***ChemSearch Journal 10(1): 79 – 86, June, 2019***
Publication of Chemical Society of Nigeria, Kano Chapter

Received: 16/05/2019 Accepted: 27/06/2019

# Synthesis and Characterization of some Transition Metal Complexes of *N*'-[(*E*)-(1*H*-indol-2-yl)methylidene]pyridine-4-carbohydrazide

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## ABSTRACT

*N*'-[(*E*)-(1*H*-indol-2-yl)methylidene]pyridine-4-carbohydrazide was prepared by refluxing indole-2-carbaldehyde and isonicotinic hydrazide in ethanol for 4 hrs. $Fe^{3+}$, $Co^{2+}$ and $Cu^{2+}$ complexes of the hydrazone ligand were similarly prepared and the compounds characterized spectrophotometrically. The melting point and conductivities of the ligand and complexes were recorded. The asymmetric hydrazone and the metal complexes obtained showed melting points/decomposition temperature range 156 - >300 °C. Two ligands was found to coordinate to the metal centre via the carbonyl O and azomethine N along with two chloride ions giving rise to octahedral geometry. Ligand and complexes are insoluble in water, ethanol and other common organic solvents but soluble in DMSO and DMF. Molar conductivity values obtained (2.55-7.23 $cm^{-2}mol^{-1}$) shows they are non-electrolytes in solution.

**Keywords**: Asymmetric, Bioactive, Hydrazone, indole, Isoniazid

## INTRODUCTION

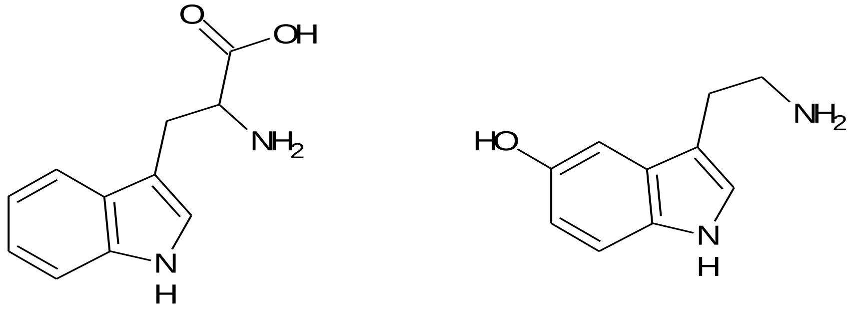
Hydrazones belong to the class of asymmetric Schiff base. This class of compounds have found several applications in catalysis and biological chemistry due to their structural and electronic chemistry (Menati *et al*, 2013). Generally, hydrazones and other hydrazine derivatives have received great attention due to their biological, therapeutic and physiological activities and these activities are enhanced on coordination with metal ion (EL-Saied *et al,* 2011; Chowdhury *et al*, 2008; Grochala *et al*, 2001; Hueso-Urena *et al*, 2000; Nwabueze, 1996); Abd El Waheed *et al*, 1992). This is because metal ions are well recognised as tuneable materials owing to the dependence of their redox potential on the electronic/structural properties of the ligands (Grochala *et al*, 2001). The reversibility nature of hydrazones has endeared the class of Schiff base as a candidate of choice as library in the emerging dynamic combinatorial chemistry (DCL). This new interest has witnessed the screening of several low and medium molecular weight hydrazone DCL which is providing lead in drug discovery (Williams and Lehn, 2004; Regis and Ivan, 2003; Bunyapaiboonsri *et al*, 2001; Lehn, 1997).

Similarly, recent interest in the investigation of certain complexes, principally as well defined precursor material for synthetic chemistry lies in their rich reaction chemistry, including alteration of molecular nitrogen (Oldham *et al*, 2002). The coordination mode of the hydrazone Schiff base is well established to be through the carbonyl oxygen and the azomethine nitrogen (Nwabueze and Salawu, 2007; Hermes-Lima *et al*, 2001). However, recent findings reveal that depending on pH, those derived from isoniazid can coordinate through the nitrogen atom of the pyridine ring of isoniazid. This development might give rise to a network of redox and structural events which are expected to have useful applications (Ramadevi, *et al*, 2014).

