

**SYNTHESIS, CHARACTERIZATION AND FLUORESCENCE STUDY OF *N'*-[(*E*)-(2-HYDROXYQUINOLIN-3-YL)METHYLIDENE]-1-BENZOFURAN-2-CARBOHYDRAZIDE AND ITS METAL COMPLEXES**

**Mustapha C. Mandewale<sup>1</sup>, Babu R. Thorat<sup>1</sup>, Dnyaneshwar Shelke, Raghunath Patil<sup>2</sup> and Ramesh Yamgar<sup>3</sup>**

<sup>1</sup>*Department of Chemistry, Government of Maharashtra, Ismail Yusuf College of Arts, Science and Commerce, Jogeshwari east Mumbai-400 060, India.*

<sup>2</sup>*Dept. of Microbiology, Birla College of Arts, Science and Commerce, Kalyan, India.*

<sup>3</sup>*Department of Chemistry, Chikitsak Samuha's Patkar-Varde College of Arts, Science and Commerce, Goregaon (W), Mumbai 400 062, India.*

**ABSTRACT:**

A series of Co(II), Ni(II), Cu(II), Zn(II) and La(III) complexes of *N'*-[(*E*)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide has been prepared. It is synthesized by the condensation of 2-hydroxy-3-formylquinoline with benzofuran-1-carbohydrazide in absolute ethanol. The prepared hydrazone was characterized by <sup>1</sup>H NMR, FTIR and MASS Spectroscopy. Subsequently fluorescence properties of all the prepared complexes and *N'*-[(*E*)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide have been studied. The fluorescence wavelength as well as intensity of ligand showed a remarkable change after the formation of metal complex. The hydrazone shows weak emission at 522 nm for the absorption wavelength 356 nm whereas its complexes show moderate to strong emission i.e. Cu(II) complex 524 nm (moderate), Ni(II) complex 526 nm, Co(III) complex 526 nm (moderate), Zn(II) complex 508 nm (strong) and La(III) complex 519 nm (strong). All the synthesized compounds have been screened for the antibacterial study against microorganisms such as Escherichia coli, Salmonella typhi, Corynebacterium diptheriae and Staphylococcus aureus.

**KEY WORDS:** Quinoline, hydrazone, ligand, metal complex, fluorescence, antimicrobial activity.

**1. INTRODUCTION**

Quinoline was discovered in coal tar distillate by Rungel in 1834 and named "Leukol". The base was also obtained by Gerhardt in 1842 by alkaline distillation of quinine, cinchonine, or strychnine and was named by him "Chinolein" or "Chinolin". But Dewar in 1871 suggested that quinoline bear the same relationship to pyridine that naphthalene bear to benzene. Quinoline and its derivatives are receiving increasing importance due to their wide range of applications in biological and pharmacological area. Substituted quinolines are prominent building blocks in both organic and inorganic molecular chemistry with their p-stacking ability and coordination properties.

New techniques have been generated quinoline's heterocyclic ring synthesis. To date, there are six named reactions used to generate the quinoline ring system. Those named reactions can be broken down into two classes based on the substitution pattern of the starting materials. Those begin with unsubstituted anilines include the Skraup, Doebner-von Miller, Conrad-Limpach-Knorr, and Combes synthesis. Those synthesis begin with ortho-substituted anilines include the Friedländer, Pfitzinger, Niemantowski and Borsche synthesis. Although each technique has its own set of advantages and limitations, the Skraup and Friedländer work set the baseline for all other variations.

In 1995, Otto Meth-Cohn reviewed his longstanding "Vilsmeier Approach" and described a newer "Reverse Vilsmeier Approach" to quinolines. The "Vilsmeier Approach" converted acylanilides to  $\alpha$ -chloroenamines with  $\text{POCl}_3$ , then used *N,N*-dimethylformamide to formylate the enamines. After electrocyclization, the quinoline ring was formed, producing 2-chloro-3-formyl-quinolines [1].

