


# Metal Complexes with 8-Hydroxyquinoline: Synthesis and *In Vitro* Antimicrobial Activity

Amira Cipurković<sup>1</sup> , Emir Horozić<sup>2</sup> , Snježana Marić<sup>1</sup>, Lejla Mekić<sup>3</sup>, Halid Junuzović<sup>2</sup>

<sup>1</sup>Faculty of Natural Sciences and Mathematics, University of Tuzla, Tuzla, Bosnia and Herzegovina

<sup>2</sup>Faculty of Technology, University of Tuzla, Tuzla, Bosnia and Herzegovina

<sup>3</sup>Faculty of Pharmacy, University of Tuzla, Tuzla, Bosnia and Herzegovina

Email: amira.cipurkovic@untz.ba

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## Abstract

In this paper, three complexes with 8-hydroxyquinoline (8-HQ) were synthesized, their spectral analysis was performed and the antimicrobial effect was examined *in vitro*. The stoichiometric ratio of the complex was determined conductometrically and spectrophotometrically. FTIR and UV/VIS spectroscopy were used for structural characterization. Antimicrobial activity was examined by diffusion technique on selected gram-positive and gram-negative bacteria, and *C. albicans*. Square planar and octahedral geometry complexes were synthesized by mixing in a molar ratio of 1:2 (M:L). Based on the spectral data, it is concluded that both oxygen and nitrogen atoms from 8-HQ are involved in the formation of the complex. The antimicrobial activity of the complexes is high, with zones of inhibition in the range of 15 - 28 mm. 8-HQ was shown to have a significantly higher ability to inhibit the growth of the tested microorganisms.

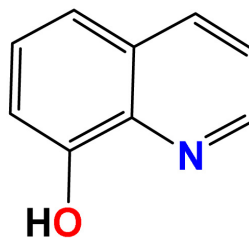
## Keywords

8-HQ, Metal Complex, Antimicrobial Activity, *In Vitro* Study

## 1. Introduction

8-Hydroxyquinoline (8-HQ), also known as oxine or 8-quinolinol, is an alkaloid which exists in plants of Asteraceae and Euphorbiaceae families [1] [2]. It is a monoprotic, bidentate agent (Figure 1) that consists of two donor atoms, oxygen and nitrogen [2]. The 8-HQ molecule acts as potent metal ion chelator, due to its oxygen and nitrogen atoms [3]. Many studies on 8-hydroxyquinoline complexes were conducted to date. After metal binding, 8-HQ changes its fluorescence. Construction of

sensitive fluorescent chemosensors for the recognition of metal ions lays on this feature [4] [5]. 8-HQ based chemosensors are developed for sensing zinc, cadmium, lead, mercury ions etc. [5] [6] [7]. Another feature of metaloquinolates is its use as electroluminescent materials. Alq3 (tris(8-hydroxyquinoline)aluminium) is the most widely used as the emissive and electron transporting material in OLEDs [8] [9] [10] [11]. 8-HQ is used to modify different adsorbents in order to enhance its potential in removing heavy metals from aqueous solutions [2]. Heterocycles compounds based on 8-HQ show efficient corrosion inhibition in an acid medium [12]. 8-HQ is derivative of quinoline which is considered as a “privileged structure” in medicinal chemistry [3] [13]. The derivatives of 8-HQ exert different, pharmacologically useful, activities such as antimicrobial, antioxidant, anticancer, anti-inflammatory, antineurodegenerative activity, antimalarial, antituberculous activity [3] [13] [14]. The copper (II) complexes with 8-HQ derivatives are potent in the treatment of Alzheimer’s disease [15]. Antimicrobial activity is present due to 8-HQs ability to chelate with metal ions essential for enzyme functioning [14] [16].



**Figure 1.** Structure of 8-HQ.

## 2. Material and Methods

All chemicals used were of analytical grade and were used as received without any further purification. Chemicals were purchased from Semikem (Bosnia and Herzegovina) and Sigma Chemical Co. (St. Louis, Missouri, USA).

### 2.1. Preparation of the M(II) Complexes

A solvent mixture of 96% ethanol:water (80:20 v/v) was used to prepare the reactant solution. The concentration of ligand was 0.2 mol/L and concentrations of metal salts (chloride) were 0.1 mol/L. Volumes of 30 mL of the metal and ligand solution were mixed in a beaker and stirred on a magnetic stirrer while adjusting the pH of the model system (7.3 for the nickel and cobalt system and 5.6 for the copper system). After adjusting the pH with 1 mol/L sodium hydroxide solution, the mixtures were stirred for 30 minutes and then left in the dark for seven days to precipitate the complex, after which they were filtered through blue tape filter paper and stored in a desiccator until analysis began.