Whether for effective synthesis of metal complexes as precursor materials and/or effective remediation of metal pollutants on the one hand and having good knowledge of the nature and interaction/association of the hydrazones ligand for exploiting its application in bio-mimic, biological agents and indeed supramolecular assemblies on the other hand, or even in catalysis studies, a detailed understanding of the structural and physical properties of transition metal complexes with the Schiff base is required.

Literature search reveal that despite large volume of Schiff base derivatived from aldehydes and primary amines, there is no previous report involving indole carboxaldehyde and isoniazid. Isonicotinic hydrazide is a well-known anti tuberculosis, antitumor and antibacterial agent (Nwabueze and Salawu, 2007; Hermes-Lima *et al*, 2001). Our choice of this starting material is targeted at bio-compatible materials that will give a new product with diverse structural chemistry thereby enhancing it activity as drug candidate with minimal or no toxic substrate, hence the choice of an indole based compound.

The indole moiety with its aromatic benzene ring fused to a five membered nitrogen containing pyrrole ring has well established role in medicinal chemistry (Kaushik *et al*, 2013; Biswal *et al*, 2012; Sharma *et al*, 2010). Indole derivatives are some of the vital naturally occurring biomolecules (Fig 1), tryptophan is an essential amino acid which serves as constituent of several proteins, and serotonin; a natural neurotransmitter in the central nervous system, cardiovascular and gastrointestinal systems (Kaushik *et al*, 2013).



2-amino-3-(1*H*-indol-3-yl)propanoic acid (Tryptophan)

3-(2-aminoethyl)-1*H*-indol-5-ol (Serotonin)

Fig1: structure of some naturally occurring indole based biomolecules

Properly derivatised moieties based on indole framework have played diverse, yet significant roles as antibacterial, antifungal (Raju *et al*, 2015), anticonvulsant, tranquilizing, antimicrobial (El-Gendy, 2008) as well as anticancer, antihypertensive agents, there are known inhibitor of acetylcholine esterase (ACE) (Sharma *et al*, 2010). Over thirty marketed drugs in these areas have been reported (Kaushik *et al*, 2013; Biswal *et al*, 2012). Here we report the synthesis and spectroscopic characterization of a hydrazone derived from isoniazid and indole carboxaldehyde and its complexes with Fe$^{III}$, Co$^{II}$ and Cu$^{II}$.

## MATERIALS AND METHODS

### Reagents and solvents

Isonicotinic acid hydrazide and indole-2-carboxaldehyde were obtained from Sigma-Aldrich while, the metal salts, iron (III) chloride, cobalt (II) chloride and cupper (II) chloride hexahydrate were all purpose reagents. Solvents used were analytical grade (AR) from Sigma Aldrich and were used without further purification.

### Instrumental measurement

Proton and $^{13}$C NMR spectra of the ligand were obtained from Agilent-NMR-vnmrs400 Spectrometer. Infrared spectra were recorded as nujol disc on Agilent Mattson Genesis II FTIR spectrophotometer (400-4000 cm$^{-1}$). The conductivity and melting point/decomposition temperature measurements were made on Conductor Meter model DDSJ 308A and model 441306114 melting point apparatus respectively.

### Preparation of *N*'-[(*E*)-(1*H*-indol-2-yl)methylidene]pyridine-4-carbohydrazide

Ethanolic solution of isonicotinic acid hydrazide (0.514 g; 0.056 moles) was added to 0.549 g (0.056 moles) of indole-2-carbaldehyde in 40ml absolute ethanol in a round bottom flask. The mixture was refluxed for four hours over steam bath. The product was collected in a beaker and left to crystallize. The crude solid was separated by filtration and then recrystallized from ethanol and dried over calcium chloride in vacuum desiccators and then weighed (Yield 83 %). Selected vibrational frequencies: FTIR: 1659(C=O), 1551(C=N); 1499(C-N), 3543, 3391(OH) 3034(NH NH$_2$), 2929.