Hydrazones are used as intermediates in synthesis [II], as functional groups in metal carbonyls [III], in organic compounds [IV-V] and in particular in hydrazone Schiff base ligands [VI-IX], which are among others employed in di-nuclear catalysts [X]. Furthermore, hydrazones exhibit physiological activities in which are attributed to the formation of stable chelate complexes with transition metals which catalyze physiological processes [XI-XIII]. They also act as herbicides, insecticides, nematocides, rodenticides, plant growth regulators, sterilants for houseflies, among other applications [XIV]. Metal complexes shows significant antifungal activities compared to its Schiff base ligand. Schiff base metal coordination complexes can be used not only as an approach to enhance their activity but also to overcome the drug resistance. [XV] In analytical chemistry hydrazones find applications as multidentate ligands for transition metals in colorimetric or fluorimetric determinations [XVI-XVII]. Many fluorescent metal complexes based on quinoline derivatives have been reported [XVIII-XXI], Hydrazones are now being used extensively in detection and quantitative determination of several metals, for the preparation of compounds having diverse structures, analytical chemistry for the identification and isolation of carbonyl compounds [XXII]. More recently, 8-hydroxyquinoline aluminum has been widely used as the emissive and electron transporting material in organic light emitting devices [XXIII-XXIV]. El-Sonbati et al. [XXV] reported the supramolecular structures and stereo-chemical versatility of azoquinoline containing novel metal complexes. The complexes show very high quantum efficiency than the Schiff bases [XXVI].

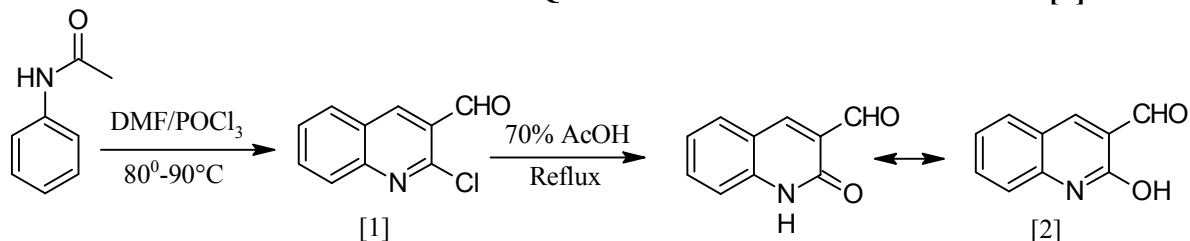
In this paper we have synthesized *N'*-[(*E*)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazone and its Cu(II), Ni(II), Zn(II), Co(II), La(III) complexes. Further we have studied their fluorescence as well as antibacterial properties.

## 2. EXPERIMENTAL SECTION

Chemicals used in the synthesis of compounds were purchased from Sigma–Aldrich, S. D. Fine-Chem Limited and Spectrochem Pvt. Ltd. All the solvents were of reagent grade and when necessary, they were purified and dried by the standard methods. Melting points (M.P.) of the synthesized compounds were determined in open capillary tubes and are uncorrected; Infrared spectra were recorded on FTIR-7600 Lambda Scientific Pty. Ltd. using KBr pellets. <sup>1</sup>H-NMR spectra were recorded on Varian-NMR-Mercury 300 MHz instruments using DMSO-*d*<sub>6</sub> as a solvent and TMS as an internal standard; chemical shifts are expressed as  $\delta$  values (ppm). Mass spectra (MS) were taken in Mass spectra were recorded on BRUKER ESQUIRE HCT spectrometer. UV–Visible absorption spectra were obtained with UV spectrophotometer Shimadzu UV-1800 and recorded in quartz cells with 1 cm optical path length. Fluorescence spectra were acquired on a spectrofluorophotometer Shimadzu RF-5301pc and equipped with quartz cuvette of 1 cm path length.

Analytical thin-layer chromatography (TLC) was performed on pre-coated TLC sheets of silica gel 60 F254 (Merck, Darmstadt, Germany), visualized by long- and short-wavelength UV lamps. Chromatographic purifications were performed on Merck silica gel (70–230 mesh).

