EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 11
361-371
Year: 2017

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF ISONIAZID DRUG BASED TRANSITION METAL COMPLEXES

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Article Received on 05/09/2017 **Article Revised on 25/09/2017** **Article Accepted on 15/10/2017**

ABSTRACT
A series of five transition metal complexes of the type, $[M(INH)_2(H_2O)(NO_3)]$ (NO_3), where M = Mn(II) **(1)**, Co(II) **(2)**, Ni(II) **(3)**, Cu(II) **(4)**, Zn(II) **(5)** and INH =isoniazid, have been synthesized with the drug, isoniazid (INH) Nitrate ion and water as ligands. The complexes were characterized by elemental analyses, conductance measurements, electronic, infra red, electron spin resonance and thermal studies. All complexes adopt octahedral geometry around the metal ion. The redox properties of the complexes were investigated by cyclic voltammetry (CV). All the complexes, exhibited quasi-reversible single/two electron transfer behavior. The ligand and its metal complexes have been screened for in vitro antibacterial and antifungal properties. These results revealed that all complexes showed significant activity. DNA binding and cleavage studies showed that all metal complexes have significant activities than the Isoniazid ligand.

KEYWORDS: Isoniazid complexes, Redox behavior, Thermal studies, Antimicrobial activity, Cyclic voltammetry.

INTRODUCTION
Antibiotics are compounds which inhibit the growth of bacteria.[1] Tuberculosis is a disease caused by Mycobacterium tuberculosis, the bacteria that are passed from people to people through the air. Combinations of the drugs are used to treat tuberculosis (TB) which is normal for effective treatment.[2,3] Tuberculosis (TB) is a public health disease that produces several millions of deaths annually worldwide.[4] In developing countries, it is still a leading cause of mortality. Nowadays, the number of people infected is growing in developed countries also, especially, in immunocompromised patients, such as those co-infected with human immunodeficiency virus (HIV) and in individuals receiving therapy for anti-tumor activity or diabetics.[5,7] A big associated problem is the alarming increase of drug resistant microbial strains (MDR-TB) that makes difficult the effective control of the disease. Besides, to further complicate the matter, drug-drug interactions between TB drugs and anti HIV treatments or other chronic disease medications such as those used in diabetics are observed.[8] Due to this critical situation, innovation in TB drug discovery and evolving strategies to bring new agents with the best performance is a current health priority. Isoniazid (pyridine-4-carbohydrazide, isonicotinicacidhydrazide) has been used to treat tuberculosis (TB) and to prevent it in people who had contact with tuberculosis bacteria. Isoniazid (INH) is a prodrug that requires cellular activation by Kat G protein in its active form before exerting its toxic effect on the bacillus.[9] Studies on the interaction of transition metal ions with organic ligands continue to attract the diligence of researchers due to their enhanced activity and ability to overcome resistance.[10] There have been a number of reviews on the utilization of transition metal complexes as models for biological important species.[11] Transition metal complexes with biologically important ligands have received immense interest in bio inorganic chemistry.[12,13] Based on the widely diverse coordination environment of the transition metal complexes and variation in the identities of the coordinating ligands, synthesis of such complexes with desired molecular geometry can be realized. It is well known that several metal chelates have been shown to inhibit tumor growth and some drugs, even exhibit increased activity when administered as metal complexes.[14,15] Growing interest in the study of hydrazones are obviously due to their antibacterial, antimicrobacterial, anticonvulsant, analgesic, anti-inflammatory and antitumor activities, coordinating capability and applications in analytical chemistry.[16]

INH is capable of coordinating with metal cations through different chemical groups such as heterocyclic nitrogen from the pyridine ring and/or carbonylic O and N atoms of the hydrazide group.[17,18] Numerous research papers have described the bactericidal and fungicidal properties of various mixed ligand complexes of metal ions with isonicotinoyl-hydrazone ligands.[19,23] Taking into account these antecedents and as a part of our work in the research on new antimicrobial molecules, this paper describes the synthesis, characterization and antimicrobial studies of Isoniazid drug based transition metal complexes derived from N and O Bidentate ligands as such type of complexes attract intense attention due to their interesting properties.

MATERIALS AND METHODS

Microanalyses (C, H and N) were carried out with a Perkin-Elmer 2400 elemental analyzers at SAIF, Cochin University, Kerala, India. IR spectra were recorded on FT-IRJASCO 460 PLUS spectrophotometer with samples prepared as KBr pellets. Electron paramagnetic resonance spectra were recorded on JEOL-FA200EPR spectrometer. UV-Vis spectra were recorded on a Shimadzu UV-3101PC spectrophotometer using cuvettes of 1 cm path length and conductivity measurements were carried out in non aqueous solutions of the complexes with an Elico conductivity bridge type CM 82 and a dip-type cell with a cell constant of 1.0. Cyclic voltammetry measurements were made on Princeton EG and G-PARC model potentiostat. The thermal analyses were performed with a Perkin Elmer Diamond instrument at a heating rate of 5°C/min under a dynamic air atmosphere (150 ml/min). All complexes were investigated in the temperature range of 20-800°C, with the exception of the cobalt complexes, which were investigated up to 960°C.

Synthesis of complexes containing Isoniazid drug as ligand

To a solution of Isoniazid, (4pyridine-4-carbohydrazide, isonicotinicacidhydrazide), (0.274 g, 2 mmol), in 23 ml of methanol, was treated a methanolic solution of manganese (II) nitrate (0.245 g, 1 mmol). The reaction mixture was stirred on a magnetic stirrer. The light brown crystalline product, formed after 7-8 hours were collected by filtration. The solid was washed several times with methanol (50 mL), then with diethyl ether (30 mL) and finally dried in a vacuum. Mol. Formula of Complex **1**: $C_{12}H_{16}MnN_8O_9$: Mol.Wt. 470.93, Yield: 0.215 g, Colour- light brown.

