SYNTHESIS, STRUCTURAL CHARACTERIZATION, BIOLOGICAL ACTIVITY OF COMPLEXES OF Ni(II) WITH 5-BROMO-6-HYDROXYL-3-SULFOQUINOL-7-YLOXYACETIC ACID

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Abstract: *In this research, a derivative of quinoline, namely 5-bromo-6-hydroxyl-3-sulfoquinol-7-yloxyacetic acid as well as one complex of Ni(II) with this ligand [Ni(QBr-2H).H_2O].3H_2O (NiQBr) was synthesized. The molecular formulas and structures of the complex were determined using a combination of IR, EDX, ESI MS, ^{1}H NMR spectra and thermal analysis. In this complex, Ni(II) coordinated with QBr ligand through the oxygen atom of OH phenol, oxygen atom of OCH_2 groups and the oxygen atom of carboxylate groups. The results of antimicrobial resistance testing of complex showed that NiQBr complex exhibited high activities on Bacillus subtilis and Lactobacillus fermentum with low IC_{50} from 0.61 - 0.71 μg/ml and NiQBr complex exhibited activities on Candida albican and Staphylococcus aureus with IC_{50} from 26.30 - 104.30 μg/ml.*

Keywords : *Ni(II) complex, quinoline, antimicrobial.*

1. Introduction

Heterocyclic compounds containing nitrogen, especially quinoline and its derivatives, are of the important organic ligands. They have many applications in medicine such as for treating malaria, or antibiotics, antibacterial agents [1,2,3]. Complexes of transition metals with quinoline derivatives are of great interest to research, they often have high coordination numbers and diverse structures. In addition to the magnetic and optical properties, the complex bioactivity of transition metals with quinoline derivatives also has antibacterial, antifungal, antiviral, antitumor, and antioxidant properties [4-7]. Therefore, the design and synthesis of substituent quinoline ligands as well as their complexation with transition metals, thereby finding compounds with high biological activity has scientific and practical significance. This will not only enrich the basic research on complex chemistry, but also the prospect of finding modifiable substances for application in the field of pharmaceutical chemistry.

From eugenol, the main constituent of *Ocimumsanctum* L. oil, a sulfoquinoline derivative with naming is 5-bromo-6-hydroxy-3-sulfo-quinolin-7-yloxiaxetic acid (denoted by QBr) has been synthesized [8]. From this key compound, quinoline's

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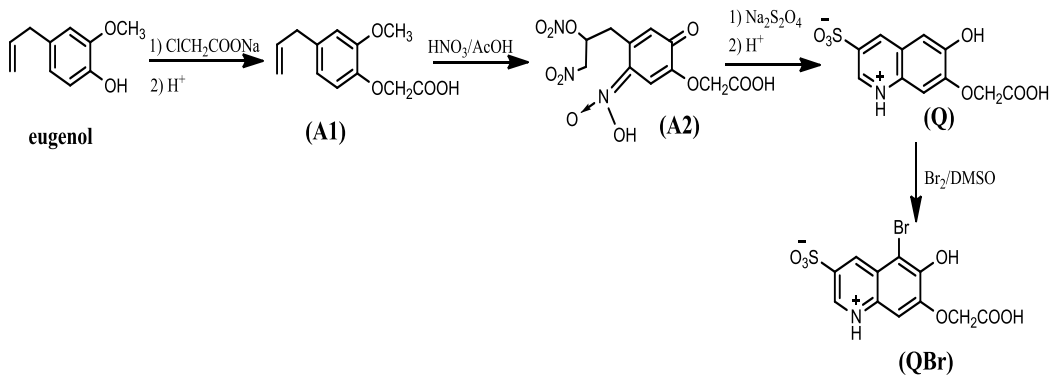
derivatives can be created with many substituents such as OH phenol group, COOH group, etc. These groups are capable of forming complexes with transition metal ions. Several transition metal complexes with ligands of this type were initially investigated [9]. In this paper, the results of synthesis, structure, and biological activity of the complex of Ni(II) with 5-bromo-6-hydroxy-3-sulfoquinol-7-yloxiacetic acid (QBr) are presented.