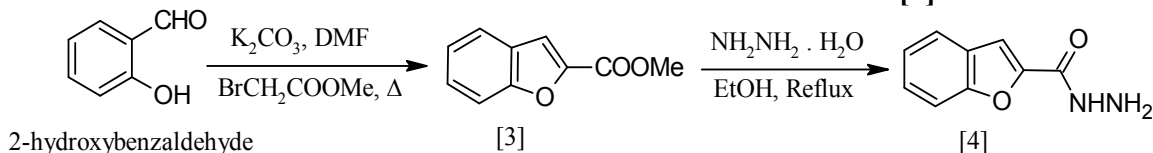
## 2.1. SYNTHESIS OF 2-HYDROXYQUINOLINE-3-CARBALDEHYDE. [2]



Titled compound was prepared according to the literature procedure <sup>[XXVII]</sup>. Required Acetanilide was readily prepared from reaction of aniline with acetic anhydride in aqueous medium. To a solution of Acetanilide (5 mmol) in dry DMF (15 mmol) at 0°-5° C with constant stirring POCl<sub>3</sub> (60 mmol) was added drop wise and the mixture stirred at 80°-90° C for 8 hrs. The mixture was poured into crushed ice, stirred for 5 min. and the resulting solid [1] filtered washed well with water and dried. The compound purified by recrystallization from Ethyl acetate. The suspension of substituted 2-Chloro-3-formylquinoline in 70% Acetic acid (10 mmol) was heated under reflux for 4 hrs. Upon cooling the reaction mixture a solid product [2] precipitated out which was filtered. The precipitate was washed well with water, dried and purified by recrystallization from DMF.

**Yield:** 93%, **M.P.:** 303-304° C; **Color:** Yellow; **<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ ppm:** 7.25(m, 1H, H-7), 7.35(m, 1H, H-8), 7.66(m, 1H, H-6), 7.92(m, 1H, H-5), 8.50(d, 1H, H-4), 10.24(s, 1H, CHO), 12.23(s, 1H, OH); **FTIR(KBr cm<sup>-1</sup>):** 3276, 3154, 3097, 3002, 2942, 2869, 1687, 1621, 1556, 1488, 1434, 1141, 1106, 898, 756. **MASS SPECTRA:** [M+] 174.05

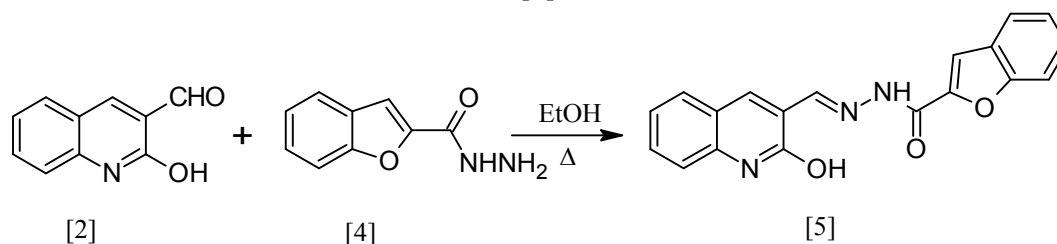
## 2.2. SYNTHESIS OF BENZOFURAN-2-CARBOHYDRAZIDE [4]:



Benzofuran-2-carbohydrazide was synthesized according to literature procedure <sup>[XXVIII]</sup>. The mixture of Salicylaldehyde (3.5 g, 0.029 M), K<sub>2</sub>CO<sub>3</sub> (7.5 g, 0.054 M), and Ethyl bromoacetate (7.64 g, 0.046 M) in ethyl alcohol (15 ml) was refluxed for 6 h. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed with water, 1N NaOH and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The mixture of hydrazine hydrate (15 ml) and ethyl benzofuran-2-carboxylate [3] (0.01 M) in ethanol was stirred at 0-5 °C for 30 min. The reaction was monitored by TLC (hexane: ethyl acetate, 4:6). Then, the reaction mixture was stirred at room temperature to obtain benzofuran-2-carbohydrazide [4] as a colorless solid product. This was filtered and washed with ethanol and dried.

