Synthesis, Characterization, Antibacterial and Antioxidant Activities of Cu(II), Ni(II), and Zn(II) Mixed Ligand Complexes Containing Isoniazid Based Bidentate Schiff Base

Abstract

Two mixed ligands (L1, L2), L1 = N-(4-methoxybenzylidene) isonicotinohydrazone, L2 = 2-aminophenol, and their metal ((Cu(II), Ni(II), and Zn(II)) complexes with stoichiometry (1:1:1) were synthesized and characterized by analytical and physico-chemical techniques such as conductivity, magnetic susceptibility measurements, IR-spectra, and UV-Visible spectra. All of the metal complexes were 1:1 electrolyte, according to the molar conductance measurements. It can be concluded from the IR study that the ligands were coordinated to the corresponding metal ions through N and O donor sites of the azomethine nitrogen atom and the carbonyl oxygen atom. Magnetic moment and UV-Vis spectra data confirmed that square planar geometry for Cu(II), Ni(II) ion complexes, and tetrahedral structure for Zn(II) ion complex. The metal complexes of L1 were tested against *Escherichia coli* and *Pseudomonas sp.*Among the tested compounds, Cu(II)complex showed higher antibacterial activity over both bacterial strains against reference drug kanamycin.Moreover, synthesized metal complexes exhibited moderate antioxidant activity than the Schiff base. Cu(II) complexes were found to be most active whereas, Zn(II) complexes showed the lowest antioxidantactivity comparable to the BHT.

Keywords: Schiff base; Transition metals; Antibacterial; Antioxidant

1.Introduction

Schiff base is a condensation product formed when a primary amine reacts with an aldehyde or ketone.It is also known as imine or azomethine (-C=N-) and is a nitrogen analog of an aldehyde or ketone in which the C=O group has been replaced by an imine or azomethine group [1].Due to its ability to connect with multiple metal centers involving different coordination sites and enabling the production of coordination compounds, Schiff base metal complexes with nitrogen(N), sulphur(S), or oxygen(O) as ligands have become more remarkable [2].

Schiff bases are a kind of chemical compound with diverse uses. They've been utilized as ligands in a range of transition metal complexes [3]. Schiff bases are very essential in inorganic chemistry, especially coordination chemistry, since they quickly form stable complexes with a wide range of transition metal ions [4]. Schiff-bases and their metal complexes have attracted the attention of researchers due to their diverse biological actions

[5, 6]. Nevertheless, they are utilized in organic synthesis, medicine, chemical catalysis, pharmaceutics, chemical analysis, and new technologies [7]. These complexes exhibit a wide range of activities, including antibacterial [8-10], antifungal [11, 12], anticancer [13, 14], and anti-inflammatory agents [15,16]. Schiff base metal complexes are efficient catalysts in both homogeneous and heterogeneous processes [17-19], and the function of these metal complexes varies depending on the ligands, coordination sites, and metal ions [20]. In the biological arena, mixed ligand complexes play a significant role in the activation of enzymes by metal ions in a number of different ways. Schiff bases, for example, based on heterocyclic molecules such as P- anisaldehyde and furan 2carbaldehyde, have generated growing interest in bio-inorganic chemicals [19-21]. Isoniazid is one of the most potent medications and is the first-line treatment for tuberculosis (tuberculosis). Because of its high degree of antibacterial action, it is a recommended therapy material for Mycobacterium tuberculosis. It forms metal chelate complexes with a variety of physiologically significant bivalent ions [22-25]. We disclosed here the synthesis and characterization of novel mixed ligand complexes of Cu(II), Ni(II), and Zn(II) with 2-aminophenoland N-(4-methoxybenzylidene)isonicotinohydrazoneobtained from p-anisaldehyde and isoniazid. Some bioactivity test findings, such as antibacterial and antioxidant properties for ligands and their metal complexes, were also mentioned.

2.EXPERIMENTAL METHODS

The weighing operation was performed with the help of a METTLER PM 200 electronic balance.The melting or decomposition temperatures of all the prepared metal complexes were observed in an electro thermal melting point apparatus model o.AZ6512.Infrared spectra of the ligands and complexes were recorded on a FTIR-8400, SHIMADZU, Japan using a KBr disc at the Central Science Lab of Rajshahi University.The Electronic spectra of the complexes in solution phase (1×10^{-5} M) were recorded in the range of 200-800 nm on a Thermo-electron Nicolet evolution 300 UV-Vis spectrophotometer. Conductivity measurements of the complexes were carried out in *N, N´*-dimethylformamide (DMF)using Horiba conductivity meter B173 in which cell constant is fixed.^{1}H NMR spectra were measured on a Bruker400, Ultra Shield TM spectrometer using $CDCl_3$ as asolvent.A Sherwood Scientific Magnetic Susceptibility Balancewas used to measure the magnetic moment values.Elemental analysis was carried out on a LECO (CHNS-932) elemental analyzer. The purity of all thesecompounds was tested by thin layer chromatography (TLC) on Silica gel-GF 254 (Merck)coated plates.

