture was allowed to reach room temperature and the resulting precipitate was filtered, washed with water, dried, and recrystallized in ethanol [25].

Synthesis of 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (compound L_6): Compound L_1 (1 mmol) was heated to 110 °C for 12 h in acetic acid (70%), and at the end of the reaction, the reaction mixture was allowed to reach room temperature. The precipitate formed was filtered and washed with water, dried, and recrystallized in ethanol [26].

Synthesis of 3-(2-chloroquinolin-3-yl)-1-phenylprop-2-en-1-one (compound L_7): To 20 mL of ethanol, 1 mmol of acetophenone, 1 mmol of compound L_1, and 5 mL of 10% NaOH solution were added. After 8 h of stirring at room temperature, the precipitate formed was filtered, washed with water, and recrystallized in ethanol [27].

NMR data of all these ligands are available in the file Supplementary Materials.

4. Conclusions

The results of this study show that the studied quinoline-derived complexes possess catalytic activities, and in particular, the complexes formed between the ligands and the metal salt $Cu(OAc)_2$ efficiently catalyze the oxidation of catechol to *o*-quinone. The 2-chloroquinoline-3-carbohydrazide ligand (compound L_4) exhibits the highest catalytic activity, and 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (compound L_6) exhibits the lowest catalytic activity. In general, the oxidation efficiency of the studied complexes depends on the ions' nature and the ligands' chemical structure. Ions weakly bound to the metal and electron-rich coordination sites yield stable complexes that strongly catalyze catechol oxidation. Further studies are still in progress in our laboratory to synthesize new quinoline derivatives, evaluate their biological and catalytic activities, as well as to obtain more details on this compelling catalytic process.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12111468/s1.

Author Contributions: R.S. and S.T.: conceptualization, supervision, project administration, methodology, resources, data curation, writing of the original draft, review, and editing; M.M.: conduct of experiment; V.H.M.: review and editing, methodology; J.J.: project administration; Z.M.A., M.I.A.-Z. and A.B.B.: project administration, methodology, writing of original draft and paying publication fees. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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