**Yield:** 78%, **M.P.:** 190-192° C. **Color:** White, **<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ ppm:** 10.010 (s, 1H, NH-CO); 7.74 (d, 1H, Ar-H); 7.62 (d, 1H, Ar-H); 7.49 (s, 1H, Furan-H); 7.43 (t, 1H, Ar-H); 7.30 (t, 1H, Ar-H); 4.56 (bs, 2H, NH<sub>2</sub>). **FT-IR (in KBr):** 3324, 3178, 3114, 3019, 1660, 1600, 1546, 1454, 1328, 1089, 823, 736 cm<sup>-1</sup>. **Mass spectra:** 177 (M + 1).

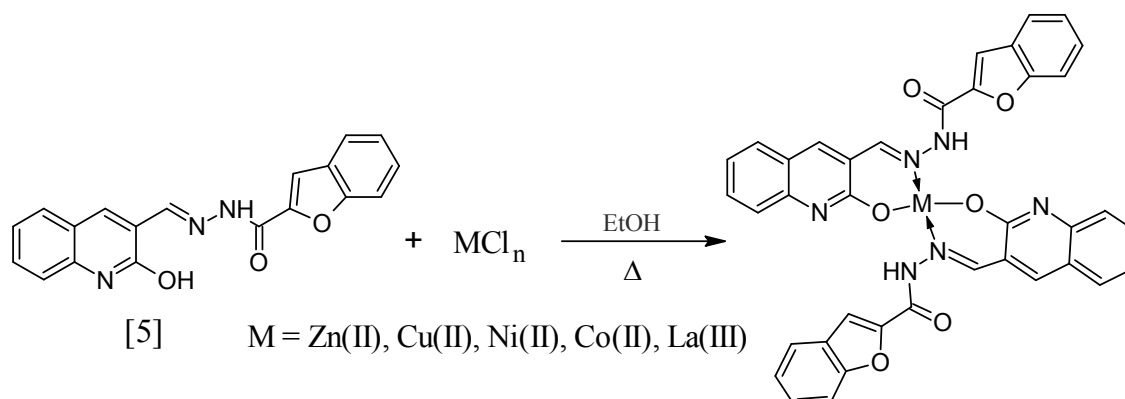
### 2.3. SYNTHESIS OF N'-[(E)-(2-HYDROXYQUINOLIN-3-YL)METHYLIDENE]-1-BENZOFURAN-2-CARBOHYDRAZIDE [5]:



0.01 mol of 2-hydroxyquinoline-3-carbaldehyde and 0.01 mol of 1-benzofuran-2-carbohydrazide taken in round bottom flask containing 10 cm<sup>3</sup> of ethanol. Reaction mixture was refluxed for 45 min. Completion of reaction is checked with TLC. Upon cooling the reaction mixture a solid product [5] precipitated out which was filtered, dried and purified by recrystallization from ethanol.

**M.P.:** stable up to 300<sup>0</sup>C (not melt up to 300<sup>0</sup>C); **Color:** Yellow; **<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ ppm:** 7.22(d, 1H), 7.40-7.41(m, 2H), 7.60(m, 2H), 7.62(m, 1H), 7.79(m, 1H), 8.12(m, 2H), 8.35(s, 1H), 8.56(d, 1H), 10.84(s, 1H), 12.23(s, 1H); **FTIR (KBr cm<sup>-1</sup>):** 3376, 3153, 3106, 3006, 2958, 2894, 2862, 1668, 1616, 1563, 1432, 966, 760. **MASS SPECTRA:** [M<sup>+</sup>] 331.17

### 2.4. SYNTHESIS OF METAL COMPLEXES:



N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide 0.050 mmol was dissolved in 10 ml of absolute alcohol in round bottom flask fitted with reflux condenser and calcium chloride guard tube. Corresponding metal salt (CuCl<sub>2</sub>, NiCl<sub>2</sub>, CoCl<sub>2</sub>, ZnCl<sub>2</sub>, LaCl<sub>3</sub>) (0.025 mmol) was added and stirred the reaction mixture, finally 0.050 mmol Potassium hydroxide was added and reaction mixture was refluxed for 5 hours in water bath. It was cooled and filtered the solid separated and dried in oven at 70-80<sup>0</sup>C.