Synthesis of Co, Ni, Cu and Zn complexes with Isoniazid: (2-5)

These metal complexes **(2-5)** were synthesized by adopting the same procedure used for the above mentioned complex except, that in place of metal manganese, Co, Ni, Cu and Zn were used. Mol. Formula (Complex **2**), $C_{12}H_{16}CoN_8O_9$: Mol. Wt. 474.93, Yield: 0.376 g, Colour- pale pink; Mol. Formula (Complex **3**), $C_{12}H_{16}NiN_8O_9$: Mol. Wt. 474.69, Yield: 0.384 g, Colour-Green; Mol. Formula (Complex **4**), $C_{12}H_{16}CuN_8O_9$: Mol. Wt. 479.55, Yield: 0.326 g, Colour-Dark brown; Mol. Formula (Complex **5**), $C_{12}H_{16}ZnN_8O_9$: Mol. Wt. 481.38, Yield: 0.326 g, Colour -White. The complexes formed between is isoniazid with different metal ions have structures as shown in **Fig.1.**

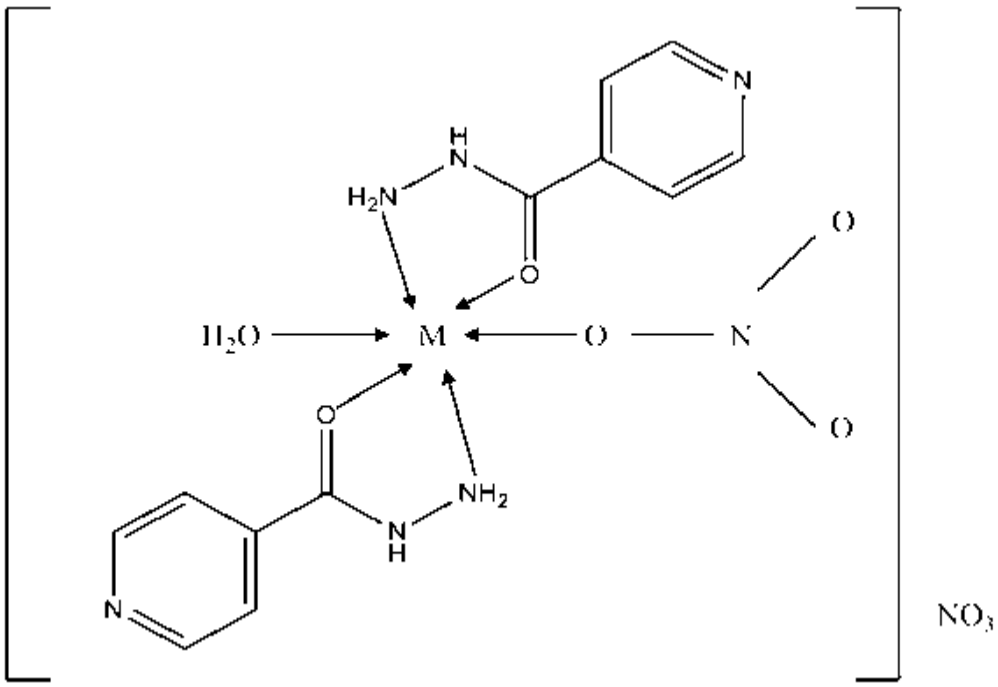

Fig.1. Structure of Complexes, 1-5, formed by isoniazid with various metal ions M=Mn, Co, Ni, Cu and Zn.

RESULTS AND DISCUSSION

Melting point and conductance

The melting points and conductivities of complexes **1-5** are presented in **Table. 1** and all these complexes were soluble in DMSO. The melting points of all synthesized complexes are found to be higher than their parent ligand (INH) suggesting the formation of complexes. Complex **3** shows a lower melting point among all types of complexes due to increase in covalency character of complex. Elemental analysis and conductivity obtained for these complexes are in good agreement with the assigned formula [M $(INH)_2$ (H_2O) (NO_3)] (NO_3). Further, the conductivity was measured in the same solution after 24 hours and no major changes were observed showing the stability of the complex in DMSO.

Table. 1: Analytical data for Isoniazid and its metal complexes, 1-5.

Complexes/Drug	Melting Point(°C)	Conductivity(Ω^{-1} cm^2 mol^{-1})
Isoniazid	171	0.08
$[Mn(INH)_2(H_2O)(NO_3)](NO_3)$ **1**	330	0.16
$[Co(INH)_2(H_2O)(NO_3)](NO_3)$ **2**	310	0.21
$[Ni(INH)_2(H_2O)(NO_3)](NO_3)$ **3**	225	0.19
$[Cu(INH)_2(H_2O)(NO_3)](NO_3)$ **4**	370	0.14
$[Zn(INH)_2(H_2O)(NO_3)](NO_3)$ **5**	198	0.33

Elemental analysis

The purity of the complexes were derived from C, H, N analysis, and the results were found to be in good agreement with the calculated values given as follows: Complex **1;** Found: C, 29.22%; H, 2.94%; N, 22.11%; Mn, 10.58%; $C_{12}H_{16}MnN_8O_9$ calcd: C, 30.52%; H, 3.39%; N, 23.74%; Mn, 11.64%; Complex **2** Found: C, 29.99%; H, 3.39%; N, 23.06%; Co, 11.96%; $C_{12}H_{16}CoN_8O_9$ calcd: C, 30.32%; H, 3.36%; N, 23.58%; Co, 12.41%; Complex **3** Found: C, 30.01%; H, 3.13%; N, 23.06%; Ni, 11.99%; $C_{12}H_{16}NiN_8O_9$ calcd: C, 30.33%; H, 3.38%; N, 23.59%; Ni, 12.36%; Complex **4** Found: C, 29.73%; H, 2.93%; N, 23.00%; Cu, 12.95%; $C_{12}H_{16}CuN_8O_9$ calcd: C, 30.03%; H, 3.33%; N, 23.36%; Cu, 13.25%; Complex **5** Found: C, 28.98%; H, 3.30%; N, 22.98%; Zn, 12.98%; $C_{12}H_{16}ZnN_8O_9$ calcd: C, 29.91%; H, 3.32%; N, 23.37%; Zn, 13.59%.