### 2.2. Structural Analysis

In order to determine the structure of the complex, samples were recorded by

ATR technique on a Nicolet iS10 FT-IR spectrophotometer, in the wavelength range of 4000 - 525  $\text{cm}^{-1}$ . UV spectra were recorded in three solvents (methanol, chloroform and dimethyl sulfoxide) on a Perkin Elmer Lambda 25 spectrophotometer.

Determination of stoichiometric ratios for the copper-8-HQ model system was performed by conductometric titration. For this purpose, a solution of Cu(II) ions and an 8-HQ concentration of 1 mmol/L were prepared. 10 mL of the metal solution was taken and transferred to laboratory beakers and diluted with 40 mL of distilled water. After each added aliquot of 8-HQ (1 mmol/L), the conductivity of the solution ( $\mu\text{S}/\text{cm}$ ) was measured.

A spectrophotometric method published by Joe and Yones [17] was used to determine the stoichiometric ratios of the Ni(II) and Co(II) model systems with 8-HQ. A series of solutions with a constant concentration of M(II) ions of  $1.35 \times 10^{-4}$  mol/L were prepared, while 8-HQ concentrations were changed. Based on the obtained results, the stoichiometric composition of the complex was determined and the values of  $K_{ML}$  stability were calculated.

### 2.3. *In Vitro* Antibacterial Activity Testing

The *in vitro* antimicrobial activities of the metal complexes with 8-HQ and standard antibiotic drugs were investigated using four Gram-positive bacteria (*B. subtilis*, *S. aureus*, *L. monocytogenes* and *E. faecalis*) and three Gram-negative bacteria (*E. coli* and *P. aeruginosa*) by applying the diffusion technique. *C. albicans* was used to investigate antifungal activity. Solutions of a concentration 2.5 mg/mL, prepared by dissolving the complex and 8-HQ in dimethyl sulfoxide, were used for the assay. The sample volumes applied to the agar wells were 100  $\mu\text{L}$ . Ciprofloxacin (conc. 1 mg/mL) was used as a control.

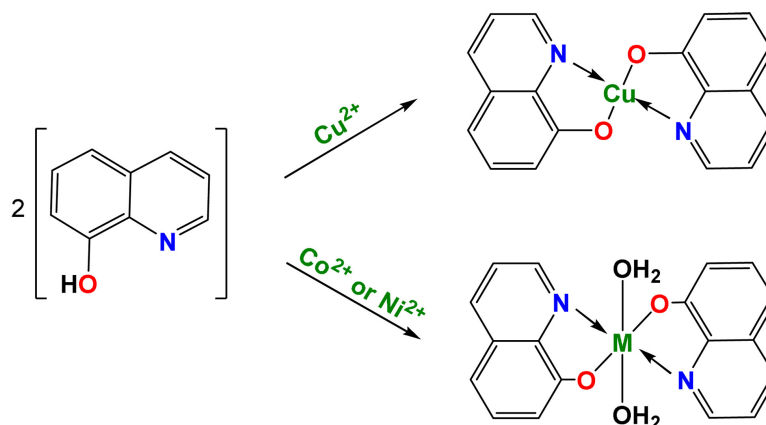
## 3. Results and Discussion

The highest yield of the reaction was recorded in the case of Ni(II) complex (63.5%), followed by Cu(II) complex (53%) and Co(II) complex (51.4%). The complexes are insoluble in water, sparingly soluble in diethyl ether, acetone and 96% ethanol. Good solubility was observed in dimethyl sulfoxide, dimethyl formamide, chloroform and methanol.

### 3.1. Structure of the M(II) Complexes

The reaction scheme and the proposed structure of the complex are shown in **Figure 2**.

Mixing Cu(II) and 8-HQ in a molar ratio of 1:2 (M:8-HQ) forms a complex of square planar coordination geometry. Since the remaining two complexes on the FTIR spectra recorded a band characteristic of the O-H bond, it is assumed that the water molecules are coordinated for the metal centers and in that case an octahedral geometry complex is formed. Donor atoms (oxygen and nitrogen) from 8-HQ participate in the formation of the bonds with metal ions.



