ज्ञान-विज्ञान विमुक्तये

UNIVERSITY GRANTS COMMISSION
MAJOR RESEARCH PROJECT

Title of the Project	**: Synthesis and Characterization of Mixed Ligand nano metal complexes and their Intercalative study with biomolecules**
UGC F. No.	**: 42-238/ 2013 (SR), dated 25.03.2013**
Name and Address of the Principal Investigator	**: Dr.(Mrs.). V. Violet Dhayabaran Associate Professor P.G. & Research Department of Chemistry Bishop Heber College (Autonomous) Tiruchirappalli- 620017, Tamilnadu, India.**
Tenure of the Project	**: 01.04.2013 to 31.12. 2017**
Total Grant Allocated	**: Rs. 8,03,252/-**

SUMMARY OF THE FINDINGS

The project describes detailed studies on DNA binding, cleavage and pharmacological activities of Co(II), Cu(II) and Zn(II) metal complexes containing new biologically active mixed Schiff base ligands having N, O donor atoms derived from amino acids, diketones and 1,10-phenanthroline. The following ligands and their Co(II), Cu(II) and Zn(II) complexes were prepared.

- **1,4-Naphthoquinone - Histidine (L1)**

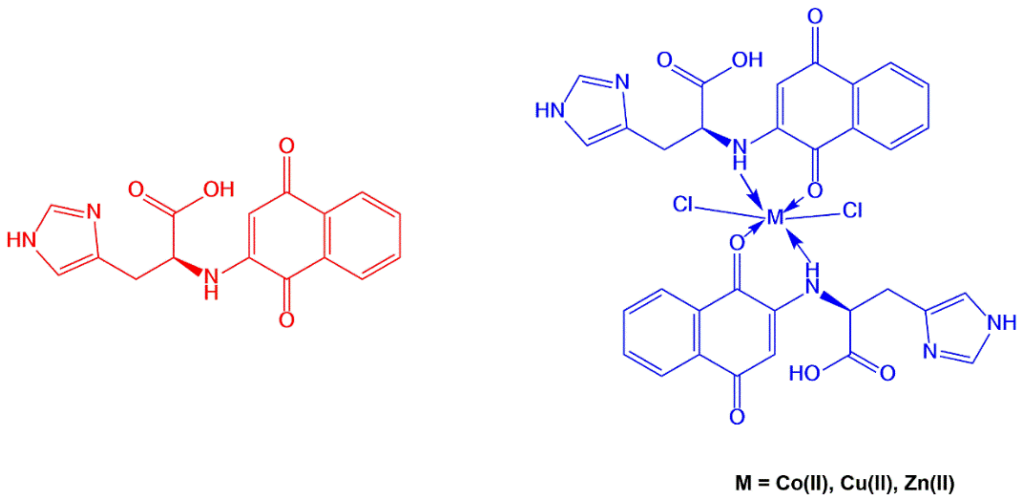

Figure 1. Structure of the ligand **(L1)** and its Co(II), Cu(II) and Zn(II) complexes

- **1,3-Indandione - Histidine (L2)**

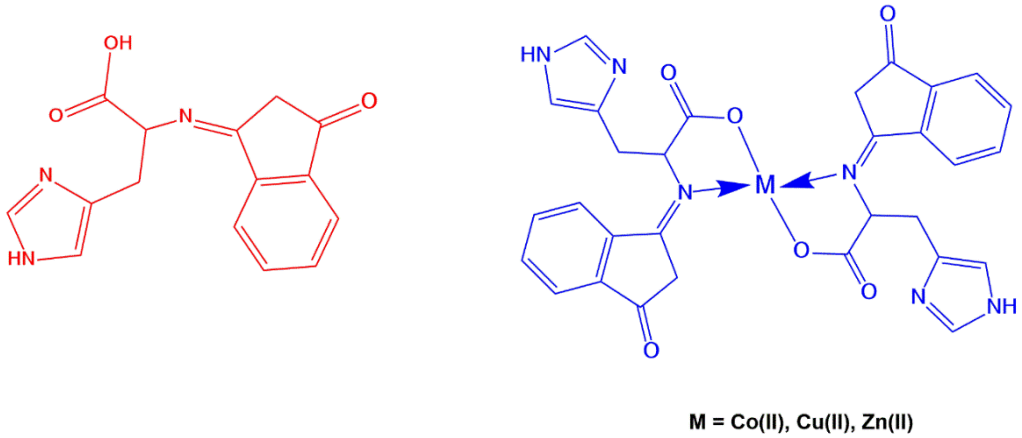

Figure 2. Structure of the ligand **(L2)** and its Co(II), Cu(II) and Zn(II) complexes