Magnetic moment and Electronic spectral studies

The UV-Vis spectrum of the ligand showed two bands at 220 and 260 nm assignable to transitions $\pi\rightarrow\pi^*$, $n\rightarrow\pi^*$. The electronic spectra of complexes to exhibit the same bands, but displaced to higher wave numbers. This reveals that the ligand is coordinated to the metallic ions. The electronic absorption spectra of the metal complexes (**1-5**) were recorded in the range 250-1100 cm^{-1}. The magnetic moment determined for Complex **1** is 5.91 BM and showed a weak band in the range of 460-880 nm. The electronic spectrum of nickel complex consists of three bands; one at ~10000 cm^{-1} due to $^3A_{2g}(F)\rightarrow{}^3T_{2g}(\sqrt{1})$,~ one at 15000 cm^{-1} due to $^3A_{2g}(F)\rightarrow{}^3T_{1g}(\sqrt{2})$ and third at ~29000 cm^{-1} for $^3A_{2g}(F)\rightarrow{}^3T_{2g}(\sqrt{3})$ which clearly indicate the octahedral geometry of the complex. The magnetic moment of the Complex is 2.31 BM which is comparable with the well known values for Ni (II) complex in octahedral geometry. The magnetic moment determined for complex copper complex is 2.1 BM which lies in the range of 1.7-2.2 BM, characteristic of Cu (II) complex with octahedral geometry. Copper complex showed a broadband near 700 nm which corresponds to octahedral environment around copper. For Complex **2**, the experimentally determined magnetic moments are 5.44 BM, indicating a high-spin character and excluding oxidation to Co (III). These values are within the range of 4.3 -5.7 BM, indicating an octahedral geometry for Co (II) ion. [24,25] Complex **2** exhibited three bands (i) 400 nm $[^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)]$, (ii) 570 nm $[^4T_{1g}(F)\rightarrow{}^4A_{2g}(P)]$ and (iii) 1018 nm $[^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)]$ which correspond to octahedral geometry around the cobalt (II) ion.

FT-IR Spectra

Infrared spectroscopy is used to distinguish the mode of coordination of the ligands to the central metal ion. The IR spectra of the Complexes **2** and **4** are shown in **Fig. 2 & 3**. The tentative assignments of the selected bands for the complexes are given in **Table 2**. The broad bands appearing at 3304 cm^{-1} and 3110 cm^{-1}, which were assigned to the $\nu_{(NHas)}$ and $\nu_{(NHsym)}$ vibrations and very intense bands at 1669 cm^{-1} and 1558 cm^{-1} correspond to amide-I and amide-II groups. Upon complexation the $\nu_{a(NH2)}$ was shifted to lower frequencies while the $\nu_{s(NH2)}$ was not identified due to the broad bands in the region.[26] The band at 1117 cm^{-1} assigned as $\nu_{(NH)}$, does not shift in the complex showing that this group does not participate in the coordination. In accordance with this is the fact that the vibration frequency ν_{N-N} is displaced towards lower values in IR spectra of the complexes. In all Complexes (**1-5**), the $\nu_{C=O}$ band at 1660 cm^{-1} is shifted to a lower frequency (~1620-1640 cm^{-1}) remarking the metal coordination through carbonyl group. This behavior allows the INH ligand to act as a bidentate ligand coordinating through-NH_2 and the C=O groups. The strong band observed at 1570-1530 cm^{-1} and 1080-1010 cm^{-1} are tentatively assigned to asymmetric and symmetric $\nu_{C=C}$ and $\nu_{C=N}$ of pyridine ring and pyridine ring breathing and deformation respectively. Upon coordination, these bonds remain unchanged. This reveals that the non-involvement of pyridinic nitrogen in complex formation. The broadband at 3420 cm^{-1} confirms the presence of the water molecule in the complex. The medium intense band at 887 cm^{-1} was attributed to the N-N vibration frequency.[27] In all these Complexes (**1-5**), a very intense band appears in the

region of 1383 - 1389 cm^{-1} which is assigned to free NO_3^- anion.[28] A very sharp and intense band appeared in the range of 1180-1250 cm^{-1} in all complexes indicating the presence of coordinated nitrate ion. Further, the presence of ionic nitrate is supported by the appearance of the medium band in the region of 810-820 cm^{-1}.

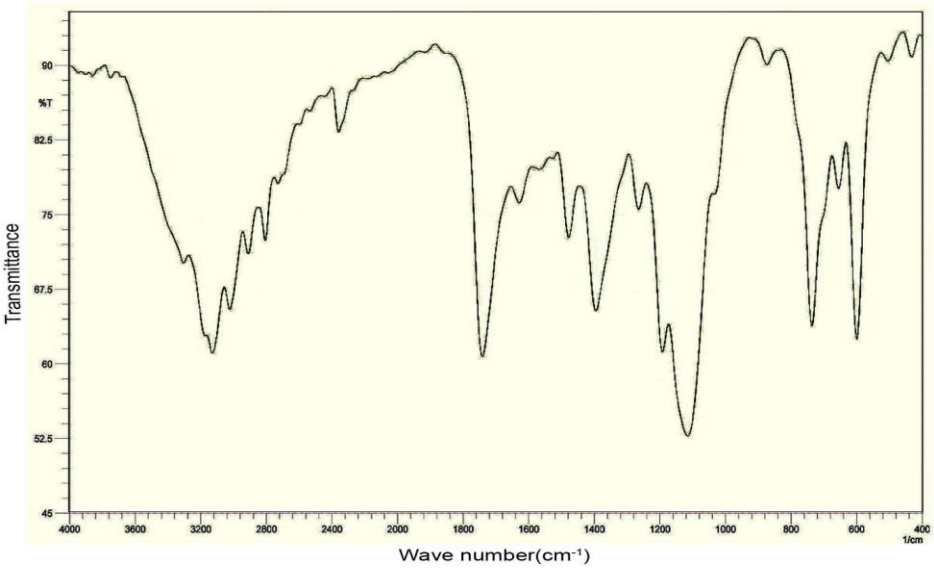

Fig. 2. FT-IR Spectrum Co Complex (2) with Ligand (INH).