### 3. ANTIMICROBIAL ACTIVITY

Ditch plate method is performed for these compounds as all of these compounds were insoluble in water. Sterile Nutrient agar plate was taken and ditch of 1cm x 1cm x 8cm was made across the medium plate. Then test chemical was mixed with molten and cooled sterile Nutrient agar butt of 3 ml and poured in previously formed ditch and allowed to solidify. After solidification four test organisms (two Gram negative organisms such as *Escherichia coli* and *Salmonella typhi* and two Gram positive organisms such as *Corynebacterium diphtheriae* and *Staphylococcus aureus*) streaked across the ditch in which chemical compound to be tested was added. The plates were incubated at 37<sup>0</sup> C for 24 hrs. Plates were observed for zone of inhibition. Series of metal complexes and ligand were evaluated for the antimicrobial activity and the results are summarized as follows

Sr.No.	Compound	<i>E. coli</i>	<i>S. typhi</i>	<i>C. diphtheriae</i>	<i>S. aureus</i>
01	Hydrazone	-	-	-	-
02	Cu-complex	+	-	+	+
03	Ni-complex	+	+	-	+
04	Co-complex	-	-	-	-
05	Zn-complex	+++	++	++	++
06	La-complex	+	-	-	-
07	Streptomycin	+++	+++	+++	+++
Key: - = No inhibition of test organism + = Inhibition of Test organism					

**Composition of Nutrient Agar Medium:** (Peptone-10 gm, Meat Extract- 3 gm, NaCl- 5 gm, Distilled Water – 1000 ml, pH- 7)

#### 4. RESULT AND DISCUSSION:

Synthetic strategies adopted to obtain the target compounds are depicted in above schemes. FTIR, <sup>1</sup>H-NMR and Mass Spectral data are in agreement with the proposed structures of all the synthesized compounds. The hydrazones obtained from the 1-benzofuran-2-carbohydrazide showed carbonyl amide stretching at 1668 cm<sup>-1</sup> and N–H bands at 3376 cm<sup>-1</sup>. The strong peak in the region 1616 cm<sup>-1</sup> in the ligand was assigned to azomethine (HC=N). Upon complexation azomethine (HC=N) shows negative shift in La (III) complex, but in case of Ni (II) complex positive shift was observed in IR spectra. Collectively these observations signify the coordination of azomethine nitrogen. <sup>1</sup>H NMR data is also in agreement with the formation of hydrazones. <sup>1</sup>H NMR spectrum of [5] showed one singlet at δ 8.56, one singlet at δ 10.84 and δ 12.23 which were attributed to the CH, NH, and OH protons, respectively. The mass spectrum of compound [5] showed a molecular ion peak at m/z 331.17 which is in conformity with the molecular formula, C<sub>19</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>. *N'*-[(*E*)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide shows weak emission at 522 nm for the absorption wavelength 356 nm. Formation of metal complex improves emission intensity as well as show blue shift for Zn (II) and La (III) complexes. Zn (II) complex shows most intense emission. Antimicrobial activity enhanced upon complexation of hydrazone with different metal complexes. Zinc complex shows good antimicrobial activity against *Escherichia coli*, *Salmonella typhi*, *Corynebacterium diphtheriae* and *Staphylococcus aureus* as compared with other metal complexes.

#### 5. ACKNOWLEDGMENT:

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## 6. FIGURES, TABLES AND SPECTRA:

Figure 1: FTIR Spectra of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide.

