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# Theoretical and experimental studies of novel histidine derived Schiff base metal complexes, active towards biomedical and MCF 7 cell lines

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Novel tri-dentate ligand-metal complexes [Mn(II), Co(II), Cu(II), Ni(II) and Zn(II) (**1-5**)] have been synthesized using L-histidine amino acid derived Schiff base ligand and characterized using analytical and spectral methods like UV-visible, FT-IR and ESI-MS techniques. The antioxidant studies of the Schiff base ligand and 1-5 complexes reveal that complexes exhibit significant free radical scavenging activity against the free radical DPPH. *In vitro* cytotoxic activity of the **1-5** complexes evaluated against the breast cancer cell lines (MCF-7), reveal that complex **3** exhibits higher cytotoxicity than any other synthesized metal complexes. The docking studies have been carried out using BSA protein and DNA biomolecules with synthesized metal complexes. Antimicrobial studies has demonstrated that Cu(II) complexes possess higher activity against both Gram positive and Gram negative bacteria as well as Fungi.

**Keywords:** Amino acid Schiff base, Histidine biomolecule, Metal complexes, Anticancer activity, Docking studies, Antimicrobial activity

Metal ions produce considerable results in many cellular methods, including metabolism and cellular divisions that opens up a new route to examination of metal-organic frameworks as biological imaging and drug delivery agents. The properties of these lead the researchers to appraise the impact of metal based compounds for the treatment of several diseases, along with most cancers in humans. Schiff bases are generally used in coordination because of their great potential to form solid complexes with numerous metallic ions[1-8]. Schiff bases have also been discovered to show off a massive type of biological activities, consisting of antibacterial, anti-fungal, anti-viral, anti-inflammatory, anti-malarial, anti-proliferative and anti-pyretic properties[9-11]. Multi-dentate Schiff bases are extensively used as ligands, considering the fact that they form complexes due to their clean of coordination with metallic ions[12-29]. On previous few decades, the development of applications of transition steel complexes with N, O-donor ligands draws significant interest of the researchers. The practice of N, O-donor ligands via Schiff base condensation reaction is famous amid scientists. Most of the transition steel complexes with Schiff base ligands had been developed in some of essential fields of packages, for example, magnetism[30], optoelectronics[31], biological sciences[32], catalysis[33], sensing[34] etc. These areas reflect some of the most recent and yet largely unexplored trends in inorganic and bioinorganic chemistry that could be interesting and beneficial research topics for the community concerned with "metals in medicine". On the other hand, because of the coordination behaviour and high biological interest, some of the Schiff base complexes derived from amino acids have come to be a hot studies topic for years[35,36].

The complexation of amino acid with metal ion and its functionality enlarges the selective effect of DNA binding in addition to a few different therapeutic targets, which also gives key recognition thing for synthetic nuclease activity to the molecules[37]. Amino acids are biologically important natural molecules that play an essential position in production of proteins and are intermediates in metabolism. All the amino acids having one-of-a-kind functional groups including amine and carboxylic acid agencies, they are able to act as potential donor ligands to shape solid complexes with steel ions. The amino acid derivatives of Schiff base complexes play an essential position in mutating the gene expression due to their binding capacity with DNA double helix[38]. Among various amino acids, L-histidine is one of the clearly

occurring important amino acids for human vitamins and its miles having imidazole ring. Among the heterocyclic compounds present in nature, imidazoles are biologically energetic compounds[39,40]. Moreover, maximum of the herbal products containing imidazole group is also medicinally crucial[41,42]. Histidine may additionally even help with the making of serotonin, niacin, and auxin. Serotonin is a neurotransmitter related to mood, pressure response, sleep and urge for food regulation. Histidine coordinates with steel through the functional organizations of $NH_2$ and $COO^-$ moieties. As a part of our studies program, the designing of amino acid derived Schiff base metallic complexes has been performed by using the use of N, O, O tri-dentate Schiff base ligand which having L-Histidine and complexation with Cu(II), Co(II), Ni(II), Mn(II) and Zn(II) metallic ions. Further, these metallic complexes had been characterized by way of diverse spectral techniques like elemental analysis, FT-IR and mass spectrum.

Our purpose is the structural elucidation of the synthesised metal complexes and the look at the theoretical interactions of metal complexes with DNA and BSA protein molecule carried out using docking stimulation which helps to predict the mechanism of interactions. The binding interactions help to study furthermore biological activity with the synthesised compounds. The antimicrobial activities of the compounds had been evaluated in opposition to Gram-advantageous and Gram-poor bacteria. The antioxidant studies were carried out and show the compounds have a chance to become a good antioxidant property. The cancer studies were carried out using MCF-7 cell line cells, which prove that the complexes have a great potential towards cancer cells.