2. The Experimental

2.1. Synthesis of the QBr

From eugenol in basil essential oil we have synthesized the 5-bromo-6-hydroxy-3-sulfoquinol-7-yloxyacetic acid (QBr) according to published procedure.[8]



The QBr crystal has been crystallized by a slow evaporation of the aqueous solution. The results of the single crystal X-ray diffraction measurements at the Faculty of Chemistry, Hanoi University of Science-Vietnam National University-Hanoi showed that the molecular formula of this ligand was $[2(C_{11}H_8O_7NSBr).3H_2O]$. The spatial structure of the QBr ligand is shown in Fig. 1 and some of the crystallographic data are presented in table 1.

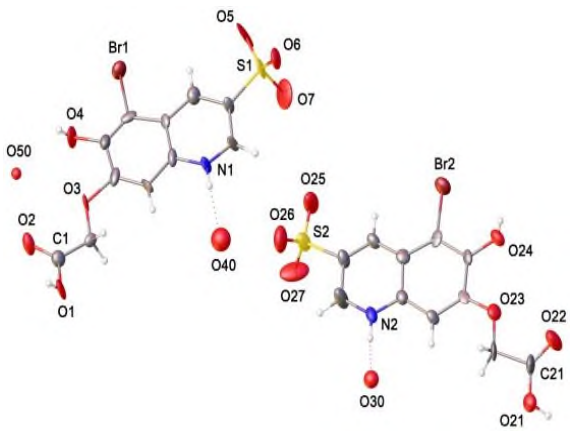


Fig.1. *The spatial structure of QBr by single crystal X-ray diffraction measurements*

Table 1. *Some crystallographic data of QBr*

Molecular formula	$2(C_{11}H_8O_7NSBr).\ 3H_2O$	a ($\overset{o}{A}$)	18.968(3)
Molecular mass	804.31	b ($\overset{o}{A}$)	7.302(2)
Crystal system	Orthorhombic	c ($\overset{o}{A}$)	21.455(4)
V ($\overset{o}{A}$)	2971.6(11) Å3	α (°)	90
Number of molecules / unit cell	4	β (°)	90
R_1/wR_2	R_1 = 0.1329 wR_2 = 0.2393	γ (°)	90

2.2. Preparation of complex NiQBr

Adding 0.0756 grams of QBr (0.2 mmol) to 10 ml of H_2O, slowly add NH_3 solution, stirring well at room temperature until QBr is completely dissolved, obtaining a homogeneous yellow solution, pH = 5 (solution 1). Slowly adding 2ml of solution containing 0.064g. $Ni(NO_3)_2.6H_2O$ (0.22 mmol) into solution 1 obtained a pale yellow precipitate. Stirring for another 2 hours at room temperature. Filtering and washing the precipitate with water and ethanol to give a pale yellow solid. Recrystallization with an ethanol-water mixture (ratio 1:1) yields a yellow solid. The product is slightly soluble in water, slightly soluble in ethanol and soluble in DMSO, denoted NiQBr. The yield was 75% ÷ 80%.

2.3. Chemicals and Instrumentation

The EDX spectrum of the complex was measured on a FESEM machine at the Advanced Institute of Science and Technology - Hanoi University of Science and Technology. ESI MS spectra were measured on an LC-MSD-Trap-SL instrument, infrared absorption spectra were recorded on an IMPAC 410 NICOLET in the region of 4000 ÷ 400 cm^{-1}, the sample was measured in tablet form with KBr, and 1H NMR spectrum of the complex. The substance was measured on a Bruker AVANCE machine (500MHz), in DMSO solvent, at the Institute of Chemistry, Vietnam Academy of Science and Technology. The thermal analysis pattern was measured at the Department of Chemistry, Hanoi National University of Education.