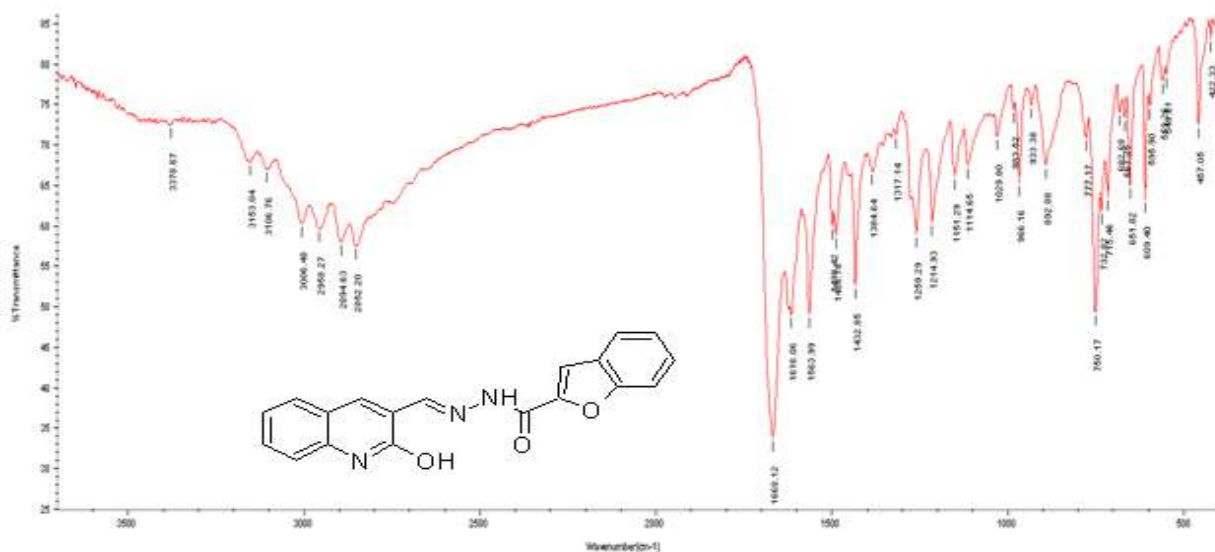


Figure 2: MASS Spectra of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide.

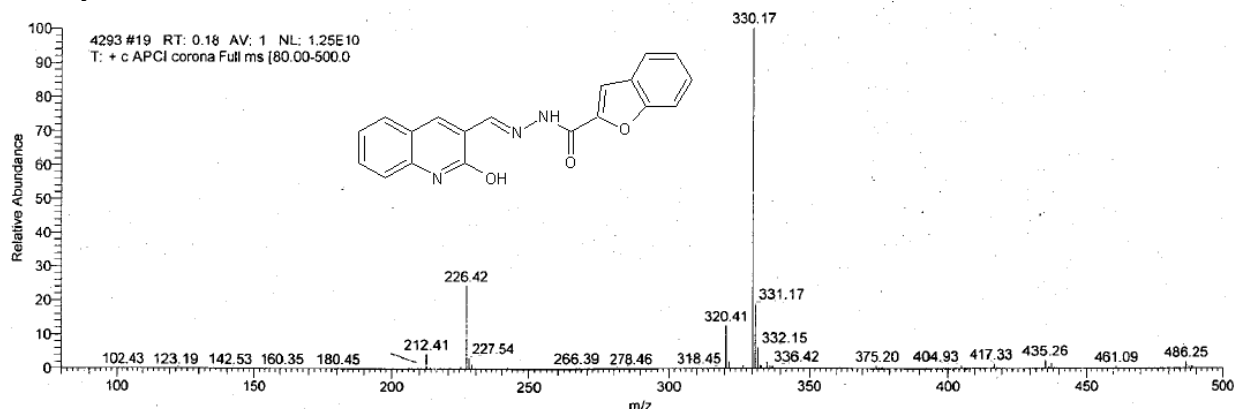
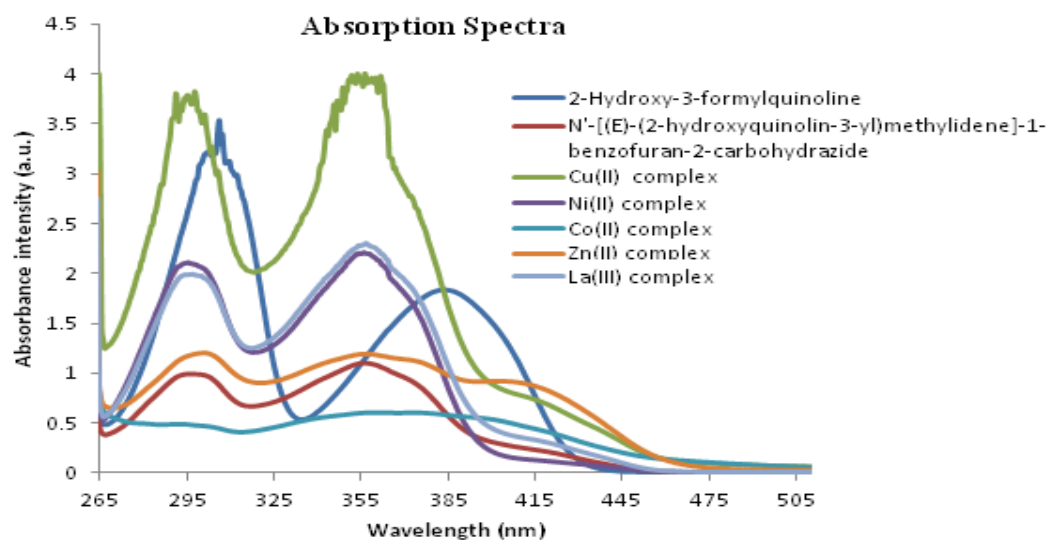