2.1.Synthesis of N-(4-methoxybenzylidene) isonicotinohydrazone Schiff base Ligand(L1)

N-(4-methoxybenzylidene) isonicotinohydrazone Schiff base Ligand was prepared (Scheme 1) by the condensation reaction of Isoniazid (INH) and P-anisaldehyde in anequimolar ratio (1:1). INH(1.374 g, 10.00mmol) was intermixed with ethanol (15 mL) and then the mixture was poured in a round bottom flask with extra ethanol for a homogeneous mixture solution. Moreover, 4-methoxybenzaldehyde (1.22 mL, 10.00 mmol) was added up drop-wise over 5 minutes and washed with ethanol (5mL). The reaction mixture was refluxed for 5 hours and also the color of the solution (yellow) converted into white. After completion of the reaction, it allowed to cool slowly and to stand overnight. Eventually, it produced a white crystalline solid which was filtered off and dried in a desiccator over anhydrous $CaCl_2$.

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N-(4-methoxybenzylidene) isonicotinohydrazone

$C_{14}H_{13}N_3O_2$; White solid, yield 74 %, mp., 110 ^{0}C, IR spectrum, ν, cm^{-1}: 1658.70 (C=O), 1593.61 (C=N). UV-Vis spectrum, λ_{max}, nm: 267, 318. Elemental analysis for $C_{14}H_{13}N_3O_2$:Found, %: C, 65.87; H, 5.12; N, 16.45; O, 12.55. Calculated, %: C, 65.86; H, 5.10; N, 16.46; O, 12.54

Scheme 1: Synthesis of Schiff base ligand L1

2.2.Synthesis of Mixed Ligand Complexes

The synthesizedSchiff base ligand (L1) having 0.255g, 1mmol was dissolved in methanol (10 mL). Then, the hot methanolic solution of ligand andequimolar 2-aminophenol (0.110 g, 1 mmol)which was used as a secondary ligand (L2) were added up drop-wise unitedly in the heatedmethanolic solutions (10 mL, 1 mmol) of nitrate salts (0.254 g, 1mmol)of metals for-instance; Cu(II), Ni(II), and Zn(II). In addition, the mixture was refluxed for 3 hours and after completion of the reaction, it allowed tocool slowly and to stand overnight.The obtained precipitate was filtered, washed with a-few times with methanol, and dried under vacuum on anhydrous $CaCl_2$. The synthesized metal complexes were soluble in dimethyl sulfoxide (DMSO) and N, N-dimethylformamide(DMF).

[Cu(L1)(L2]NO$_3$:

[Cu$C_{20}H_{19}N_5O_6$]; F.wt.(g/mol): 488.94; Yield: 78%; Color:Dark olive green solid, mp.,>300 °C. Molar conductance (Ω^{-1} cm^{2}mol^{-1}): 85. μ_{eff}, B.M: 1.83. IR spectrum, ν, cm^{-1}: 452.12 (M–N), 528.02 (M=O), 1552.72 (C=N), 1607.46 (C=O). UV-Vis spectrum, λ_{max}, nm: 272, 352. Elemental analysis for $CuC_{20}H_{19}N_5O_6$;Found, %: C, 49.13; H, 3.92; N, 14.32; O, 19.63; Cu, 13.00. Calculated, %: C, 49.09; H, 3.89; N, 14.32; O, 19.63; Cu, 13.00.

[Ni(L1)(L2)]NO$_3$:

[$NiC_{20}H_{19}N_5O_6$]:F.wt.(g/mol):484.09; Yield: 67%; Color:Gold solid, mp.,>300 °C. Molar conductance (Ω^{-1} cm^{2}mol^{-1}): 90. μ_{eff}, B.M: 1.23. IR spectrum, ν, cm^{-1}: 459.02 (M–N), 530.97 (M=O), 1552.49 (C=N), 1608.04 (C=O). UV-Vis spectrum, λ_{max}, nm: 269, 354.Elemental analysis for $NiC_{20}H_{19}N_5O_6$;Found, %: C, 49.62; H, 3.96; N, 14.47;O, 19.83; Ni, 12.12. Calculated, %: C, 49.58; H, 3.92; N, 14.46; 0, 19.83; Ni, 12.12.