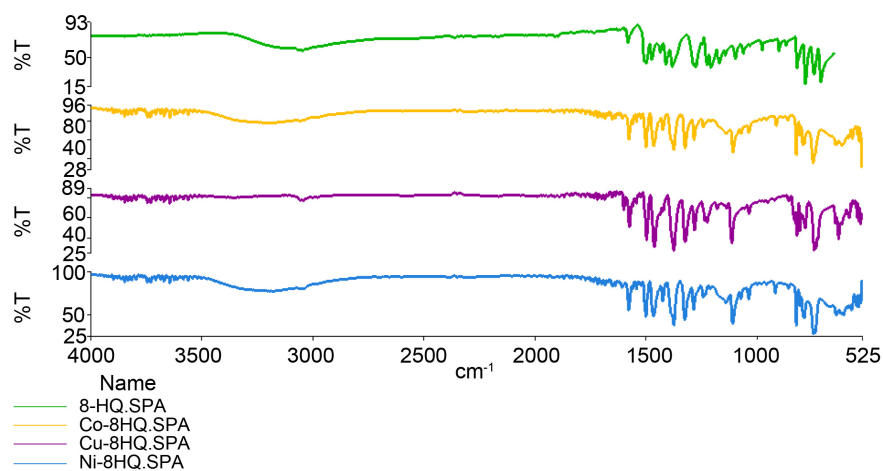
**Figure 2.** Reaction scheme and proposed structure of the complexes.

### 3.2. Spectral Analysis and Stoichiometric Ratio M(II)-8-HQ

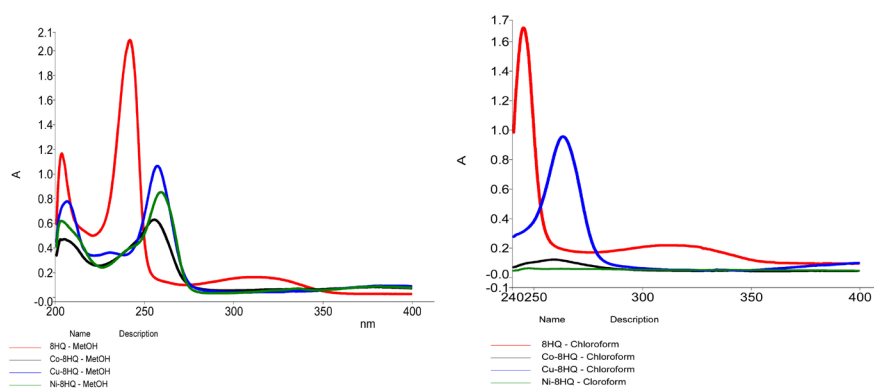
FTIR spectra of ligands and synthesized complexes are shown in **Figure 3**. **Table 1** shows the spectral data obtained by FTIR spectroscopy. On the FTIR spectra of the ligand, a broad band of medium intensity was observed in the region of about  $3181\text{ cm}^{-1}$  that would correspond to the O-H bond [18]. This band was observed on the spectra of the Co(II) and Ni(II) complexes, with a shift of the band towards higher wavenumbers. This could indicate the coordinative binding of water molecules in these two complexes. O-H bending vibrations occur on the FTIR spectra of the ligand at about  $1300\text{ cm}^{-1}$ . They are not visible on the spectra of the complex, which confirms the involvement of the oxygen atom in the formation of a bond with the metal center. In the Cu(II) complex, no band was observed in this wavenumber range. The band C=N was recorded at  $1581\text{ cm}^{-1}$  [19] at 8HQ, while in all complexes this band was slightly shifted towards smaller wavenumbers. The newly formed M(II)-N bond was observed on the spectra of the complex at about  $583\text{ cm}^{-1}$  (for the Cu(II) complex), and at  $567$  and  $569\text{ cm}^{-1}$  for the remaining two complexes [19]. Since the FTIR spectra of the Co(II) and Ni(II) complexes show a band for the O-H bond that probably originates from bound water molecules, this could indicate the octahedral geometry of these complexes, which will be the subject of research in the coming period.

**Table 2** shows the spectral data obtained by UV/VIS spectroscopy. The spectra of 8-HQ and  $M(8\text{-HQ})_2$  complexes were recorded in different solvents (methanol, chloroform, dimethyl sulfoxide). **Figure 4** and **Figure 5** show the UV spectra of 8-HQ and synthesized complexes recorded in different solvents.