Table 1: The excitation and emission wavelength with intensity:

Compound	Color	$\lambda_{\max}$ Absorption (intensity)	$\lambda_{\max}$ Emission (intensity)
2-Hydroxy-3-formylquinoline	Faint yellow	306.50 (3.535)	458.0 (1.696)
N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide	Bright yellow	356.00(1.101)	522.0 ( 3.473)
Cu(II) complex	Greenish yellow	356.50 (4.000)	524.0 (10.485)
Ni(II) complex	Yellow	356.00(2.206)	526.0 (14.660)
Co(II) complex	Grayish yellow	360.50 (0.602)	526.0 (27.654)
Zn(II) complex	Dark yellow	<b>356.50 (1.190)</b>	<b>508.0 (222.200)</b>
La(III) complex	Yellow	357.00(2.311)	519.0 (56.908)

**Figure 3: Absorption Spectra of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide and its metal complex.**



**Figure 4: Emission Spectra of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide and their metal complexes.**

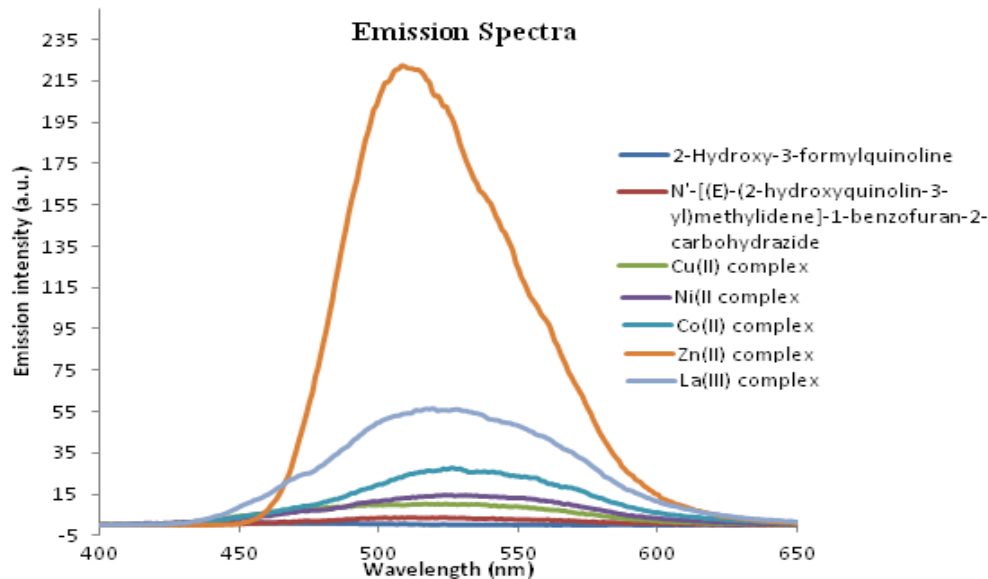


Figure 5: Graph of comparative intensity of emission of N'-[(E)-(2-hydroxyquinolin-3-yl)methylidene]-1-benzofuran-2-carbohydrazide and its metal complexes.

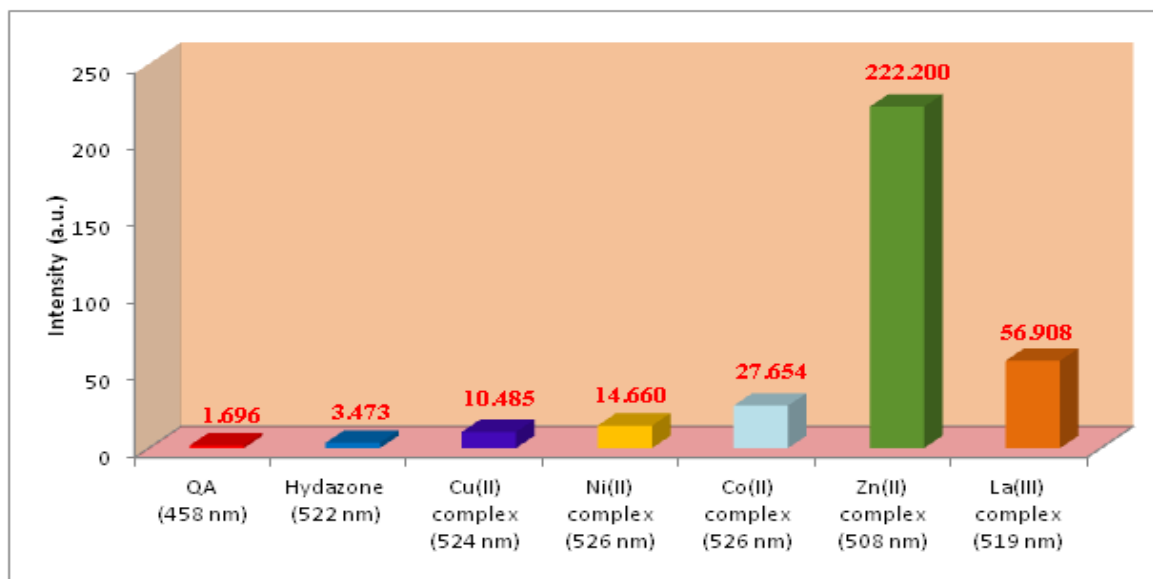


Figure 6: Effect of UV light:

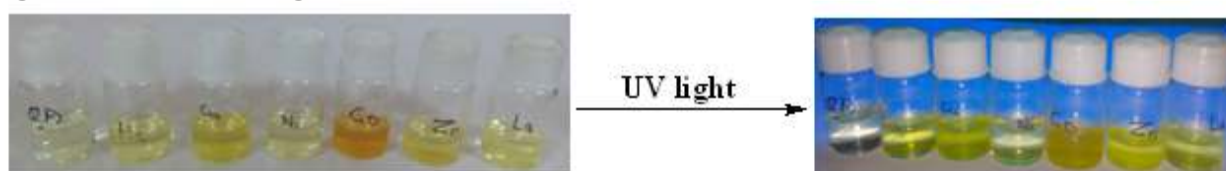


Figure 7: Biologically study images:

Ligand



Cu-complex



Ni-Complex



Co-Complex



Zn-Complex



La-Complex



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