### Preparation of the complexes

**Fe$^{3+}$- complex**

Iron (III) chloride (0.19 g ; 0.1 moles) in 12.5 mL distilled water was added to hot aqueous solution of 0.93 g (0.3 moles) of indole carbaldehyde isonicotinoylhydrazone under stirring. The mixture was left to reflux for one hour. The brown solid formed was removed by filtration, washed with cold diethyl ether and dried over calcium chloride in vacuum desiccator.

(Yield 48%) Selected vibrational frequencies: FTIR: 1670(C=O), 1506(C=N); 1443(C-N), 3253; 3048(NH NH$_2$), 2851

**Co$^{2+}$- complex**

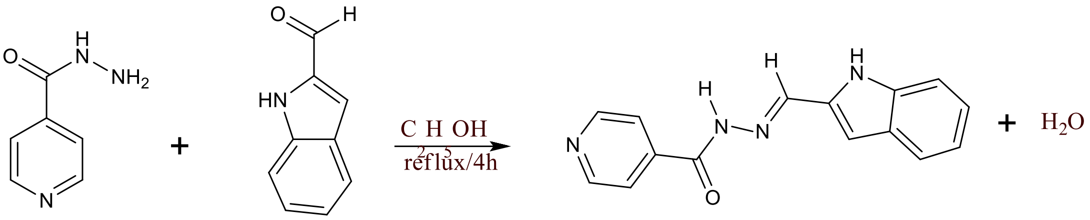
Anhydrous cobalt (II) chloride (0.309 g 0.0013mol) in 15 mL distilled water was added to hot aqueous solution of 1.00 g (0.004 moles) of indole carbaldehyde isonicotinoylhydrazone under stirring and the mixture left to reflux for one hour. The orange coloured solid obtained was removed by filtration, washed with cold diethyl ether, recrystallized and dried over calcium chloride in vacuum desiccators over calcium chloride. (Yield 64 %) Selected vibrational frequencies: FTIR: 1665(C=O), 1577(C=N); 1495(C-N), 3149b(OH, NH $NH_2$), 2851, 814(M-Cl).

**$Cu^{2+}$- complex**

Addition of aqueous solution of 0.19 g (0.0012 mol) copper (II) chloride hexahydrate, to an ethanolic solution of the Schiff base ligand 0.96 g (0.0039 mol) was transferred to a 250 mL round bottom flask and refluxed with continuous stirring on a water bath for one hour. A brown precipitate was formed, which was filtered, washed with cold ethanol and dried in a desiccator over anhydrous calcium chloride and weighed. (Yield 59 %). Selected vibrational frequencies: FTIR: 1659(C=O), 1551(C=N); 1495(C-N), 3541(OH) 3041(NH $NH_2$).

## RESULTS AND DISCUSSION

Coloured hydrazones solids were obtained via the reaction route in Scheme 1. The yield and ther physiochemical properties are shown in Table 1.



pyridine-4-carbohydrazide (Isoniazid)

1*H*-indene-2-carbaldehyde (indole-2-carbaldehyde)

*N'*-[(*E*)-(1*H*-indol-2-yl)methylidene]pyridine-4-carbohydrazide

**Scheme 1**: route to the synthesis of indole-2-cabaldehyde isonicotinoylhydrazones.

**Table 1: Some Physical properties of the ligands and complexes**

| Ligand/Complex | Formula | Formula weight | Colour | M.Pt/Dec Temp °C | %Yield | Molar Conductivity $cm^{-2}mol^{-1}$ |
|---|---|---|---|---|---|---|
| **Ligand** | $C_{16}H_{13}N_3O$ | 263.29 | Yellow | 235 | 83 | 6.37 |
| **1** | $C_{30}H_{24}Cl_2FeN_8O_2$ | 655.31 | Brown | 156 | 49 | 4.27 |
| **2** | $C_{30}H_{24}Cl_2CoN_8O_2$ | 658.40 | Orange | >300 | 64 | 2.55 |
| **3** | $C_{30}H_{24}Cl_2CuN_8O_2$ | 663.02 | Brown | >300 | 59 | 7.23 |

The ligand was sufficiently soluble in ethanol and other common organic solvents, it was however insoluble in water. The complexes were insoluble in ethanol and most organic solvents tested, but soluble in DMSO and DMF.