## Materials and Methods

All the chemicals have been received as reagent grade and used without any similarly purification. The L-Histidine, 2,4-dihydroxybenzophenone had been bought from Sigma Aldrich. The copper perchlorate, nickel perchlorate, manganese chloride, cobalt chloride and zinc perchlorate have been purchased from Aldrich. All different chemical reagents had been from AR grade and received commercially. The C, H and N analysis become accomplished on Elemental Vario EL III CHNOS elemental analyzer. Infrared spectra were carried out on an FT-IR Shimadzu 8400S spectrophotometer within the spectral variety 4000–400 $cm^{-1}$ the usage of KBr pellets. The UV-visible spectra have been measured on Shimadzu 2450 spectrophotometer. The ESI mass spectra of synthesised complexes had been recorded on DMSO UPLC-TQD Mass Spectrometer. The docking studies were carried out using Auto dock vina program.

### Synthesis of Ligand (L)

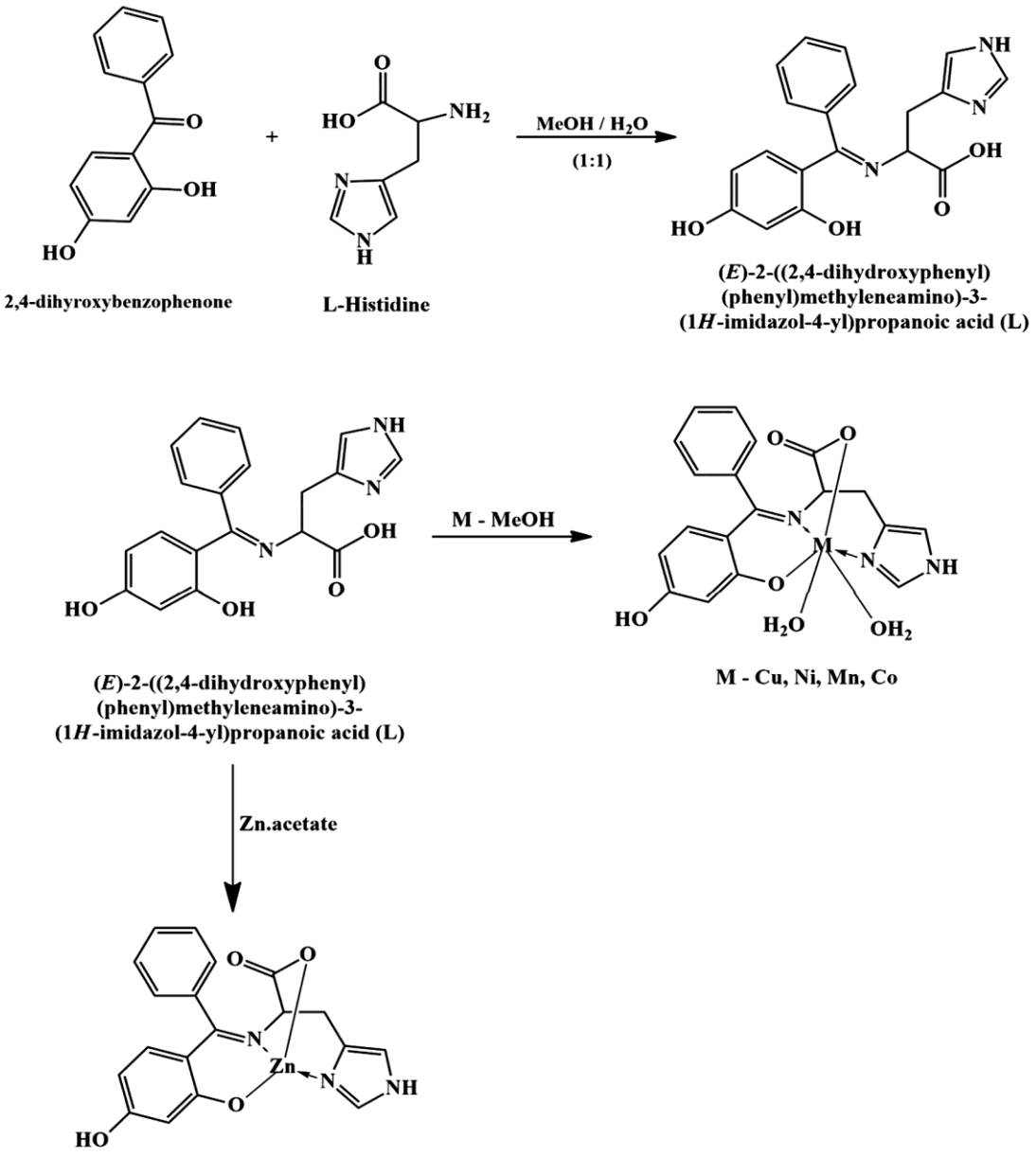
2,4-dihydroxybenzophenone (1.5 g) was dissolved in methanol (10 mL) and was added to a solution of L-Histidine (1.08 g) in hot water (10 mL). The resulting mixture was refluxed on a water bath for 4 h. The reaction mixture was kept into a beaker. When the solution got evaporated the yellow-coloured compound was thrown out after one day. The formed Schiff base compound was filtered, washed with acetonitrile, and dried in a vacuum. The ligand **L** was highly soluble in water.