Chemicals used to synthesize ligands: basil oil (Vietnam, 75%); monochloroacetic acid (UK, 99.5%); sodium dithionite (UK, 99.5%), liquid bromine (Russia, 99%); HNO_3 65% (Vietnam), chemicals NaOH, CH_3COOH, DMSO, ethyl acetate, dimethyl sulfate, methanol were of molecular purity grade, China. $Ni(NO_3)_2 \cdot 6H_2O$ was of Aladdin (China, 99%).

2.4. Exploration of biological activity

The tested antimicrobial activity of the complex was determined at the Department of Applied Biochemistry, Institute of Chemistry, Vietnam Academy of Science and Technology.

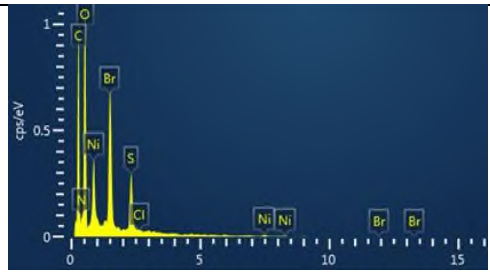
3. Results and duscussion

The results of measuring energy dispersive X-ray (EDX) spectroscopy and the peaks on the ESI MS spectrum of the NiQBr complex have been attributed and presented in Table 1, Figure 1. The EDX spectral measurement results show that in the NiQBr complex The ratio of Ni:S or Ni:Br atoms is ≈ 1:1, and each QBr ligand contains only 1 S atom and 1 Br atom, so in the NiQBr complex the Ni metal atom complexes with the QBr ligand according to The ratio is 1:1

Based on the results of EDX spectrum analysis, combined with other experimental data, it is possible to suggest that the molecular formula of the complex is [Ni(QBr-2H).H_2O].3H_2O (NiQBr)). On the +MS spectrum of the NiQBr complex (Figure 1b), there is a cluster of ion peaks containing ionic peaks with the value m/z = 436,9 corresponding to ion 436.9 = {Ni(QBr-2H) +H^+}$^+$, this is an ion fragment. The positive of the complex is separated and combined with H^+ present in the measuring chamber. Thus, the molecular formula of the proposed NiQBr complex is suitable.

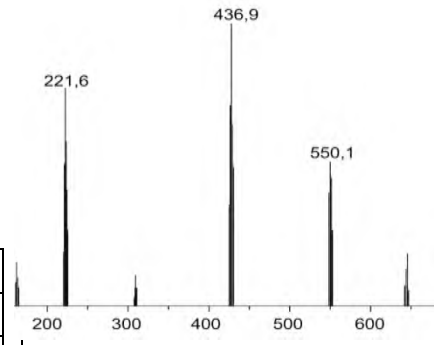
Table 2. *Result of elemental analysis (EDX), ESI MS spectral of complex*

Numerical order	Complex	Analysis results ESI MS spectral	Result of EDX	
		Assignment (m/z)	Ratio atom (TN/LT) Ni:S or Ni:Br	
1	[Ni(QBr-2H).H_2O].3H_2O	436.9={Ni(QBr-2H)+H^+}$^+$	2.39:2.42 ≈ 1:1	1:1



Element	C	O	S	Ni	Br	total
Weight (%)	46.89	24.07	4.74	7.57	12.34	100
Atomic (%)	63.95	24.65	2.42	2.39	2.53	100

a)



(b)