**Ligand NMR Analysis**

The $^1H$ and $^{13}C$ spectra of the ligand are presented in Fig 2 and 3. In the proton NMR spectrum, the aromatic C-H of the indole carbaldehyde isonicotinoyl hydrazone ligand gave sets of multiplet signals from 8.33 – 10.03 ppm. These signals are due to the C-H on the indole and pyridine rings of the ligand moiety. The multiplet signal centred at around 12.9 ppm is assigned to O-H signal arising from the hydrogen bonding interactions of the hydrazone ligand (scheme 2). The N-H signal appear at 3.7 ppm. These signals and those of the $^{13}C$ signify that these groups on the ligand resonate under the influence of hydrogen bonding. The C of the carbonyl group on the ligand gave a signal at 162 ppm.

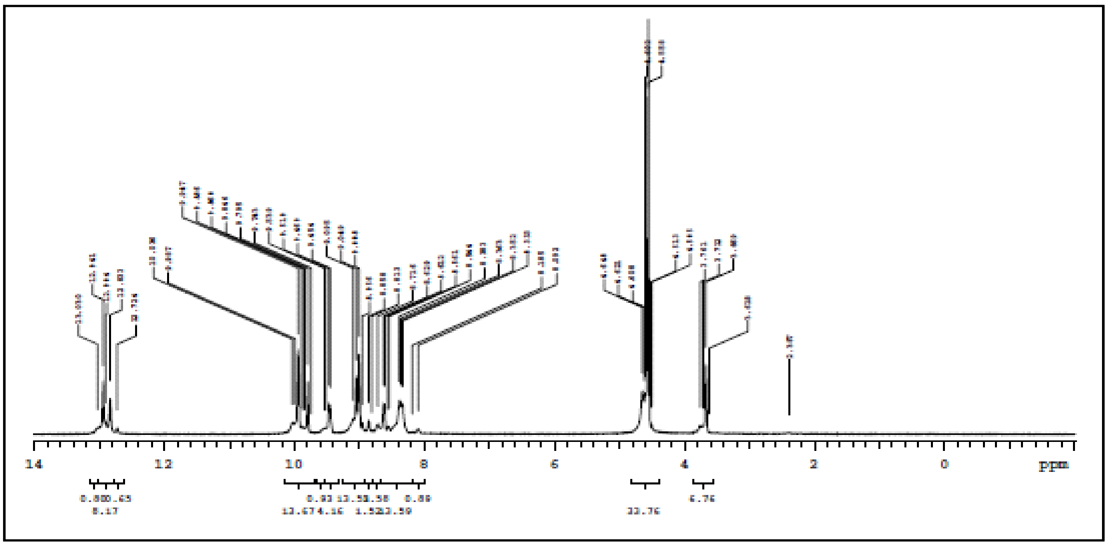


Fig 2. 1H NMR spectrum pf the ligand

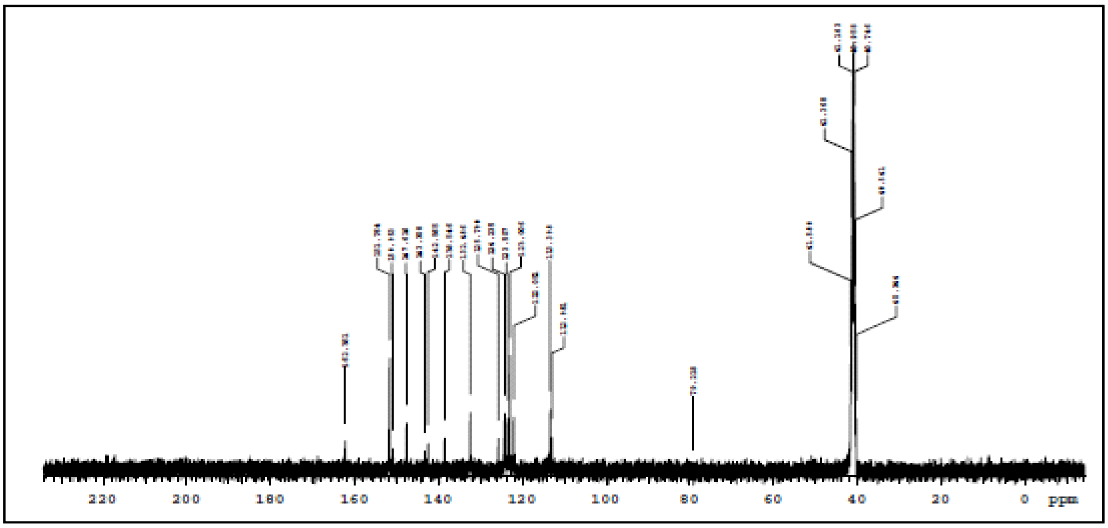
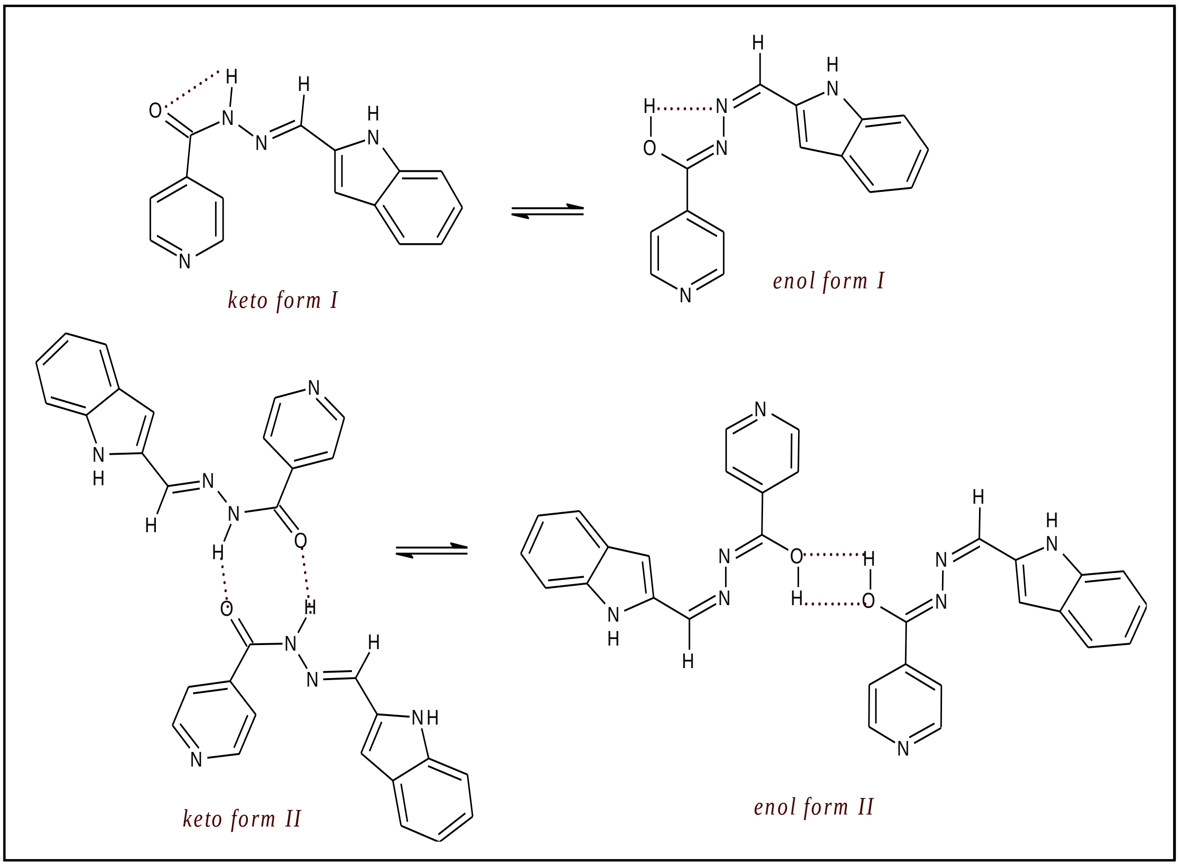