- **1,3-Indandione - Methionine (L3)**

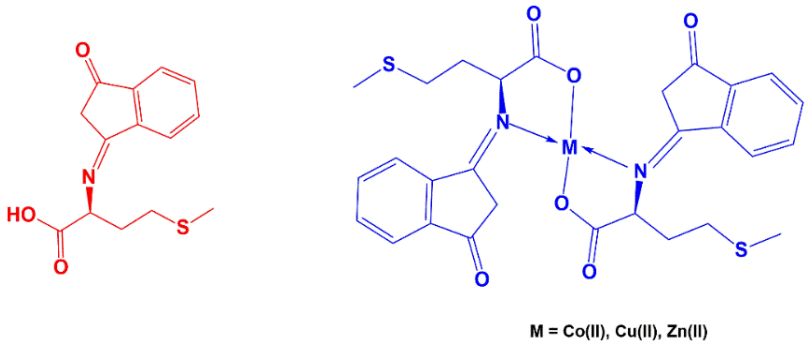

Figure 3. Structure of the ligand **(L3)** and its Co(II), Cu(II) and Zn(II) complexes

- **1,4-Naphthoquinone – Histidine - 1,10-Phenanthroline (L4)**

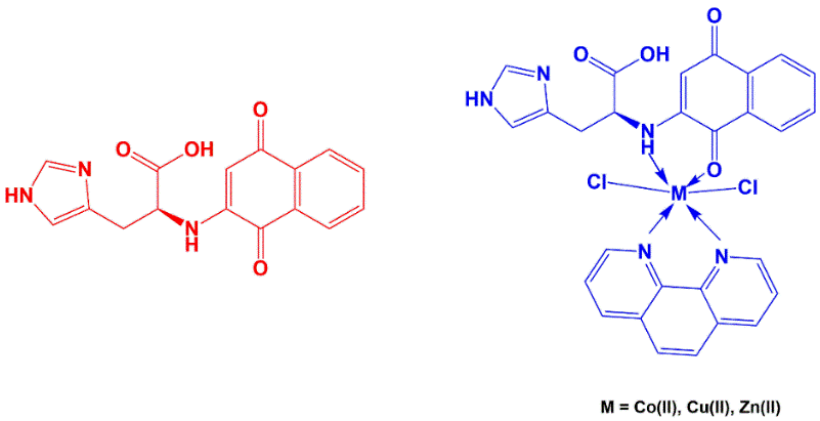

Figure 4. Structure of the ligand **(L4)** and its Co(II), Cu(II) and Zn(II) complexes

- **Adenine - Histidine (L5)**

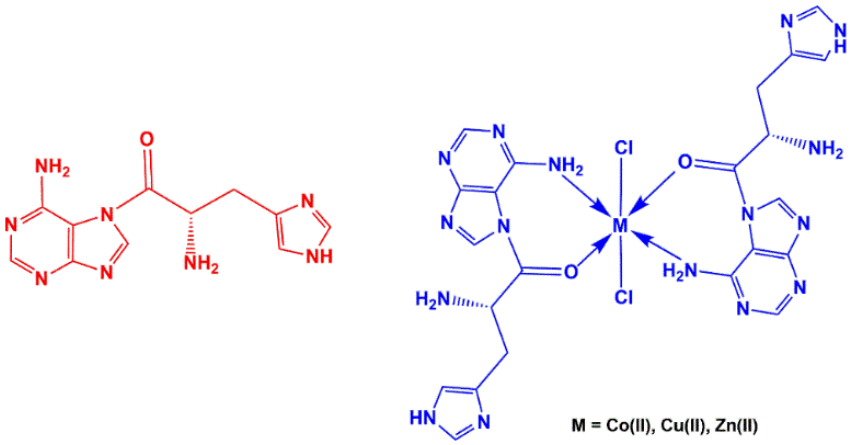

Figure 5. Structure of the ligand **(L5)** and its Co(II), Cu(II) and Zn(II) complexes

The structural framework of the synthesized amino acid derived ligands **(L1 – L5)** and their Co(II), Cu(II) and Zn(II) complexes were characterized by elemental analysis, conductometric measurements, magnetic susceptibility, mass spectrometry, UV-Visible, Fourier transform infrared (FT-IR), electron spin resonance (EPR), proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopic techniques. General structure of all the complexes was reported.

DNA binding study

The *in vitro* DNA binding ability of the synthesized ligands **(L1-L5)** and their Co(II), Cu(II) and Zn(II) complexes were studied by absorption titration, fluorescence spectroscopy, cyclic voltammetry, circular dichroic spectroscopy, thermal denaturation studies and viscosity measurements. The results indicate that these types of complexes can strongly bind with CT-DNA presumably *via* an **intercalation mechanism**.