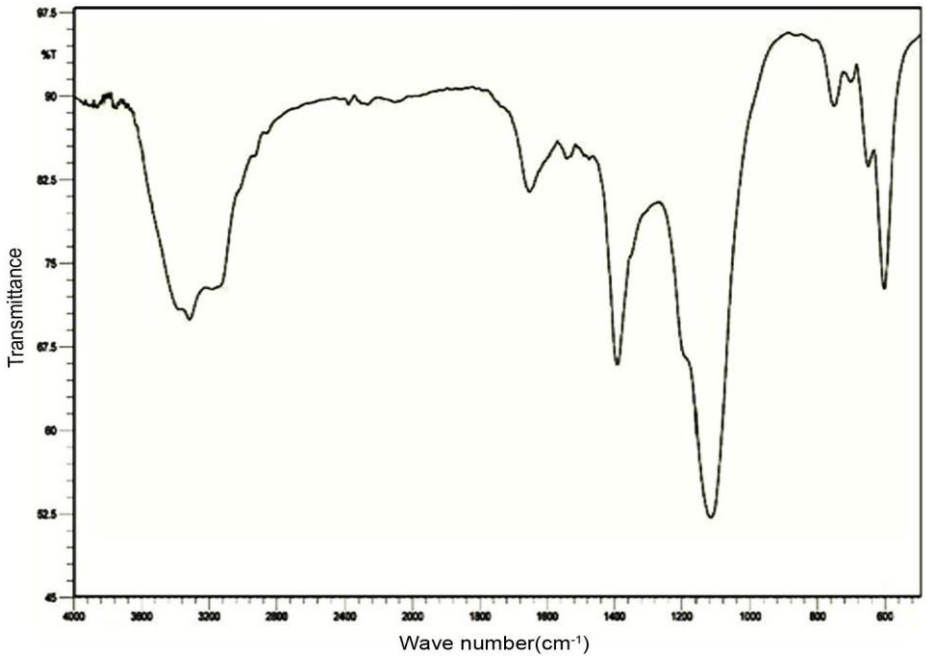

Fig 3. FT-IR Spectrum of Cu Complex (4) with ligand (INH).

Table 2: Important infrared frequencies (cm^{-1}) of pure drug and their metal complexes.

No	Drug/Complex	$\nu_{(OH)}$	ν_{N-H}	$\nu_{C=O}$ amide I	ν amide II	δ_{H2O} coord	$\nu_{N=N}$
	Isoniazid (INH)	-	3312 3118	1657	1549	-	878
1	$[Mn(INH)_2(H_2O)(NO_3)](NO_3)$**1**	3441	-	1620	1531	916	849
2	$[Co(INH)_2(H_2O)(NO_3)](NO_3)$**2**	3438	3240	1645	1546	914	846
3	$[Ni(INH)_2(H_2O)\ (NO_3)](NO_3)$**3**	3425	3050	1652	1542	901	859
4	$[Cu(INH)_2(H_2O)(NO_3)](NO_3)$**4**	3421	3147, 3054	1650	1541	907	860
5	$[Zn(INH)_2(H_2O)\ (NO_3)](NO_3)$**5**	3416	3149	1653	1556	905	847

EPR spectra

The EPR spectra of copper complex provide information about the metal ion environment. The EPR spectrum of a polycrystalline sample of [Cu (INH) $_2$(H_2O) (NO_3)] (NO_3) at X-band is shown in **Fig. 4**. The X band EPR spectrum of the copper (II) complex in DMSO, at 300 K shows one isotropic peak in highfield, but does not reveal any hyperfine structure due to tumbling motion of the molecule. The exact geometry of the metal ion ($i_{sotropic}$= 2.112) could not be derived from it. However, this complex shows four well resolved peaks at 77 K in the low field region. In Octahedral copper (II) Complex **4**, the unpaired electron lies in the d_{x2-y2} orbital and will show $g_{\|} > g_{\perp} > 2$. From the observed values for 4, it is clear that $g_{\|}$ (2.248) > $g_{\perp}$ (2.081) > 2 which indicates that the unpaired electron is in d_{x2-y2} ground state orbital. However, no hyperfine lines are obtained for the Complex **4** which is a situation usually observed in the cases where copper-copper interaction are observed.[29] The value of exchange interaction term, G, can be estimated from the expression G = $g_{\|}$- 2.0023/$g_{\perp}$-2.0023. G (3.121) < 4.0, significant exchange coupling is present and misalignment is appreciable. The observed value for the exchange interaction term G suggests that the complexes have distorted octahedral geometry and the ligand forming copper (II) complex is considered as a strong field one.

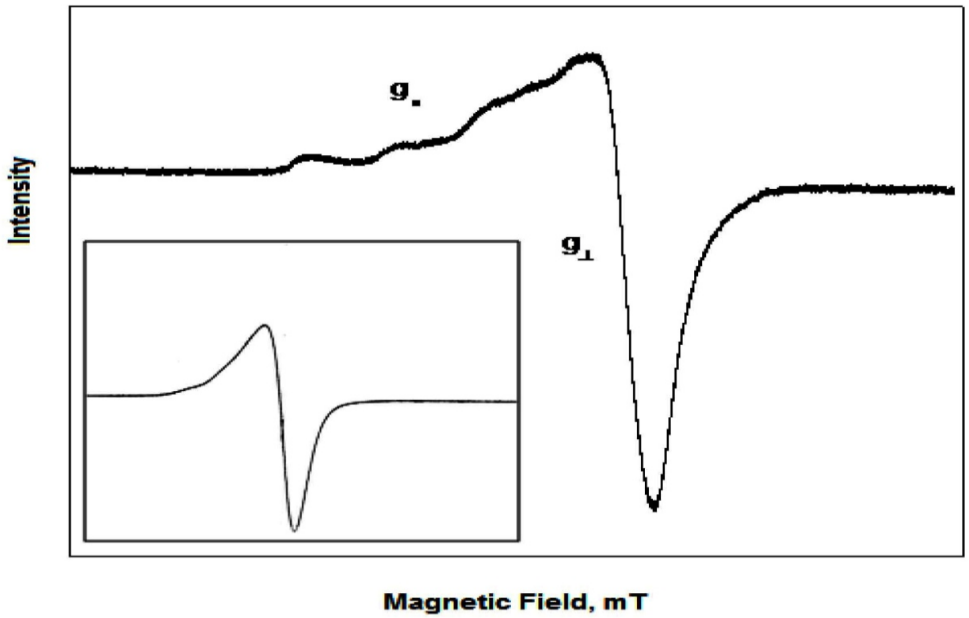

Fig.4. X-band EPR Spectrum of polycrystalline sample of copper Complex 4 at RT and LNT.