Fig 3: 1H NMR spectrum of the indolecarbaldehyde isonicotinoyl hydrazone ligand

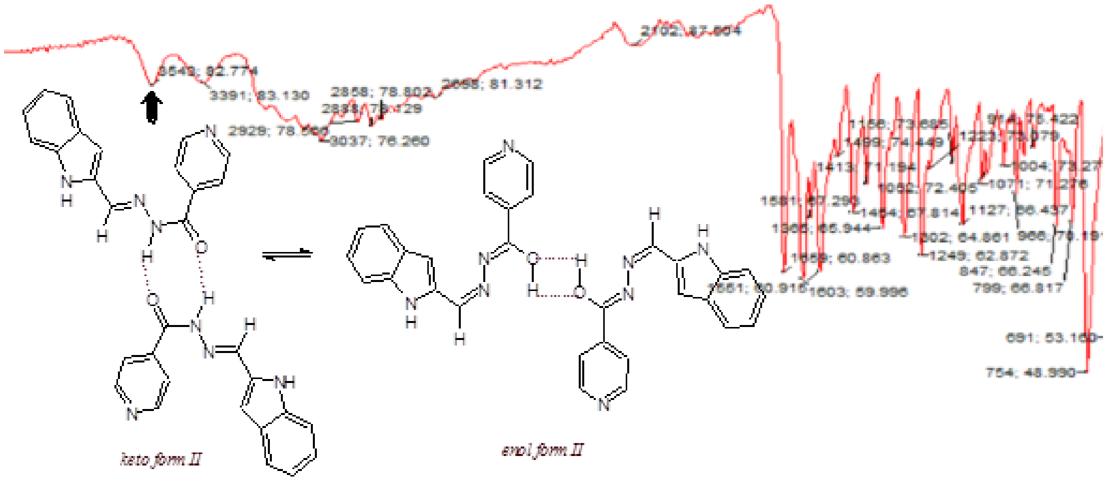
**Infrared spectra**

The IR bands at 3391 in the spectra of the free ligand is assigned to hydrogen bonded hydroxyl group stretching vibrations, suggesting that the ligand is hydrogen bonded via OH group. The possible modes of OH hydrogen bonding in the molecules are presented in Scheme 2 and this is consistent with hydrogen bonding modes found in similar molecules.



scheme 2: the possible modes of intramolecular and intermolecular hydrogen bonding of the ligand

The intensities and positions of the hydrogen bonded OH bands in the ligand changed drastically or absent in the complexes. The presences of typical band around 3550-3450 in the spectral of the ligand suggest dimeric OH stretching which implicate form II in the possible mode shown in Scheme 2.



The ligand is most likely H-bonded as shown in form I in Scheme 2. The mode of coordination of the ligand to the metal ion was examined by a comparison of the IR spectra of complexes to those of the free ligands. Absorbance peaks at 1659 $cm^{-1}$ and 1551 $cm^{-1}$ which were unambiguously assigned to amide I and C=N stretching vibrations respectively. In the spectra of the complexes these bands are slightly shifted or weakened signifying coordination through the carbonyl O and the azomethine N of the hydrazone ligand.