Fig.2. *Result of EDX (a) and part of the +MS spectrum of NiQBr complex (b)*

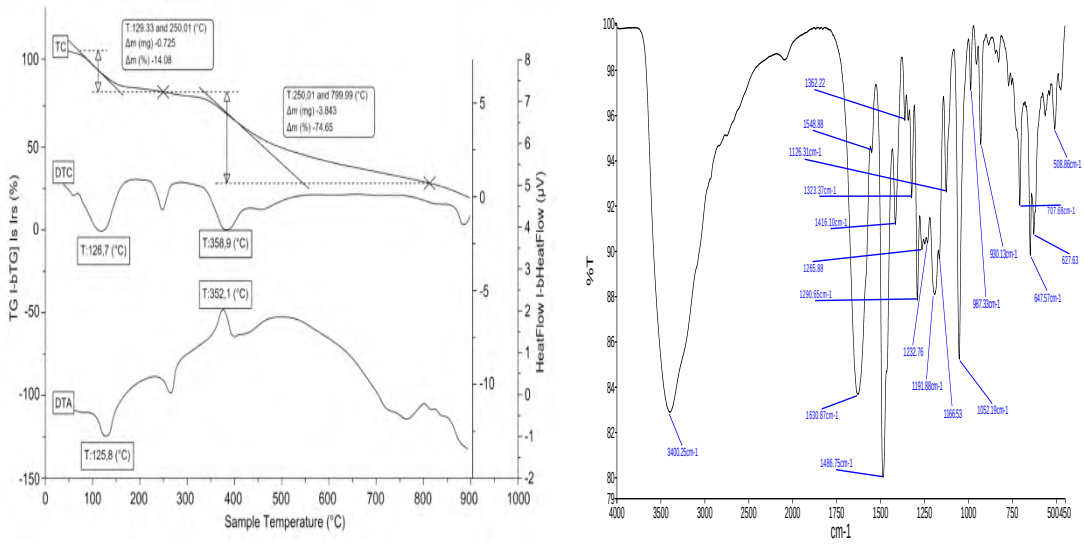
On the IR spectrum of the NiQBr complex, there were fully visible absorption bands representing the valence vibrations of groups of atoms in the molecule, some main absorption fringes have been attributed and presented in Table 2. The infrared spectrum of the NiQBr complex is different from the infrared spectrum of the QBr ligand. In the infrared spectrum of the NiQBr complex, There was no absorption band at 1713cm^{-1}, but two strong absorption bands appeared with the frequency reduced to 1630 and 1487 cm^{-1}, respectively υ_{COO^-kdx} and υ_{COO^-dx}. This proves that Ni(II) is coordinated to the QBr ligand via the O atom of the COO^- group.

On the thermal analysis method of the NiQBr complex, the first effect was the endothermic effect on the DTA curve, the minimum on the DTGA curve accompanied by a decrease in mass on the TGA curve in the temperature range from 60÷ 230^{o}C corresponding to the loss of crystallization and coordination water. Based on the decrease in mass in each phase, the number of molecules of water of crystallization and coordination water of the complex can be suggested as shown in Table 2

On the thermal analysis method of the NiQBr complex, in the temperature range from 60 ÷ 120^{o}C, there was a decrease in mass on the TGA curve, accompanied by endothermic effects on the DTA curve corresponding to the loss of 3 molecules of water of crystallization, (The mass % of water of crystallization calculated according to the molecular formula is expected to be 10.61%, the schematic is 10.52%). In the temperature range from 120 ÷ 230^{o}C, there was a decrease in mass on the TGA curve, accompanied by an endothermic effect on the DTA curve corresponding to the loss of 1 coordination water molecule, (% by mass of coordinated water calculated by the formula expected molecular weight is 3.56%, schematically it is 3.53%). Thus, the proposed NiQBr complex molecular formula [Ni(QBr-2H).H_2O].3H_2O was quite suitable

Table 3. *The main absorption bands on the infrared spectrum (cm^{-1}) and result of thermal analysis method of complex NiQBr*

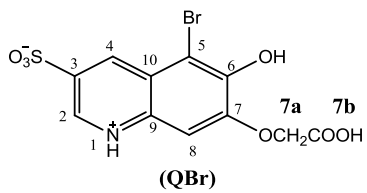
Form name	The main absorption bands on the infrared spectrum (cm-1)					Result of thermal analysis method		
	υ_{OH}	υ_{COO^-kdx}	$\upsilon\upsilon_{COO^-dx}$	υ_{C-O}, υ_{C-N}	υ_{M-O}	Dehydration Δm %, TN/LT		% NiO After decomposition / Δm %, (TN/LT)
						Crystallize	Coordination	
QBr	3451 (tù)	1713		1294, 1182				
NiQBr	3400 (tù)	1630	1487	1232, 1192	509	10.52/10.61	3.56/3.53	11.27/14.73



a) b)