TGA and DSC studies

Thermal gravimetric analysis (TGA) is a method of thermal analysis in which changes in physical and chemical properties of the complexes and drugs are measured as a function of increasing temperature from 0^{o}C to 1000^{o}C (with constant heating rate). Thermal stability, oxidation and combustion, all of which are possible interpretations of TGA traces, will also be discussed. From thermal studies, complexation should occur between drugs and metal. The thermal studies of isoniazid and its complexes were carried out and their thermograms are given in (**Fig.5 & 6**). In the TGA of pure ligand, there is no change up to 150^{o}C which indicates the water molecule is absent in the ligand. Although all complexes showed thermal changes at 110^{o}C corresponding to release of coordinated water molecules, such a process was conspicuously absent in the TGA of pure IAH. Mass losses of 16% in **5**, 9% in **4**, 7% in **3,** 30% in complex **2** and 10% in **1** occurred at temperatures above 200^{o}C which correspond to the removal of ligand with the formation of metal oxide as end residue.

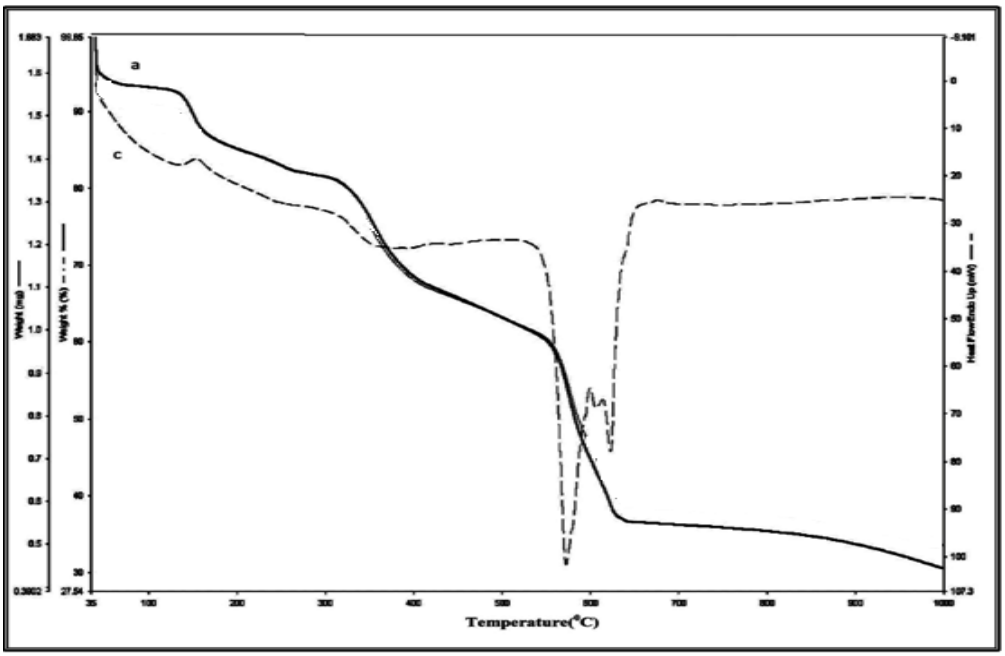

Fig. 5. Superimposed thermo gravimetric (dark solid line (a)) TG) and differential scanning calorimetric (dash line(c)) DSC) curves for Complex 2; heating rate:10°C/min.

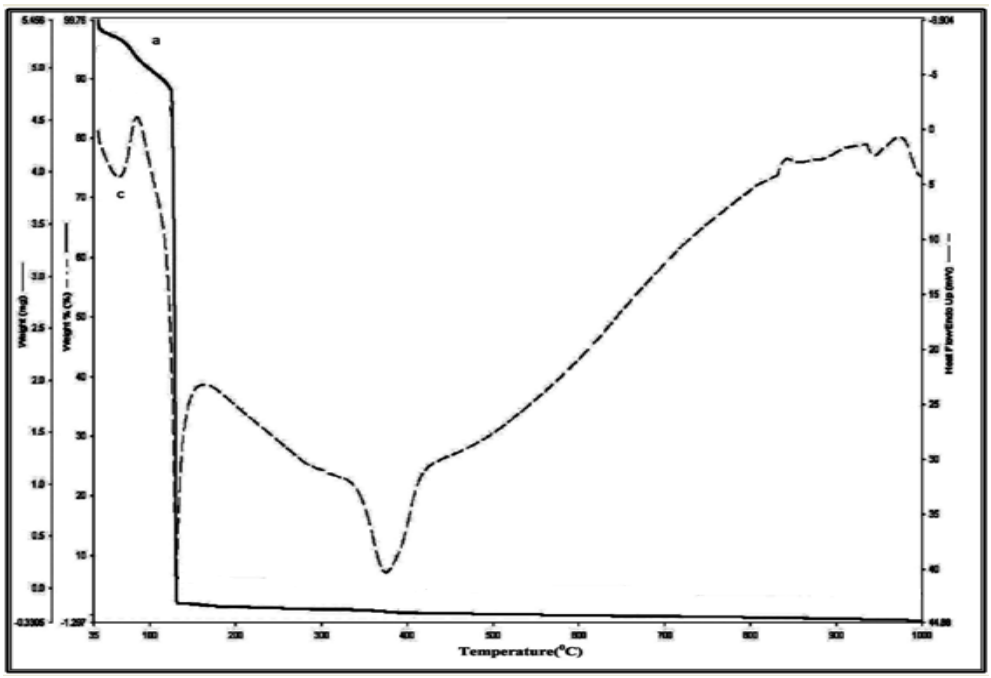

Fig.6. Superimposed thermo gravimetric (dark solid line (a)TG) and differential scanning calorimetric (dash line(c) DSC) curves for Complex 3; heatingrate:10°C/min.

