## POTENT CYTOTOXIC AND ANTIOXIDANT CAPACITIES OF NOVEL ISONIAZID GLEANED COPPER AND COBALT COMPLEXES

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#### **ABSTRACT:**

The hexacoordinated mixed ligand Cu(II) and Co(II) complexes have been synthesized from the condensation reactions between isoniazid and salicylaldehyde. The synthesized ligand and its metal complexes were characterized by spectral techniques such as elemental analysis, molar conductance, magnetic susceptibility, ultraviolet-visible spectroscopy (UV-Vis), Fourier transform infrared spectroscopy (FTIR), 1H and 13C nuclear magnetic resonance spectroscopy (NMR), gas chromatography mass spectrometry (GC-MS) and high resolution mass spectrometry (HRMS). The high molar conductance of the complexes showed their electrolytic nature. The octahedral geometry has been proposed for the complexes. The stretching vibration of imine group was observed in FTIR of the ligand and its shifts to lower frequency in complexes confirmed the formation of metal complexes. The electronic spectrum of complexes exhibited the charge transfer, d-d transitions in accordance with their proposed geometry. The mass spectral data also proved the structure of complexes as octahedral. DPPH antioxidant studies revealed copper complex exhibits most efficient radical scavenger. The compounds have been investigated for their cytotoxicity activity on HeLA Cervical cancer cells. Copper complex (40µg/ml  $\pm 2µg/ml$ ) showed promising cytotoxicity in the tumor cell line.

Keywords: Antioxidant, Cytotoxic, Electrolytic, Isoniazid, Octahedral

### **INTRODUCTION:**

Isoniazid(INH) is a foremost antitubercular agent whose derivatives and their metal complexes have been investigated by a lot of researchers for their antitubercular activities but their potentials as anticancer agents have still remained unexplored [1-5]. Their efficiency as anticancer agent has been published only by a few researchers. Hydrazones are also portrayed to acquire a lot of pharmacological activities, such as being anticancer agents [6]. Schiff base metal complexes have been broadly studied due to their industrial, antibacterial, antifungal, antiviral, anticancer, antioxidant, and herbicidal applications [7]. The tremendous number of mixed ligand metal complexes containing heterocyclic bases such as pyridine, bipyridine, 1,10-phenonthroline, etc., have been found to act as an active catalyst in industrial important reactions and they also show enormous biological responses [8,9]. Copper is notorious bio essential element and its complexes have ratified biological functions owing to their potent binding ability and positive redox potential [10]. Cu(II) complexes containing heterocyclic bases have been broadly investigated by the virtue of their strong interactions with DNA and cytotoxic activity [11,12]. Cobalt complexes also show interesting redox and magnetic properties that make them suitable candidate for biomedical industry. The research interest in the present work emanates from the aforesaid points. Bearing the above facts in mind, the synthesis of N'-[(E)-(2-methylphenyl)methylidene]pyridine-4-carbohydrazide and its copper and cobalt mixed ligand complexes have been reported. The antiproliferative evaluation against human cancer cell lines of the synthesized compounds have been investigated which exhibits potent and promising results. The newly designed compounds displays a

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potential source of antioxidants and serves as an effective free radical scavenger. In this context, the aim of this work was the development of antitumoral as well as anticancer evaluation. The anticancer screening will be based on measuring the anticancer activity of the complexes on cancer cell lines such as human cervical cancer cell lines (HeLa), Human laryngeal epithelial cancer (Hep2), Human liver cancer (HepG2) and Human breast cancer (MCF-7). Hydrazones are also described to possess a wide range of pharmacological activities, such as being anticancer agents. The most significant part of our research has been focussed to the development of drugs active against *Mycobacterium tuberculosis*. Hydrazones belonging to azomethine class of compounds have attracted the attention of many chemists due to their wide range of pharmacological activity with structural flexibility and ligating behavior. Hydrazones distinguished by the presence of two interlinked nitrogen atoms are most interesting, because they can function as antimicrobial, antitubercular and antitumor agents.