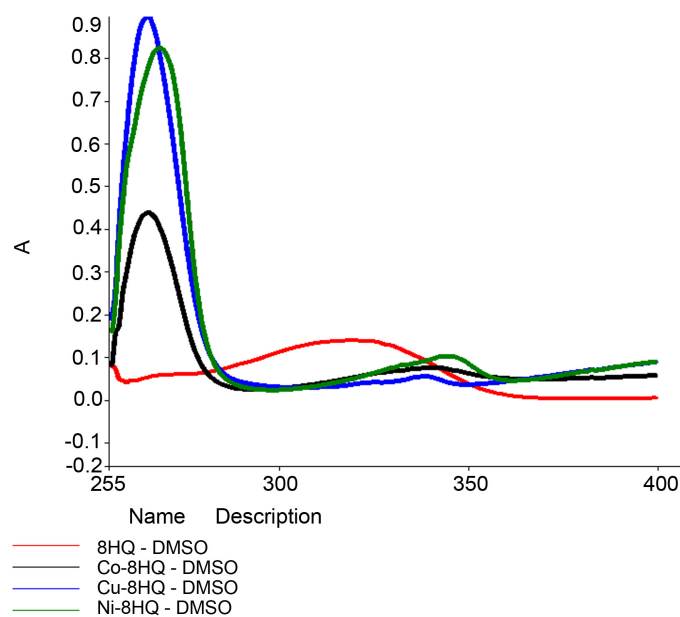
The absorption maxima for samples dissolved in chloroform and methanol are in a relatively close range of wavenumbers. For 8-HQ the absorption maximum in chloroform solution occurs at  $244\text{ nm}$  while the absorption maxima for complexes in the same solvent are shifted towards larger wavenumbers (bathochrome shift). Similar spectra were obtained for methanolic solutions of these compounds. The difference was observed in the spectra of the samples recorded with DMSO where it was observed that 8-HQ has an absorption maximum at  $319\text{ nm}$ , while for all complexes a shift of the absorption maxima was observed



**Figure 3.** FTIR spectra of 8-HQ and synthesized M(II) complexes.



**Figure 4.** UV spectra of 8-HQ and M(II) complexes recorded in methanol and chloroform.



**Figure 5.** UV spectra of 8-HQ and M(II) complexes recorded in DMSO.

**Table 1.** Infra-red spectral data for 8-HQ and metal complexes.

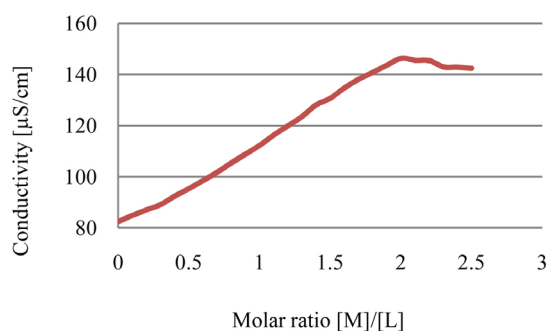
Compound	Infra-red spectral bands [ $\text{cm}^{-1}$ ]				
	O-H	C-O	C=N	C-N	M-N
8-HQ	3141 - 3241	1094	1581	1273	-
Cu(II)-8HQ	-	1110	1572	1279	583
Co(II)-8HQ	3227	1106	1576	1281	567
Ni(II)-8HQ	3208	1106	1577	1281	569

**Table 2.** UV spectral data for 8HQ and metal complexes in organic solvents.

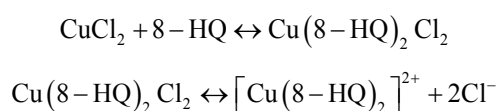
Compound	Absorption maximum, $\lambda_{\text{max}}$ [nm]		
	Chloroform	Dimethyl sulfoxide	Methanol
8HQ	244	319	241
Cu(II)-8HQ	262	264	257
Co(II)-8HQ	259	264	255
Ni(II)-8HQ	247	268	259

towards smaller wavelengths (hypsochromic shift). In methanol and chloroform solution, 8-HQ has a higher absorption compared to the complexes, while in the case of spectra recorded in DMSO, significantly lower absorption was recorded compared to M(II) complexes. Absorption bands for 8-HQ and synthesized complexes correspond to  $n \rightarrow \pi^*$  and  $\pi \rightarrow \pi^*$  transitions according to literature data [20].