Cyclic Voltammetry

Cyclic voltammeter (CV) is an important and widely used electro analytical technique to study a variety of redox processes for obtaining details on the stability of reaction products, intermediates in oxidation-reduction reactions. Reaction and electron transfer kinetics and the reversibility of a reaction.[30,32] All the complexes, showed reduction of the potential range of -0.16V to -0.4V and the reduction process is found to be quasi reversible in nature. A cyclic voltammogram of complex **2** is presented in **Fig. 7**. This exhibit one electron quasi reversible transfer process with a reduction peak at E_{pc}= -0.16V and the corresponding oxidation peak at E_{pa}= -0.4V at a scan rate of 100mV/s. The peak separation (Δ_{Ep}) of this couple is 0.24V. With the increasing scan rates, Δ_{Ep} value also increases giving further evidence for the quasi-reversible Co (II)/Co (I) couple. The difference between forward and backward peak potentials can provide a rough evaluation of the degree of the reversibility. The ratio of cathodic to anodic peak height was less than one. However, the peak current increases with the increase of the square root of the scan rates.

This establishes that the electrode process is diffusion controlled.[33] Cyclic voltammogram of Complex **3** is shown in **Fig. 8.** The redox property was studied in the potential range of +1.2 to - 1.6 V. The complex is electro active with respect to the metal center and exhibited two redox processes. Each reduction is associated with a single-electron transfer process at room temperature.[34] For both responses, the cathodic and anodic peak heights are equal and vary as the square root of the scan rate; E_{pc} and E_{pa} are virtually independent of the scan rate. Two well-defined quasi-reversible one-electron cyclic responses were observed at E_{pc}= -0.541 with a corresponding oxidation peak at E_{pa} = -0.37 V and at E_{pc} = -1.19with a corresponding oxidation peak at E_{pa} = -1.266 V respectively at a scan rate of 100mV/s. The electrochemical behavior shows moderately high reduction potentials. Δ_{Ep} values for the first redox couple, 0.171 V is higher than for the second redox couple, 0.076 V. E_p values are higher for the complex due to the difference between the original complex and the reduced species.

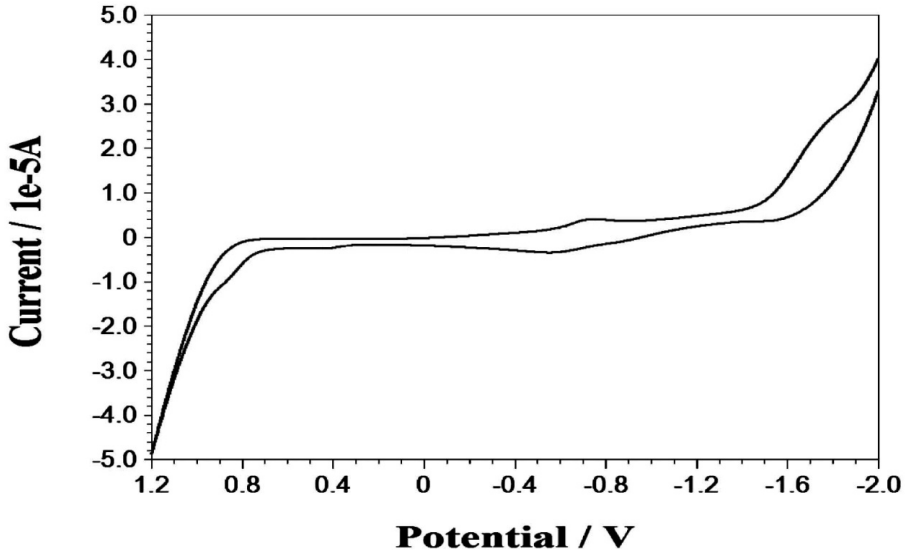

Fig. 7. Cyclic voltammogramof Complex 2 in DMSO supporting electrolyte: 0.5 M NBu_4ClO_4; Scan rate: 0.1Vs^{-1}.

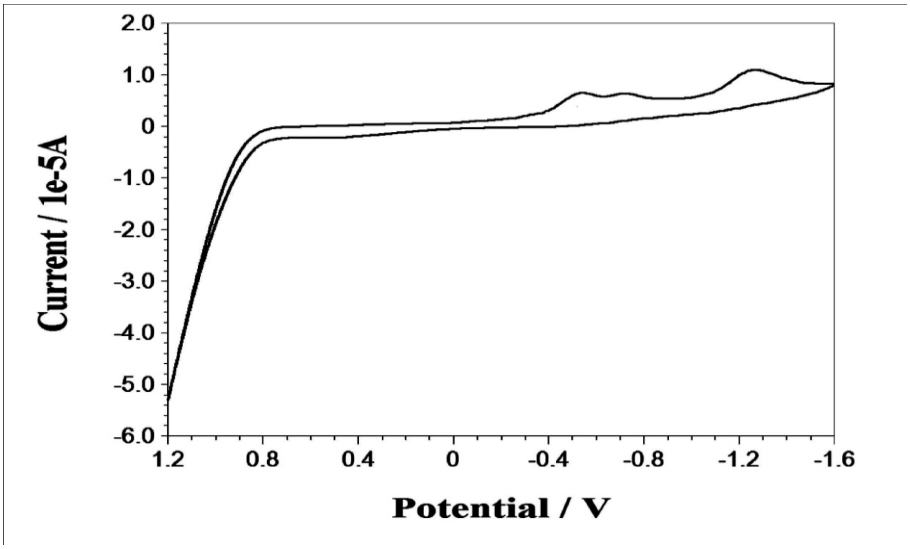

Fig.8. Cyclic voltammogram of Complex 3 in DMSO supporting electrolyte: 0.5 M NBu_4ClO_4; Scan rate: 0.1Vs^{-1}.