### MATERIALS AND METHODS:

#### **Chemicals and measurements:**

The chemicals used in the present work, viz.., isoniazid, salicylaldehyde, DPPH (2,2-diphenyl-1picrylhydrazyl), were purchased from Merck while copper and cobalt chlorides, 1,10-phenanthrolein, 1,1-diphenyl-2-picrylhydrazyl (DPPH) were obtained from Sigma-Aldrich. Solvents like ethanol, methanol, chloroform, dichloromethane, N,N-dimethylformamide(DMF), dimethyl sulfoxide (DMSO) and petroleum ether were of analytical grade and purchased from Alfa Aesar and used without purification. Ultraviolet-visible absorption spectra were recorded on JASCO (V-670 PC) UV-Visible Spectrophotometer with a wavelength range of 200-1000 nm at room temperature. Fourier Transform Infrared spectroscopy (FT-IR) spectra were analyzed on the Shimadzu FTIR spectrophotometer equipment model: IR Affinity-1 with ATR mode, scanning from 500 to 4000 cm<sup>-1</sup>. GC-MS analyses were performed by using Perkin Elmer MS spectra and were compared with the spectra gathered in the National Institute of Standards and Technology (NIST) library. <sup>13</sup>C and <sup>1</sup>H NMR spectra were recorded with a Bruker Avance 400 instrument. The spectra were measured in DMSO-D<sub>6</sub> as a solvent. High-Resolution Mass Spectrometry was used for the acquisition of mass spectra. The carbon, hydrogen, and nitrogen contents were determined for the prepared ligand and its metallic complexes using a Carlo Erba 1108 analyzer. The molar conductivity ( $\Lambda_m$ ) values of the synthesized metal complexes dissolved in DMSO  $(1 \times 10^{-3} \text{ M})$  at room temperature were determined using a Systronic Model-304 digital direct reading conductivity meter. The magnetic sensitivities of the prepared solid metal complexes were measured at room temperature by employing the Gouy method. Copper sulphate was used as calibrant. **Preparation of ligand (HL)L:** 

The ligand, N-[(*E*)-(2-methylphenyl)methylidene]pyridine-4-carbohydrazide was prepared following a literature method [5] where 1.371 g (0.01 mol) of isoniazid was slowly added to a spherical flask containing 1.06 g (0.01 mol) of salicylaldehyde dissolved in 20mL of ethanol and few drops of HCl was added to maintain the pH. The mixture was left to stir under reflux for 4 h, during which yellow coloured crystalline substance was formed. The obtained substance was then filtered and washed several times with distilled water followed by absolute ethanol and dried *in vacuo* over silica gel, yield=89%. The schematic representation of the Schiff base is given in Figure 1.



Figure 1. Synthesis of the Schiff base

### Synthesis of metal complexes

An ethanolic solution of the metal(II) chlorides (0.003) was mixed with a suitable amount of an ethanolic solution of the ligand and stired for 3 h on magnetic stirrer under reflux at 70°C. To the above mixture, an ethanolic solution of 1,10-phenanthrolein (0.003 mol) was added in a 1:1:1 molar ratio and refluxed for about ca. 2 h. A precipitate obtained filtered and washed with distilled water and then with absolute ethanol. The solid was then dried in vacuo over silica gel.

### **CYTOTOXICITY STUDIES:**

### Maintenance of cell lines:

HeLA Cervical cancer cells were maintained and grown in a humidified incubator at 37 °C with 5% CO<sub>2</sub>. Cells were grown as a monolayer in plastic tissue culture T25 flasks in Dulbecco's Modified Eagle's Medium (DMEM) (Gibco, Grand Island, New York, USA). The medium was supplemented with 10% fetal bovine serum (FBS) (Gibco, Grand Island, New York, USA) and antibiotics (penicillin 50 IU/mL, streptomycin 3.5 µg/mL and gentamycin 2.5 µg/mL) (Gibco, Grand Island, New York, USA).

## Cell viability assay:

Cell viability was determined by MTT assay. We used HeLa cervical cancer cell lines for this study. HeLa cervical cancer cell lines (5  $\times 10^3$  cells/well) were seeded in 96-well culture plates. After 24hrs of incubation, overnight serum starvation was given to cells. cells were treated with various concentrations of copper and ligand complex for 24hrs, followed by the addition of 100µl MTT(0.5mg/ml) at 37°C for 4 hrs and 150 µl of DMSO was added to each well and incubated for 30mins at 37°C. Optical density (OD) was measured at 550 nm using a microplate reader (Bio Rad, CA, USA). Cell viability was expressed as a percentage of untreated cells.

### **Antioxidant studies :**

The evaluation of antioxidant activity of newly synthesized compounds was done by DPPH radical scavenging activity assay [25]. Different concentrations (100, 50, 25, and 12.5 µg/ml) of Schiff base metal complexes were weighed respectively and dissolved in DMSO. Then, 5 ml of 0.1 mM methanolic solution of DPPH was added to each of the test tube containing the sample and the tubes were shaken vigorously. They were then allowed to stand at room temperature for 30 min. The control was prepared without any compound and methanol was used for baseline corrections in absorbance odds ratios of samples measured at 517 nm. For each concentration, the decrease in the absorbance was recorded and percentage quenching of DPPH was calculated. The radical scavenging activities were expressed as percentage scavenging activity and were calculated by the following formula.