### Synthesis of Cu(II), Ni(II),Co(II), Mn(II) and Zn(II) metal complexes

The metal complexes were prepared by a general procedure. Aqueous solutions of the metal salts (0.01 mol) were added to a hot solution of the ligand (0.01 mol) in methanol (10 mL). The pH of the solution was maintained as 6.5–7.5 range by adding triethylamine and was heated under reflux for 4 h. The reaction mixture was concentrated to half of its initial volume by evaporation. On cooling the solution, the separated complex was filtered off, washed successively with methanol: ether mixture, and dried in a vacuum. (Colours of the complexes: Cu – brown, Ni – red, Zn – yellow, Mn – dark green, Co – red). The reaction pathway is presented in Scheme.1.

### DPPH radical scavenging activity

Radical scavenging studies of **L** and metal complexes have been determined through measuring spectrophotometrically the alternate in absorbance of DPPH• at 517 nm[43]. The DPPH radical is a stable loose radical because of sizable delocalization of unpaired electron and has $\lambda_{max}$ at 517 nm. When DPPH absorbs a hydrogen radical from an external source, the DPPH absorption at 517 nm vanishes due to the absence of loose electron delocalization. Various concentrations of **L** (0, 200, 400, 600, 800, 1000, 1200 μM) or metal(II) complexes (0–500 μM) in methanol have been brought to DPPH in methanol (200 μM, 20 μL), and in each case the very last volume turned into making up to 1 ml with methanol. The final solution was shaken properly and incubated




Scheme 1 — Schematic representation of the reaction pathway for ligand formation and chelation

at 37 °C for 1 h within the dark. DPPH in methanol was used as manage without the test compounds. The actual value lowers in absorbance was measured against that of the standard. The % inhibition was calculated by using the absorbance values of control and samples.

$$\% \text{ inhibition} = [(A_{control} - A_{sample}) / (A_{control})] \times 100$$

where $A_{control}$ is the absorbance of DPPH radical without antioxidant and $A_{sample}$ is the absorbance in the presence of antioxidant. $IC_{50}$ values (concentration sufficient to obtain 50% of maximum scavenging activity) were calculated for **L** and **1–5** from the results of % inhibition.

**Molecular docking study**

The crystal systems of B-DNA dodecamer d (CGCGAATTCGCG)2 (PDB ID: 1BNA), BSA protein (PDB ID: 4F5S) and human-DNA–Topo-I complex (PDB ID: 1SC7)[26] had been received from the Protein Data Bank (http://www.Rcsb.Org/pdb). The coordinates of metal complexes were optimized and converted to the PDB format the usage of Mercury software[44]. The 'receptor' (DNA) and 'ligand' (steel complexes) files had been prepared

using Auto Dock Tools. The heteroatoms consisting of water molecules were removed and polar hydrogen atoms and Kollman expenses had been introduced to the receptor molecule. All other bonds have been allowed to be rotatable. In the docking analysis, the binding site changed into assigned throughout the complete minor and foremost grooves of the DNA molecule, which become enclosed in a container with the wide variety of grid factors in x × y × z instructions of 40 × 40 × 40 and a grid spacing of 0.375 Å. Docking research were conducted, the use of Auto Dock Tools (ADT) version 1.5.6 and Auto Dock vina program[45]. The docked systems had been exported to PyMol for visual inspection of the binding modes and for viable polar and hydrophobic interactions of the complexes with DNA. A similar technique became used for the docking of BSA protein with the complexes.

#### Antibacterial Studies

The disk diffusion method is widely used to evaluate the antimicrobial activity of test compounds. The synthesized compounds had been tested towards bacteria and various fungi traces, specifically *Bacillus subtils*, *Staphylococcus aureus* (as Gram-positive bacteria), *E.coli* (as Gram-bad bacteria) and the fungal traces, specifically *A. Niger*, *Penicillium* sp, by way of nicely diffusion method[46]. Chloramphenicol was used as the control. Stock solutions of examining compounds had been organized in 5% DMSO to a final attention of 10 mg $mL^{-1}$. The sterilized agar medium (20 mL) was poured into every pre-sterilized Petri dish and allowed to solidify by using placing it in an incubator at 37 °C for 1 h. The culture suspension was poured and smartly swabbed with the pre-sterilized cotton swabs. Then holes of 5 mm diameter have been punched cautiously the usage of a sterile cork borer and packed absolutely with the organized test compound (50 µL). These dishes had been transferred to an incubator maintained at 37 °C for 24 h. During this period, the check solution diffused and the boom of the inoculated microorganism was affected. Then the inhibition zone was evolved and measured at the end of the incubation period. Experiments were completed in triplicate and the usual deviation became calculated.

#### MTT assay: cytotoxicity measurement

The methylthiazolyldiphenyl-tetrazoliumbromide (MTT) assay was performed with the technique defined with the aid of Mossman[47]. Briefly, for 24 h the 96-multiwell dish seeded with cells ($1\times10^4$ cellular/well) changed into allowed connecting and become dealt with the varying concentration of the complexes. After the treatment, media changed, and cells were incubated for 3 h with 1.2 mM MTT dye in culture ordinary condition. Cell viability became evident by the transformation of tetrazolium salt MTT to formazan (coloured) by way of mitochondrial dehydrogenases using Micro plate Reader (7530, Technology, Inc., USA) at 570 nm, the alternate in shade was observed. In the control cost percent, cell viability is provided graphically.