Antimicrobial studies

Gram-negative organisms have an outer membrane which provides an effective control over the uptake of toxic substances, and as a consequence are generally more resistant to antibacterial agents. The ligand (INH) and its metal complexes were screened for antimicrobial activity against one strain Gram +ve bacteria (staphylococci) Gram -ve bacteria (Escherichia coli), (Pseudomonas aureginosa), and fungi (Candida albicans, Aspergillus niger). All complexes showed (**Fig.9b)** enhanced antibacterial activity in comparison to that of the INH, except Gram +ve bacteria (staphylococci) (**Fig.9a)**. This may be due to the higher hydrophobic character of the complexes which can deactivate the bacterial/fungal cellular membrane/wall. Chelation may increase the liphophilic character of the metal chelate

and thus enables it to permeate the lipid layers of the bacterial membrane more effectively. However, Manganese and copper complexes of Isoniazid showed considerable antifungal activity against Candida albicans than the ligand. Cobalt and Nickel complexes of Isoniazid showed less antifungal activity compared to the pure drug Isoniazid.

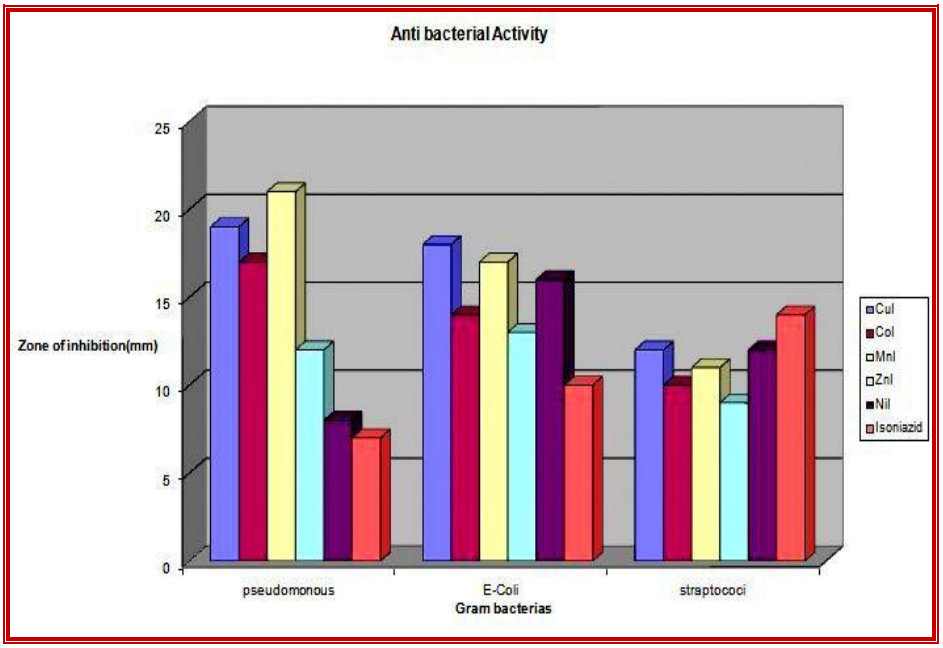

Fig. 9a. Antibacterial activity of Isoniazid and its metal complexes,1-5 against (i) Escherichia coli, (ii) Pseudomonas (iii) Staphylococci.

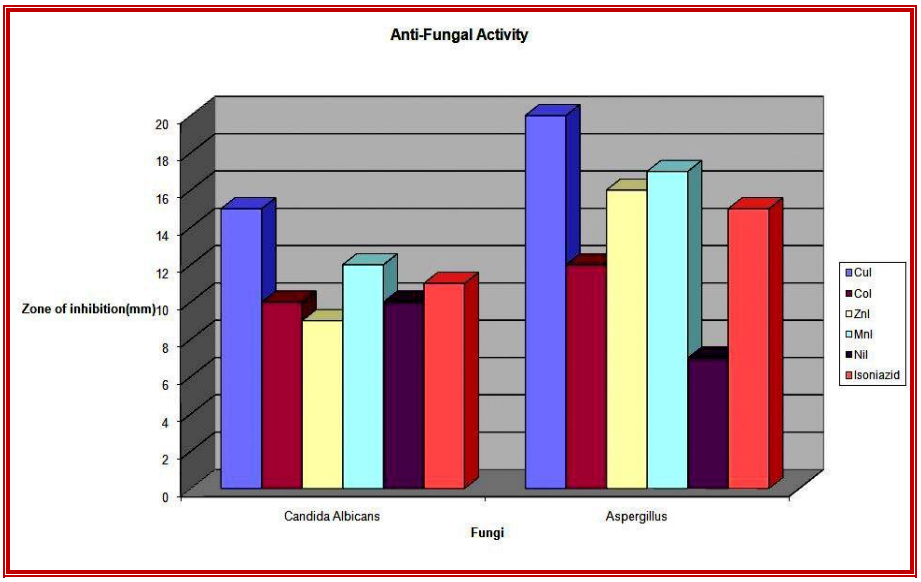

Fig.9b. Antifungal activities of Isoniazid and its Complexes, 1-5.

Gel electrophoresis-DNA cleavage study

The cleavage reaction to Human serum proteins by using Ready-to-use-precast Gel by complexes were performed with the agarose gel electrophoresis method and the results are represented in **Fig. 10**. The ability of metal complexes to mediate DNA cleavage is well documented. Control experiment using DNA alone, does not show any significant cleavage of DNA even after long exposure time. Ligand (I) has a slight effect on the cleavage of DNA at concentrations up to 40µM. Complexes (**1, 2 & 3**) show significant effect on the cleavage of DNA. From the observed results, it is concluded that Cu and Zn complexes (**4 and 5**) cleave the DNA significantly as compared to the other complexes. DNA cleavage effect of different complexes is due to the binding efficiency of the complexes to DNA.