Table 1. DNA binding properties of Co(II), Cu(II) and Zn(II) complexes of ligands **L1 – L5**

Ligands	K_b (M^{-1})		
	Co(II)	**Cu(II)**	**Zn(II)**
1,4-Naphthoquinone - Histidine **(L1)**	2.21×10^4	3.02×10^4	2.54×10^4
1,3-Indandione - Histidine **(L2)**	2.89×10^6	2.64×10^6	2.41×10^5
1,3-Indandione - Methionine **(L3)**	2.7×10^6	4.9×10^6	2.2×10^6
1,4-Naphthoquinone – Histidine - 1,10-Phenanthroline **(L4)**	2.64×10^5	3.11×10^5	2.41×10^5
Adenine - Histidine **(L5)**	2.78×10^7	3.15×10^8	2.42×10^8

The magnitude of the binding constants of Co(II), Cu(II) and Zn(II) metal complexes of the newly synthesized ligands were compared and it is found that among the 15 investigated complexes, the binding constant of the complexes with adenine and histidine have shown maximum binding efficacy with the largest binding constant value (10^7 - 10^8 M^{-1}). This might be due to smaller size of the ligands, adenine and histidine which

helps to be more accommodative for binding and thereby enhances the binding efficiency to a greater extent. It is also understood that, the presence of adenine which is a nucleobase biomolecule accomplishes the biocompatibility. From the results, it is evident that nucleobases can act as a potential ligand due to the presence of electron rich active site which can provide favorable condition for H-bonding and strong interaction.

In addition, there are few important insights obtained by exploring the DNA binding studies of metal complexes.

- Compounds with functional groups of electron accepting properties readily form donor-acceptor systems with intramolecular charge transfer. This kind of systems will make significant changes in their physiochemical properties and it will support strong binding efficacy effective binding with DNA. This information will be useful for designing drugs using inorganic metal complexes. The binding constant of metal complexes with 1,3-indandione and L-histidine support this point.
- The presence of electron rich element makes a significant effect in binding. For example, sulphur enhances diffusibility of the complex due to less steric effect of free moving atom towards the binding site of the DNA which provide favorable condition for binding. This is highlighted in the system of complexes with 1,3-indandione and methionine.
- Introduction of heterocyclic ring systems with extended conjugation will make significant impact on binding properties of the complexes. In the case of complexes with 1,4-naphthoquinone, L-histidine and 1,10-phenanthroline, the binding constant is increased 100-fold times compared to the binding constant of complexes without

1,10-phenanthroline. It is noteworthy to mention that the planarity of the ring also served as a contributing factor for effective binding.

- The results of antioxidant screening of all the complexes were compared and found to be appreciable. Among all the complexes, **Cu(II) complexes have maximum antioxidant potential** compared to other complexes through free radical scavenging mechanism.
- The antimicrobial screening data revealed that all the complexes possessed higher activity than the free ligands. This is due to chelation of ligand with the metal ions. *In vitro* cytotoxicity study of the complexes of L-histidine and 1,3-indandione revealed that the complexes have potential inhibition effect against NIH/3T3 mouse fibroblast cells. Among the set of complexes **Zn(II) complex** of L-histidine and 1,3-indandione ligand showed **higher cytotoxic effect**. This can be accounted for the significant role of Zn(II) in DNA-Zn finger recognition as gene therapy agent. The trend showed for cytotoxic activity of the complexes does not fold in line with the *in vitro* binding affinity and nuclease activity of metal complexes. This indicates that, the cytotoxic activity of the complexes follows a different mechanism. The present findings motivate further attempts to understand the relation of nuclease activity and cytotoxic effect of the complexes.
- Hence overall it can be concluded that the present studies have revealed useful insights for designing anticancer drugs. The essence of the project depicts that complexation of mixed Schiff base ligands with transition metal ions can produce synergistic effect in the biological activities of parent drug molecules and making metal conjugates more effective as therapeutic agents than their parent ligands. In

addition, it is found that copper compounds are endowed with unique bioactive properties and they exert excellent antioxidant and antimicrobial effect. Therefore, they could be active for breast cancer as well as microbial infections. This useful insight needs to be investigated further by *in vivo* studies.

Consolidated result of Binding and Biological activity

Activity	Complex
DNA binding	**Cu(II) complex** of Adenine – L-histidine
Antioxidant activity	**Cu(II) complex** of L-histidine and 1,3-indandione
Antimicrobial action	**Cu(II) complex** of Adenine – L-histidine
Anticancer activity	**Zn(II) complex** of Adenine – L-histidine