Fig.3. *Thermal analysis method (a) and IR spectra of NiQBr complex (b)*

The resonant signals of the protons on the ^{1}H NMR spectrum of QBr ligand, NiQBr complex have been assignmented and presented in Table 3. The full signal appearance of protons in the QBr ligand and their chemical shift decreases compared to the free ligands, especially at the H7a proton, near the complex center, providing that this ligand coordinated with the Ni atom through the O atom of the OCH_2 group, the O atom of the OH group and the O atom of the COO group.



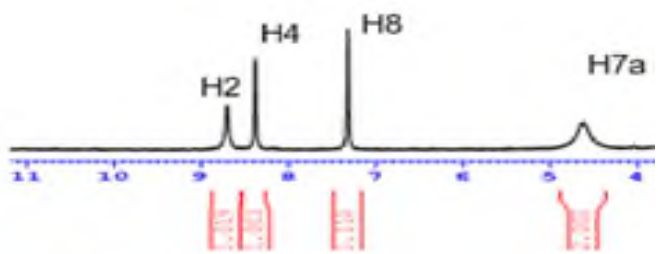


Fig.4. *Part of the 1H NMR spectrum of the NiQBr complex*

Table 4. *The signal of the protons in NiQBr complex, δ (ppm)*

The signal of the protons in complex, δ (ppm)				
Form name	H2	H4	H8	H7a
QBr	9,15	8,85	7,47	5,08
NiQBr	8,73	8,39	7,35	4,58

Based on the analysis of EDX, thermal analysis diagrams, ESI MS, IR, 1H NMR spectra, the complex NiQBr is suggested as follows:

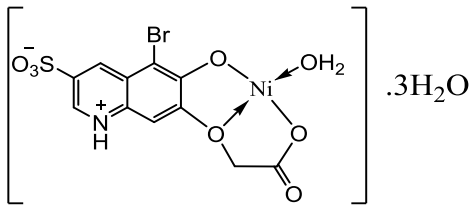


Table 5. *Antimicrobial resistance test results of complex*

Numerical order	Form name	IC_{50} values for strains (μg/ml)						
		Gram (+)			Gram (-)			
		Staphylococcus aureus	*Bacillus subtilis*	*Lactobacillus fermentum*	*Salmonella enterica*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albican*
1	QBr	>128	>128	>128	>128	>128	>128	>128
2	NiQBr	104,30	**0,71**	**0,61**	>128	>128	>128	26,30

The results of antimicrobial resistance testing of complex showed that NiQBr complex exhibit high activities on *Bacillus subtilis* and *Lactobacillus fermentum* with low IC_{50} from 0.61 - 0.71 μg/ml and NiQBr complex exhibit activities on *Candida albican* and *Staphylococcus aureus* with IC_{50} from 26.30 - 104.30 μg/ml (Table 4).

4. Conclusion

After a period of research, we have achieved some results as follows:

A complex of NiQBr was synthesized from Ni(II) and 5-bromo-6-hydroxy-3-sulfoquinol-7-yloxiacetic acid (QBr).

The structure of the complex have been determined by IR, EDX, ESI-MS, ^{1}H NMR spectra and thermal analysis method. In the complex Ni(II) has a coordination number of 4. The central metal atom binds to the ligand through the O atom of OH phenol group, OCH_2 and O of COOH group.

The results of antimicrobial resistance testing of complex showed that NiQBr complex exhibit high activities on *Bacillus subtilis* and *Lactobacillus fermentum* with low IC_{50} from 0.61 - 0.71 μg/ml and NiQBr complex exhibit activities on *Candida albican* and *Staphylococcus aureus* with IC_{50} from 26.30 - 104.30 μg/ml.

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