## Results and Discussion

All the synthesized metal complexes are air stable. The tridentate donor ligand (L) = (E)-2-((4-(benzyloxy)-2-hydroxybenzylidene) amino)-3-(1H-imidazol-4-yl) propanoic acid reacts with metal ion and shape the stoichiometry of the complexes. The metal complexes are soluble remarkably in DMSO and DMF. The analytical and spectral information of those synthesized compounds expect an octahedral geometry for the complexes and the low molar conductivity values indicate that the synthesized complexes are non-electrolyte in nature.

#### FT-IR spectra

The FT-IR spectra of the synthesized complexes offer valuable statistics on the binding of useful groups of ligand to the complexation with ions. The ligand shows 3458 $cm^{-1}$ at the range of broad –OH stretching peak. The peak at 3170 $cm^{-1}$ suggests that the imidazole –NH peak. The azomethine formation was 1648 $cm^{-1}$ confirmed in the range which denotes the formation of the imine. The –OH bending peak was appearing at the range of 1391 $cm^{-1}$. In all the synthesised metal complexes, C=N stretching frequency is shifted in the area around 1624–1646 $cm^{-1}$. This shift suggests the coordination of the carbonyl and azomethine coordinate with the metal ion. The carbonyl institution of the amino acid (His) is coordinated by way of unique maxima positions $\nu\text{-}_{asy}$ $COO^-$ and $\nu\text{-}_{sy}$ $COO^-$. These uneven and symmetric stretching frequencies of histidine containing carboxylate anion ($COO^-$) in all complexes seem at ~1430 $cm^{-1}$ and ~1320 $cm^{-1}$, respectively, which also confirm the coordination of histidine to the central metal ion[48]. In addition, the amine ($-NH_2$) institution of corresponding amino acid coordinates to the steel ion that is confirmed by using appearance of

peaks in among the range of 3000-3270 $cm^{-1}$. It signifies the incorporation of histidine to the synthesized complexes[23]. The formations of M-N and M-O bonds are hooked up by using the existence of recent peaks seemed at round 441-479 $cm^{-1}$ and 525-588 $cm^{-1}$ due to the coordination of nitrogen and oxygen atom of the ligand to the metal ion. The FT-IR spectral results were shown in Supplementary Data, Fig. S1.

**Electronic spectra**

UV-visible spectrum of the ligand suggests three absorption function bands, the susceptible band at 248 nm due to the $\pi \rightarrow \pi^*$ stacking interaction of π-electrons present inside the fragrant ring containing C=C and azomethine group of HC=N and the major band at 296 nm which represents the $\pi \rightarrow \pi^*$.transition. The major absorption peak in the range of 340 nm denotes the $n \rightarrow \pi^*$. The electronic transitions of non-bonded electrons are available within the azomethine organization. In all complexes these characteristic bands of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are barely modified either in role or intensity due to the result of coordination of ligand to the metal ion. The metallic complexes show extra band of d-d transition, this d-d transition band is useful to expect the geometry of the complexes. The digital spectrum of copper complex shows the d-d band at 645 nm, which shows the $2E_g \rightarrow 2T_{2g}$. This d-d transition suggests the distorted octahedral geometry of the copper complex[49]. The cobalt complex shows d-d band at 620 nm, this band is assigned to $4T_{1g}$ (F) $\rightarrow$ $4T_{2g}$ (F) transition as the end result of octahedral geometry. The Mn(II) complexes also represent the same transition at 642 nm which shows the octahedral geometry. Furthermore, the absorption spectrum of the Ni(II) complex shows a d-d band at 658 nm, assigned to $3A_{2g}$ (F) $\rightarrow$ $3T_{1g}$ (F) transition which is attributed to octahedral geometry. It is also supported via the acquired magnetic moment value of 3.35 BM which is the function of octahedral geometry[50]. The zinc complex does not display any d-d band because of its absolutely packed $d^{10}$ configuration and it also famous the intra ligand charge. The electronic absorption spectra were shown in Supplementary Data, Fig. S2.

**ESI-mass spectral studies**

The ESI-mass spectrum of the synthesized compounds explains the formation of the newly synthesised compounds. The ligand having the total mass of m/z 352.71 which represent the [M+1] form of synthesised ligand. All the complexes shows M+1 metal ion peak itself. The metal complex **1** shows that molecular ion peak at 441.81 and complex **2** shows the corresponding complex peak at 445.05 m/z. The metal complexes **3**, **4** and **5** express the total mass peak in the range of 445.79, 449.58 and 416.25, respectively. The entire mass spectrum denotes that the water molecule took part in the complex formation. Thus, the entire found peaks make a good settlement with the formulae expected from micro analytical data. Moreover, the ESI mass spectral data guide the belief drawn from the analytical and conductance values. The mass results were shown in Supplementary Data, Fig. S3.