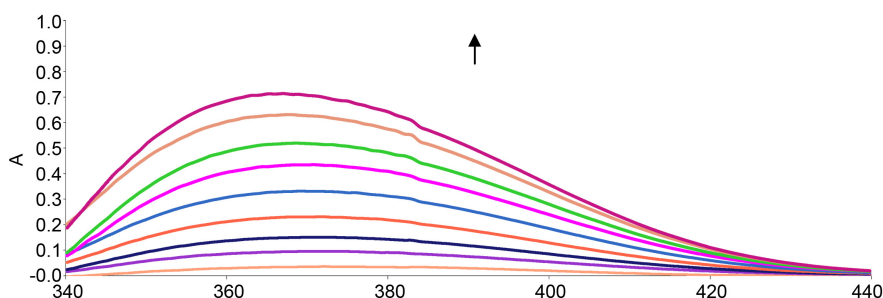
The stoichiometric ratio of Co(II):L and Ni(II):L was determined spectrophotometrically following the published method. In the case of the Cu(II)-8HQ complex, the stoichiometric ratio was determined by conductometric titration due to the precipitation reactions that occur during spectrophotometric determination. The solution formed by mixing primary solutions of Cu(II) ions and 8-HQ has a pH of about 5.5, which leads to the precipitation of the Cu(II)-8HQ complex when examining the stoichiometric ratio by spectrophotometric method. The molar conductance *vs*  $[L]/[M]$  curve for Cu(II)-8-HQ complex is shown in **Figure 6**.

**Figure 6.** Molar conductance *vs*  $[L]/[M]$  curve for Cu(II)-8-HQ complex.

For conductometric measurements, a solution of ligand was gradually added to the prepared Cu(II) chloride solution, until a concentration of 8-HQ was reached 2.5 times higher than the concentration of Cu<sup>2+</sup> ions. Conductivity measurements were performed at 25°C. The initial conductivity of the dissolved copper(II) chloride salt is very low. The addition of ligand to the metal salt solution causes an increase in molar conductivities to a level when the molar ratio of L-Cu<sup>2+</sup> = 2:1 is reached, after which the changes in molar conductivities were slight. This indicates that the Cu(II) ion forms a 2:1 stoichiometry complex with 8-HQ. It is known that when a ligand binds to a metal ion, it transfers the lipophilic character to the complexed metal ion, so that in the presence of ligand the dissociation of ion pairs increases. It is assumed that only complex ions dissociate into conductive species.



**Figure 7** shows the representative UV/VIS spectra used to determine the stoichiometric ratio of Co(II) and Ni(II) ions to 8-HQ. Both complexes have absorption maxima in a very close range (Co(II) complex at 371 nm and Ni(II) complex at 366 nm). Spectrophotometric method revealed that Co(II) and Ni(II) ions react with 8-HQ in a molar ratio of 1:2 (ML<sub>2</sub>).



**Figure 7.** Representative UV/VIS spectra used to determine the stoichiometric ratio of M(II) ions to 8-HQ.

### 3.3. Antimicrobial Activity

The results of the antimicrobial activity of the 8-HQ and M(II) complexes are shown in **Table 3**. shows significant antimicrobial activity of 8-HQ against all tested strains, with zones of inhibition of 34 - 50 mm. 8-HQ has been known as an antimicrobial agent since ancient times while the antimicrobial activity of its complexes is still being investigated.

All synthesized complexes have weaker antimicrobial activity compared to the parent ligand. A comparison of the activities between the synthesized components indicates a weaker activity of the Cu(II) complex compared to the other two. The highest antibacterial activity was observed in the Ni(8-HQ)<sub>2</sub> complex while the Co(8-HQ)<sub>2</sub> complex proved to be the most effective against *C. albicans*. Generally, it is suggested that the chelated complexes deactivated various

**Table 3.** Inhibition zones for 8HQ and synthesized complexes.

Microorganisms	Inhibition zone [mm]			
	8HQ	Cu(II)-8HQ	Co(II)-8HQ	Ni(II)-8HQ
<i>E. coli</i>	34	15	16	17
<i>E. faecalis</i>	40	20	21	21
<i>B. subtilis</i>	40	20	20	23
<i>L. monocytogenes</i>	50	19	23	26
<i>S. aureus</i>	45	20	22	28
<i>P. aeruginosa</i>	48	21	20	24
<i>C. albicans</i>	50	20	25	21

cellular factors *viz.*, stability constant, molar conductivity, solubility and magnetic moment, are also responsible for increase in the antimicrobial activity of the complexes [21].

#### 4. Conclusion

Based on the obtained results, it is concluded that copper forms with 8-HQ a complex of square-planar geometry. It is assumed that the other two complexes have an octahedral geometry due to the binding of two water molecules. M(II) ions react with 8-HQ in a molar ratio of 1:2 (M:L), which was confirmed by conductometric and spectrophotometric methods. The synthesized complexes of metal ions with 8-HQ show high antimicrobial activities. Since high antioxidant and antitumor activity have been confirmed for similar complexes, the biological activity of the complexes synthesized in this paper will be examined in more detail in the following period.

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#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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