% Radical scavenging activity 
$$= \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

### **RESULT AND DISCUSSION:**

The complexes of the type [MLXCl]Cl where, M=Cu(II) and Co(II), L=tridentate Schiff base, X=1,10phenanthroline were synthesized by the reaction of tridentate ligand, metal(II)chlorides and 1,10phenanthroline in a 1:1:1 molar ratio in ethanol. In DMSO the complexes showed high molar conductance value (58, 54  $\Lambda$ M/S cm<sup>2</sup> mol<sup>-1</sup> for Cu(II) and Co(II) complexes respectively) indicates the electrolytic nature.

### UV-Vis Spectra analysis and magnetic measurement:

The electronic absorption spectrum of the ligand showed strong absorption bands at 220 and 284 nm which is assigned to  $\pi \to \pi^*$  transition and a band at 331 nm attributed to  $n \to \pi^*$  transition. The Co(II)

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complex showed an absorption band at 327 nm assigned to  ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{1g}(P)$  transition [13,14] which confirms the coordination through azomethine nitrogen. With respect to wavelengths of bands shows a blue shift. Additionally, one new band was observed for d d-d transition at 460 nm attributed to  ${}^{4}T_{1g}(F)$  $\rightarrow {}^{4}A_{2g}$  transition. This band is assigned to high-spin octahedral cobalt(II) complex. Co(II) complex showed a magnetic moment value of 4.51 B.M., which further supports the octahedral geometry. According to electronic spectra of a Cu(II) complex, the d-d transition of strong absorption band shows at 612 nm attributed to  ${}^{2}E_{g} \rightarrow {}^{2}T_{g}$  transition suggesting a distorted octahedral geometry [15-17] which was further confirmed by its magnetic moment value of 1.72 B.M.

#### FT-IR spectra analysis:

The stretching vibrations C=N, C=C, C=O, and M-N were obtained for the structural confirmation of ligand and metal complexes [18]. The FT-IR spectra of the ligand and its metal complexes are shown in Figure 2. The FT-IR spectra of the ligand exhibits a band at 1597 cm<sup>-1</sup> which is assigned to the C=N stretching vibrations. This is a unique characteristic feature of Schiff bases. This band shifts to lower frequencies in both the complexes indicating involvement of azomethine nitrogen in coordination with metal ion [16]. The M-N band appeared at 465 cm<sup>-1</sup> and 472 cm<sup>-1</sup> for Co(II) and Cu(II) complexes respectively [19,20] while there is no band for M-N in the ligand. The IR spectrum of the complexes showed new band in the region 502-598 cm<sup>-1</sup> assigned to M-O stretching vibrations, hence the ligand binds to the metal ions through N and O respectively, further confirmation of Schiff base metal complex formation [19]. The characteristic stretching bands for (C=C) appeared at 1509 cm<sup>-1</sup>, 1548 cm<sup>-1</sup>, 1541 cm<sup>-1</sup>, 1511 cm<sup>-1</sup>, 1564 cm<sup>-1</sup> and 1538 cm<sup>-1</sup>. The Spectra of the Co(II) and Cu(II) complexes, showed a band at 843 cm<sup>-1</sup> and 850 cm<sup>-1</sup> for M-Cl bond [21]. Hence, the Metal complexes coordinated to chloride ions were confirmed.

### **GC-MS Analysis:**

The mass spectrum of the ligand was acquired using a gas chromatography-mass spectrometer. The molecular ion peak was observed at 241.37 m/z for the ligand. All the data of molecular ion peaks, base peaks, and other peaks are in accordance with the fragmentation pattern of the ligand.