**Biological screening studies**

***In vitro studies of antimicrobial screening effects***

The Schiff base metal complexes have aggravated to wide interest because they offer diverse spectrum of organic and pharmaceutical activities. The bacterial lines can gain resistance to antibiotics through biochemical and morphological modifications. In this case, the ligand and its metal complexes of Cu(II), Co(II), Mn(II), Ni(II) and Zn(II) had been studied for their antimicrobial activity. This is essential to the sphere of medicinal and pharmaceutical areas. The synthesized compounds had been tested towards Gram-positive, Gram-negative bacteria, and various fungi traces, specifically *Bacillus subtills*, *Staphylococcus aureus* (as Gram-positive bacteria), *E.coli* (as Gram-negative bacteria) and the fungal traces, specifically *A.niger*, *Penicillium* sp, screened by micro dilution method. The Streptomycin and Nystatin were used as requirements for antibacterial and antifungal screening studies. The antimicrobial pastime records of the investigated compounds are given in Supplementary Data, Tables S1. The statistics display that the ligand containing nitrogen and oxygen atoms upon coordination with metallic ion complements the inhibitory interest of manufacturing of enzyme in micro-organisms. The metallic complexes have shown higher antimicrobial activity in comparison to Schiff base ligand which could be due to the chelating impact of ligand to steel ion at the normal cell method. This enhancement of antimicrobial interest of the metallic complexes can be explained by way of basis of chelation theory. Nevertheless, the synthesized steel complexes are bulky, however the chelation of a bulky ligand to a metal cation results within the overlapping of ligand

orbital with the steel orbitals causing reduction inside the polarity of the ion and thereby resulting in a delocalization of high-quality charge. As the lipophilic nature of the metal complicated increases, it complements the penetration of the microbial mobile membrane and blockading of steel binding web sites on enzymes, in doing so the interaction among the steel ion and the lipid may result in the breakdown of the permeability blockade of the mobile ensuing in obstacle of the ordinary metabolic hobby of the cell. According to Overtone's idea of cell permeability the lipid membrane that surrounds the mobile favours the passage of only lipid soluble substances due to which liposolubility is a crucial aspect that controls antimicrobial activity. Therefore, the antimicrobial pastime is dependent on the bulkiness of the synthesized compounds. These steel complexes additionally agitate the respiration manner of the cell and block the synthesis of proteins, which controls further growth of the microorganism. The microbial images were shown in Fig. 1 denotes the clear idea about the microbial activity. The Cu(II) complex shows overall best results towards the microbial activity.

***Antioxidant activity***

According to the applicable literature reports, most of the metal complexes can also show off antioxidant activity for developing the ability antioxidant and healing reagents. Mainly the hydroxyl loose radicals involved inside the damage of tissue, which is related to inflammation, consequently the removal of this loose radical is considered as foremost goal of antioxidant administration. In this paper, we achieved experiment of DPPH assay for exploring the antioxidant pastime of synthesized ligand and its blended ligand complexes in diverse awareness levels (10–40 µg/mL) using fashionable drug of ascorbic acid (Vitamin C). The radical capability of DPPH is strong. The results of these synthesized compounds are given in Supplementary Data, Table S2. These fact simply that the metal complexes show suitable antioxidant interest compared to ligand in all attention degrees and showcase almost identical loose radical inhibitory hobby in comparison to ascorbic acid. However, the antioxidant activity of the ligand enhances upon complication and increases the scavenging capability accordingly to guard the human body against diverse diseases. The study of antioxidants for the synthesized compounds is given in Fig. 2. The Mn (II) complex shows great antioxidant activity towards DPPH radical.

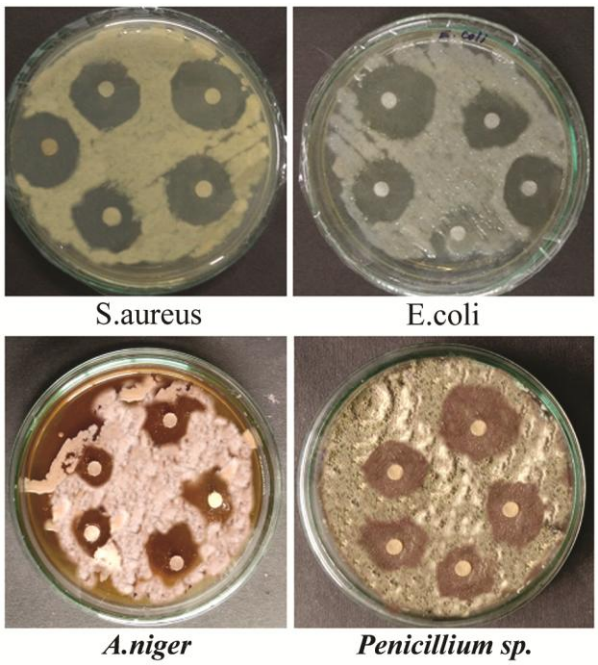



Fig. 1 — Antimicrobial studies of **1-5** metal complexes

**Cytotoxicity induction in MCF7 cells in culture**

***Cell viability: MTT Assay***

The MTT assay determines the study of feasible cells that can reduce the tetrazolium dye, MTT, to formazan, a compound of red colour. Other carefully related tetrazolium dyes also can be used. The discount of the dye determines mitochondrial activity. Nearly, for all mobile population mitochondrial activity (total) is interrelated with cell viability count, this assay is primarily used to evaluate cytotoxic impact of drugs. The determined results indicated a decrease in the viability of MCF7 mobile line when dealt with complexes (Supplementary Data, Fig. S4).