New band appearing at 814 cm$^{-1}$ in the cobalt complex which forced the disappearance or weakening of the band at 691 cm$^{-1}$ in the ligand spectra is suggested to be due to M-Cl stretching vibrations. The M-O and M-N peak could not be unambiguously resolved in the spectra of these complexes since the instrument did not tail into the near infrared region. With the assignment of the new peaks appearing at 814 cm$^{-1}$ to coordinated Cl in the complexes the structure in Fig. 5 is proposed.

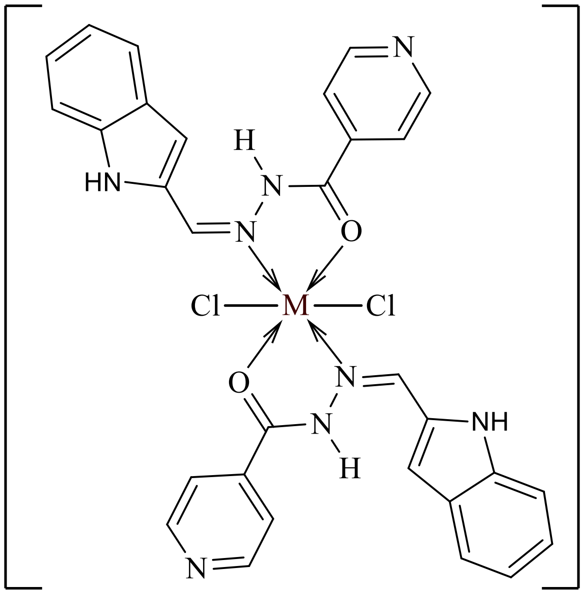


Fig 5: Proposed structure of the complexes. M = Fe$^{3+}$, Co$^{2+}$ or Cu$^{2+}$

**The Conductivity Measurements**

The values for conductivity experiments are shown in Table 1. The conductivity measurement can reveal structural information about complex species. The possible dissociation of a complex can produce ions in solution whose molar conductivity can be measured. This arises only if the complex is charged, producing a counter and complex ions (Moamen, 2007; El-Sayeed *et al* 1996). However, complexes considered to be nonelectrolyte can display non-significant conductivity values and this has been ascribed to either the interactions between pie orbital and metal orbitals which give rise to new orbitals delocalized over an entire complex specie or as a result of hydrogen bonding (Moamen et al, 2013).

The conductivity values of these complexes suggest they are non-electrolytes indicating that the chloride ions of the metal salts are not in the outer coordination sphere of the complexes. This is further confirmed by the absence of precipitate when the complex solutions were tested with silver nitrate solution. The involvement of the carbonyl O and azomethine N in the coordination process will lead to a drastic reduction in the degree of hydrogen bonding in the complexes compared to the ligand as evidenced in the FTIR spectra with the near absence of the 3543 cm$^{-1}$ peak of the ligand in the complexes and the proton signal at 12.90 ppm in the NMR spectrum. The hydrogen bonding experienced in the ligand can therefore lead to higher conductivity since hydrogen bonding gives rise to strong overlapping of molecular orbitals which in turn contribute to higher conductivity. These events are likely responsible for the higher conductivities of the ligand compared to those of complexes

## CONCLUSION

The *N*'-[(*E*)-(1*H*-indol-2-yl)methylidene]pyridine-4-carbohydrazide display hydrogen bonding due to the presence of H, O and N functionalities in the molecules, these attributes can be utilized in molecular assembly with proper ligand design. However, the bonds formed by the ligands in the current study form stable complexes, which does not qualify them as good candidate for dynamic libraries. Effort in this direction should be towards the utilization of low and medium weight hydrazides which can couple with carbonyl groups without forming stable bonds in hydrazone formation. The functional groups on these compounds are relevant in medicinal chemistry and promise to be ideal tools in the penetration or attack of microorganism's cell membrane which can lead to destruction of bacterial cell making them plausible candidates for investigation as antimicrobial agents.

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