Figure 2. FT-IR spectra of ligand and metal complexes of Cu (II) and Co (II)

## ISSN: 2278-4632 Vol-15, Issue-02, No.04, February: 2025

## NMR ANALYSIS:

The NMR analyses (<sup>1</sup>H NMR and <sup>13</sup>C NMR) of the ligand were performed to elucidate the structure is shown in figure 3. TMS was taken as an internal standard, and grade solvent DMSO was employed. Distinct multiplicity and resonance intensity patterns are assigned to the signals to be integrated from <sup>1</sup>H NMR spectra. The proton signal of H-6 (proton associated with Schiff base structural feature, of HC=N-) in ligand appeared at  $\delta = 8.55$  ppm supported the formation of azomethine group [22] and the signal observed at (H-8)  $\delta = 11 - 11.1$  (S) is attributed to the phenolic –OH group, and NH=N singlet at  $\delta =$ 12.35 - 12.4 respectively. C=C at  $\delta = 7.9$ -8 doublet (H-5),  $\delta = 7.3$ -7.34 triplet (H-3) and  $\delta = 6.97$ -6.95 triplet (H-2). C=C doublet of  $\delta = 7.6$ -7.62 (H-4) and  $\delta = 6.95$ -6.92 (H-1).

The  ${}^{13}$ C NMR spectra: Carbon C-1 in the range of 161.42ppm, 157.96(C2), 149.64(C3), the carbon signal of C4 associated with Schiff base structural feature in ligand appeared in the range of 143.71ppm, 141.68 (C5), 132.26(C6), 129.62 (C7), 122.62 (C8), 119.91 (C9), 119.16 (C10) and 116.93ppm (C11).



Figure 3. NMR analysis of ligand in DMSO D<sub>6</sub>

### **HRMS Analysis:**

Mass spectra of ligand and metal complexes were acquired using a high-resolution mass spectrometer. The spectrum of the ligand (shown in figure 4) confirms the probable formula ( $C_{13}H_{11}N_3O_2$ ) by showing a peak at 241 m/z, which is equivalent to its molecular weight and it was also confirmed by 'nitrogen rule'.



Figure 4. HRMS spectrum of ligand

## ISSN: 2278-4632 Vol-15, Issue-02, No.04, February: 2025

The mass spectrum of copper complex confirms the probable formula as  $[C_{25}H_{18}N_5O_2CoCl]Cl$  by showing a peak at 555.07 m/z, implying an odd number of nitrogen atoms in its molecular structure. The molecular ion peaks established by the ligand and its metal complexes are in good agreement with the structure proposed by elemental analysis magnetic and spectral studies and is given in figure 5. The series of peaks in the range of 194, 224, and 478 m/z may be assigned to various fragments.



## **BIOLOGICAL SCREENING:**

### **Cytotoxicity Studies:**

We studied the cytotoxic effect of ligand and copper complex in HeLa cervical cancer cells. We found the anti-proliferative activity of copper complex  $(40\mu g/ml \pm 2\mu g/ml)$  and ligand  $(60\mu g/ml \pm 2\mu g/ml)$  in the tumor cell line (shown in figure 6). This data provides evidence that copper shows more potent anticancer agent than the ligand and thus will show lower systemic toxicity when administered to the patient.

### ANTIOXIDANT ASSAY:

*N*'-[(*E*)-(2-methylphenyl)methylidene]pyridine-4-carbohydrazide and its Cu(II) and Co(II) complexes were evaluated for DPPH radical scavenging activity. Cu(II) and Co(II) complexes showed remarkable antioxidant potential with IC<sub>50</sub> values  $25.53 \pm 1.83$ ,  $29.75 \pm 3.81 \mu$ M respectively than the standard drug tert-butyl-4-hydroxyanisole (IC<sub>50</sub> =44.7  $\mu$ M). The ligand (IC<sub>50</sub>= 49.67 $\pm$ 1.51 $\mu$ M) was found to be lesser activity than the standard drug. Copper complex showed significant antioxidant activity than cobalt complex. This significant activity of the complexes might be due to the stabilization of free radical by the metal ion.



Conc of Ligand in µg/ml

I B Cytotoxic Effect of Copper Complex



Conc of Copper complex in µg/ml

## Figure 6. Antiproliferative activity by MTT assay of Ligand (1A) and Copper complex (I B) in HeLa (Cervical Cancer) cell line

## **CONCLUSION:**

In this work, the tridentate and its mixed ligand Cu(II) and Co(II) complexes were synthesized and characterized by various spectroscopic techniques such as elemental analysis, molar conductance, magnetic susceptibility, UV-Vis, FT IR, <sup>1</sup>H and <sup>13</sup>C NMR, GC-MS and HRMS. The high molar conductance revealed the electrolytic nature of the metal complexes. The synthesized compounds were investigated for anti-proliferative and DPPH radical scavenging activity. The results showed that copper complex have potent anti-proliferative and radical scavenging ability. The synthesized anticancer active drug met the challenge to reduce the cost of drug that is used in current market.

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