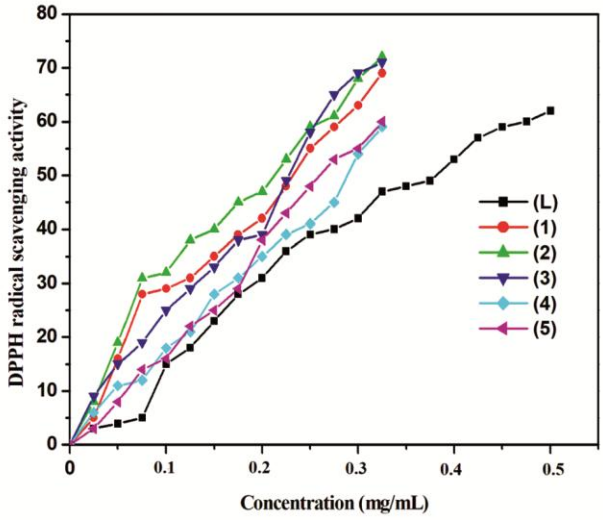



Fig. 2 — Antioxidant activity of L and metal complexes **1-5**

All the synthesised complexes affected mitochondrial enzyme interest causing a decrease in viability. Importantly, copper complex induces more cell loss of life in comparison to any other complexes. In the case of copper complex, the inhibition of cellular metabolism became statistically huge at better concentration (30 μM), whilst for the nearly equal extent of inhibition (50%) of feasible cells by other complexes become acquired at decrease concentration (20 μM) (Fig. 3). These results show the nature of primary ligand, ligand chelation with the metal ion, size of an atom, presence various parameter, pharmacokinetic factors and binding affinity of the metal complexes which are essential for anticancer activities of these newly synthesized complexes. The anticancer activity data were recorded in Supplementary Data, Table S3. The Cu(II) complexes shows great activity towards the MCF-7 cell lines.

**Docking Study**

***Molecular docking with DNA***

The molecular docking of complexes **1–5** into the DNA dodecamer collection d(CGCGAATTCGCG)2 was performed to are expecting the binding affinity and the chosen binding site alongside the sterically appropriate conformations. In general, the decrease the binding power, the more effective is the binding affinity between the 'receptor' and 'ligand' molecules. Conformations of docked complexes had been analysed in terms of strength, hydrogen bonding and hydrophobic interaction among complexes and DNA. The relative binding values are more terrible suggesting that the binding interplay between DNA and target molecule is strong. The compound containing an aromatic ring has higher free energy of binding, which offers a higher DNA binding affinity due to the extended aromatic ring, in comparison to the corresponding complicated containing aromatic ring. In addition, the most probable conformation of the mononuclear Cu(II) complexes is via the interplay of phenyl with DNA via intercalation that is stabilized through hydrogen bonding. The binding power values for docked metal complexes **1–5** are −9.1, −11.2, −10.5, −8.3 and −9.6 kcal $mol^{-1}$, respectively, with two, four and three hydrogen bonds with the DNA receptor. Complex **2** indicates a better binding power than the other complexes with docked DNA receptor due to the π–π stacking interaction of phenyl ring and also the polar interaction of the complicated with the docked receptor which offers strong hydrogen bonds. The binding electricity, binding residues and electricity-minimized docked poses for complexes **1–5** are summarized in Fig. 4. The docking effects reveal that each one the complexes interact with DNA through intercalation binding mode. Co(II) complexes shows best binding nature towards DNA molecule.