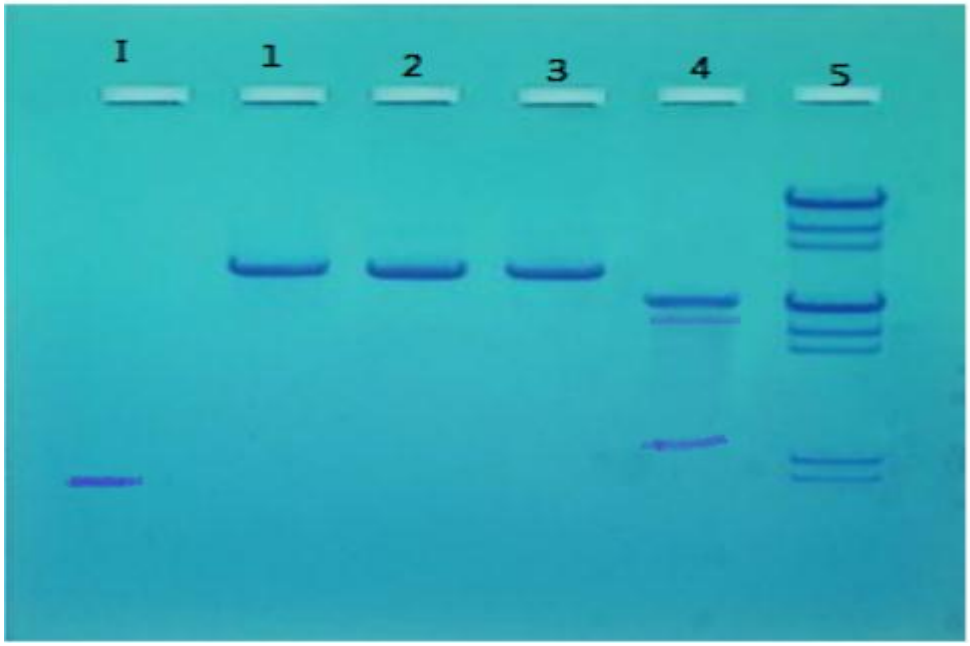

Fig.10. DNA cleavage by Isoniazid and its metal Complexes, 1-5.

DNA binding studies

UV-Vis absorption spectroscopy is very suitable for interaction studies related to DNA. However, when DNA and metal complexes are interacting, a significant change in DNA spectrum absorbance is observed. The intercalation reaction causes hypochromism and/or hyperchromism, red and/or blue shifts of the band. Hypochromism is due to the contraction of DNA to the helix axis and changes in the conformation of DNA, while hyperchromism results from the damage of the DNA double helix structure. Metal complexes contain labile ligands that can be easily replaced by covalent binding to the nitrogenous basis of DNA. Binding by the complex to DNA, through intercalative binding, generally results in hypochromism (decrease in absorption intensity). From the **Fig. 11**, it is clearly understood that all metal complexes bind to DNA through intercalative binding. Hyperchromism results from breakage of secondary structure of DNA due to the fact that phosphate group can provide the suitable anchors for coordination with complexes.

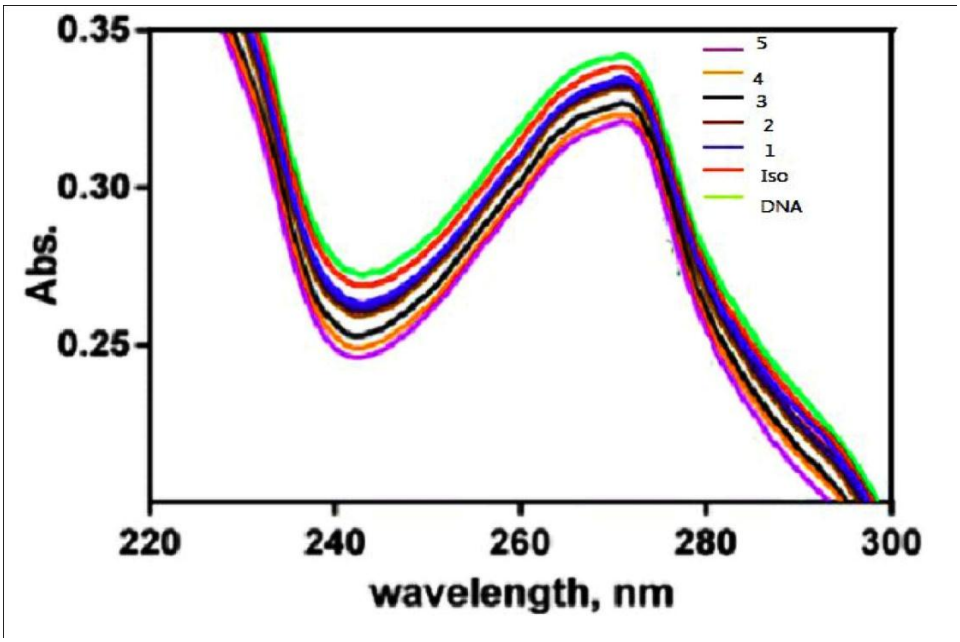

Fig. 11. Absorption Spectra for DNA binding of Isoniazid and its metal Complexes 1-5 along with that of pure DNA.

CONCLUSION

The synthesis of a series metal complexes by the interaction of Isoniazid with M $(NO_3)_2$ [M=Zn (II), Ni (II), Cu (II), Mn (II) and Co (II)] is reported. An octahedral geometry was suggested for all complexes. The IR spectral data confirmed the presence of water molecule and nitrate ion in the coordination sphere. The complexes were characterized by elemental analysis, conductivity in solution, electronic spectra measurement. The electrochemical properties of the metal complexes revealed the quasi-reversible one/two electron transfer redox processes. Metal complexes displayed enhanced activity against one or more strains and it is important to observe that they show enhanced inhibitory activity compared to the parent ligand. DNA binding and cleavage studies showed that all metal complexes have significant activities than the Isoniazid ligand.

ACKNOWLEDGEMENTS

One of the authors S. Radha is grateful to the Management of Saiva Bhanu Kshatriya College, Aruppukottai, Tamilnadu, India for providing facilities and granting permission to carry out this research work.

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