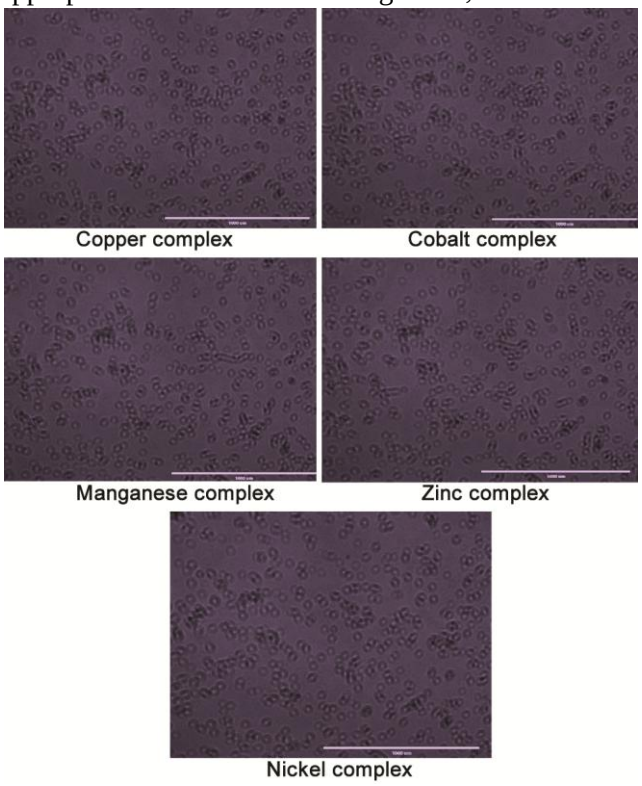



Fig. 3 — Anticancer activity of metal complexes **1-5** with MCF-7 cell lines

***Molecular docking study with BSA protein***

The binding site and the binding mechanism of complexes (**1-5**) – protein interaction, (PDB ID: 3VO3) using Auto Dock vina. The docking results show that the copper complex having great binding nature with BSA than other complexes (Fig. 5). It's found that the copper complex is most vital binding sites in BSA are within the nearness of Trp134 and Trp213. Trp213 is placed within a hydrophobic binding pocket and Trp134 is found on the surface within the hydrophilic region of the molecule. All the metal complexes effectively interact with BSA protein through hydrogen bonding and hydrophobic interactions. These interactions agree well with the many quenching of the fluorescence of BSA protein in the presence of the metal complexes. The binding power values for docked metal complexes **1–5** are −8.3, −7.3, −10.5, −7.8 and −8.9 kcal $mol^{-1}$, respectively. The Cu(II) complex shows best binding towards BSA molecule.

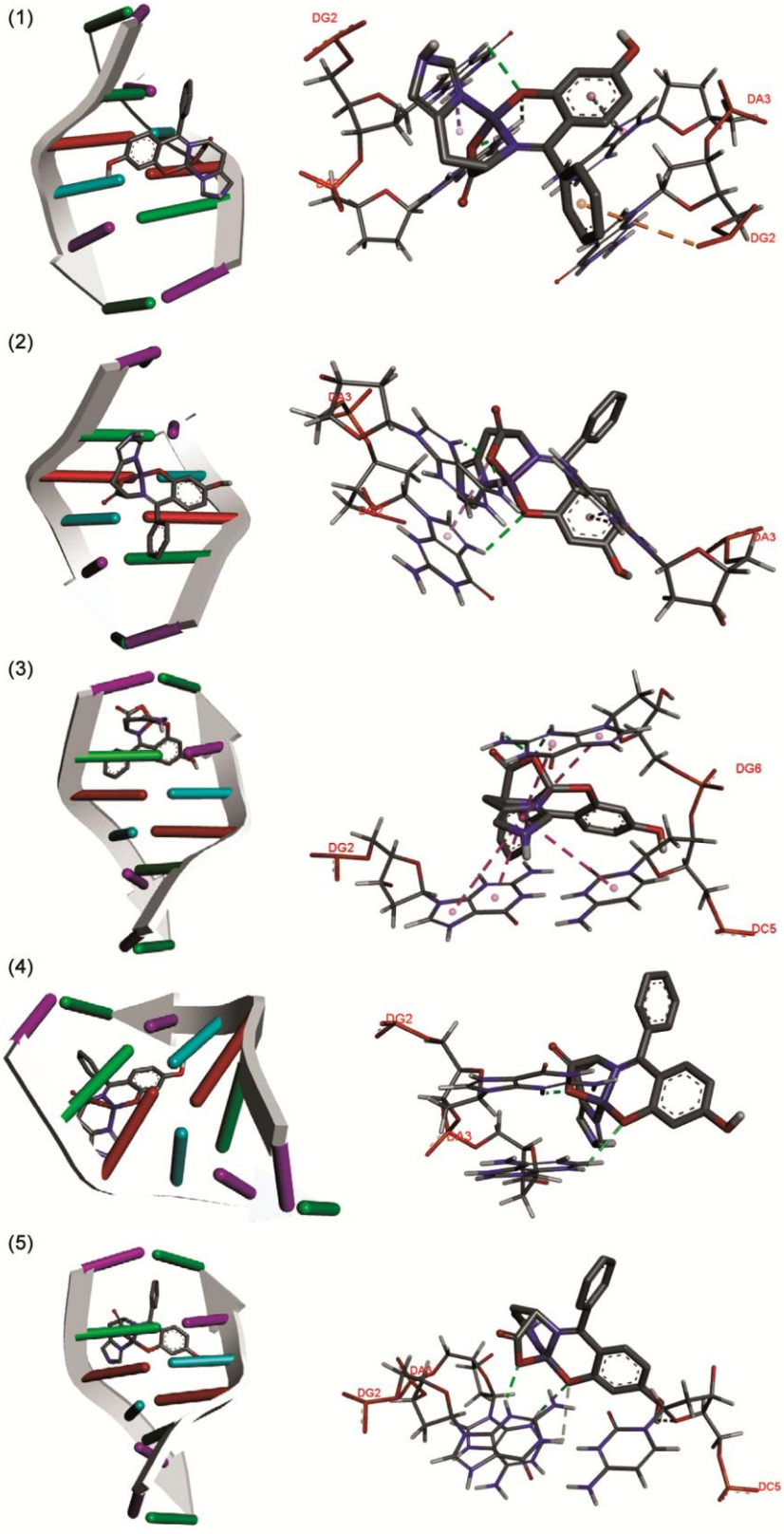



Fig. 4 — Docking studies of complexes **1-5** with DNA

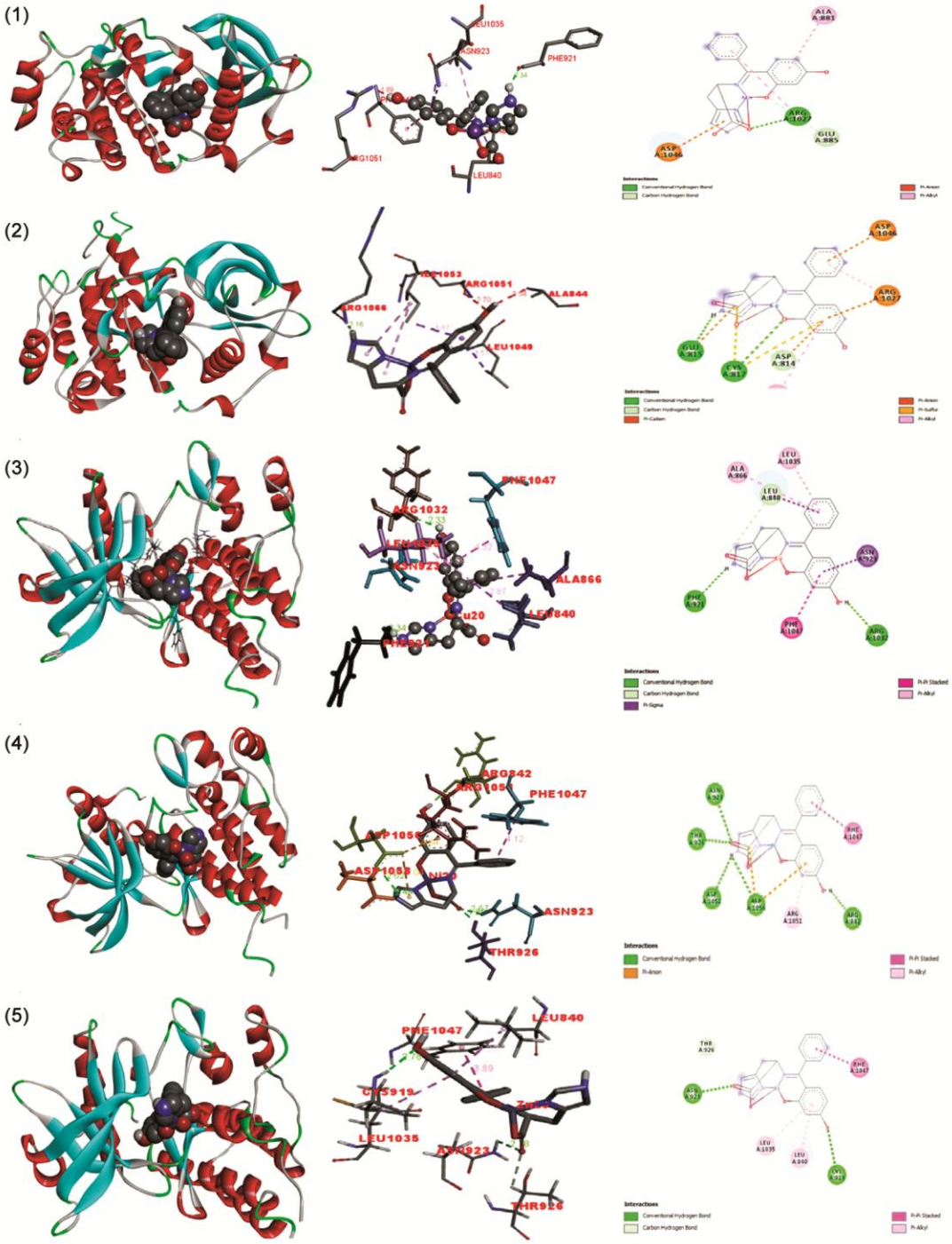



Fig. 5 — Docking studies of complexes **1-5** with BSA protein

## Conclusions

A novel Schiff base is derived from L-histidine amino acid and 2,4-dihydroxybenzophenone and its coordinated five metal complexes **1-5** were synthesized in this investigation. The synthesized complexes were characterized by UV-visible, FT-IR and ESI-MS spectral techniques. The antioxidant studies of the Schiff base ligand and **1-5** complexes reveal that the complexes exhibit significant free radical scavenging activity. The antimicrobial activities show that the Cu(II) complexes possess greater activity against gram positive, gram negative

and fungi. The Mn(II) complex shows greater antioxidant activity towards DPPH radical. *In vitro* cytotoxic activity of the **1-5** complexes were evaluated against the breast cancer cells (MCF-7), these results reveal that complex **3** (Cu(II)) exhibits higher cytotoxicity than any other synthesized metal complexes. The binding energy values of **1-5** with DNA are −9.1, −11.2, −10.5, –8.3 and –9.6 kcal $mol^{-1}$, respectively. The Co(II) complexes having enhanced binding nature value compared with other metal complexes for the docking study. For BSA protein binding the docking energy values were −8.3, −7.3, −10.5, –7.8 and −8.9 kcal $mol^{-1}$, respectively, which explains the Cu(II) complexes exhibit improved activity towards BSA molecule.

## Supplementary Data

Supplementary Data associated with this article are available in the electronic form at http://nopr.niscair.res.in/jinfo/ijca/IJCA_59A(12)1768-1777_SupplData.pdf.

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