[Zn(L1)(L2]NO$_3$:

[$ZnC_{20}H_{19}N_5O_6$]: F.wt.(g/mol): 490.78; Yield: 61%; Color: White solid, mp., 191 °C. Molar conductance (Ω^{-1} cm^{2}mol^{-1}): 88. μ_{eff}, B.M: 0.63. IR spectrum, ν, cm^{-1}: 460.38 (M–N), 530.45 (M=O), 1557.79 (C=N), 1660.51 (C=O). UV-Vis spectrum, λ_{max}, nm: 271, 326, 380. Elemental analysis for $ZnC_{20}H_{19}N_5O_6$;Found, %: C, 48.95; H, 3.90; N, 14.27; O, 19.56; Zn, 13.32. Calculated, %: C, 48.91; H, 3.87; N, 14.26; O, 19.56; Zn, 13.32.

3.RESULTS AND DISCUSSION

All complexes with a distinct color, stable at room temperature were insoluble in polar solvent but soluble in DMSO and DMF. At room temperature, the molar conductance values of all prepared complexes were measured (10^{-3} M) in DMF solvent. According to conductance investigations, all complexes were electrolytic, and nitrate complexes were 1:1 electrolyte [26, 27]. The magnetic moment value for Cu(II) complex was 1.83 B.M, demonstrating that it is paramagnetic and corresponds even with a square planar shape [28].

The result for the Ni(II) complex was 1.23, indicating diamagnetic nature with square planar geometry, while the Zn(II) ion complex was 0.62 B.M with tetrahedral structure [29-31].

IR Spectral Studies

The IR spectra of the free ligand showed two distinctive bands close at 1658 cm^{-1} and 1593 cm^{-1} owing to the ν(C=O) and ν(C=N) stretching, respectively (Figure 1) [32, 33]. The bond C=O stretching was moved to lower values (1600–1608) cm^{-1} in the spectra of Cu(II), Ni(II), and Zn(II) complexes suggesting the coordination of carbonyl oxygen to the metal ions (Figure 1). This was further confirmed by the new absorption bands at 528–531 cm^{-1} in the IR spectra of complexes due to metal-ligand M–O interaction [32, 34]. The medium peak observed close at 1593 cm^{-1} was due to imine bond C=N stretching. This band was moved to lower wavenumbers from 1552–1558 cm^{-1} region in the spectra of the produced complexes showing the coordination of the metal ions via azomethine nitrogen and this was confirmed by the other bands in the range 452–461 cm^{-1} due to ν(M–N) vibration [33-35]. The IR spectra of mixed ligand complexes revealed a prominent sharp line at 1383 cm^{-1} that may be attributed to uncoordinated nitrate ion [27].

From the IR data, it leads to infer that two ligands as a bidentate way have coupled to metal centers through azomethine nitrogen and carbonyl oxygen respectively.

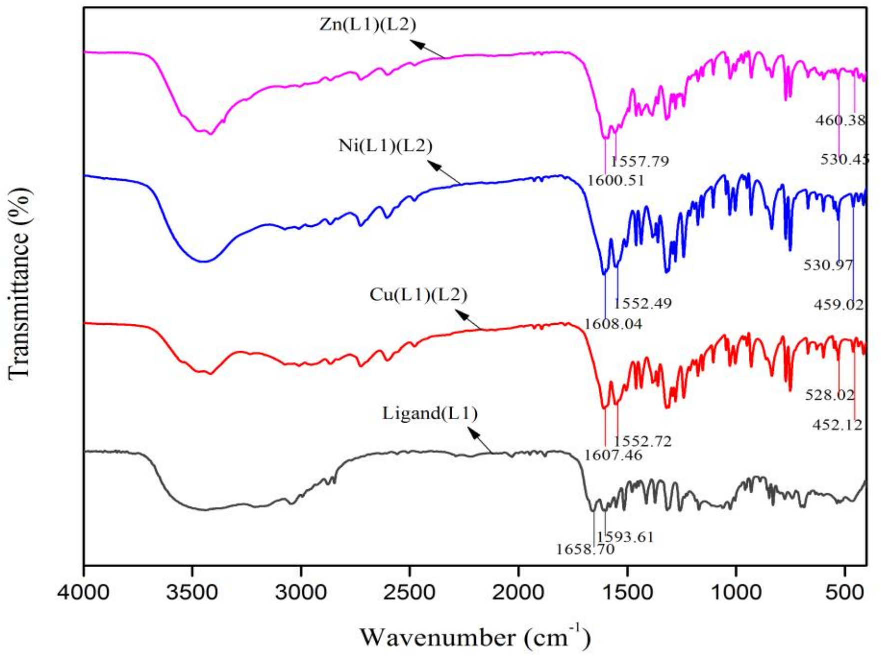

Figure 1:IR Spectra of the ligand L1, and its Mixed Ligand Complexes with L2.

UV- VisibleSpectra

UV-Visible spectrum of the ligand (L1) showed two broad bands at 267 and 318 nm region (Fig. 2), assigned to π-π* and n-π* transitions [36]. In the complexes these bands moved towards longer and lower wavelengths compared to their free ligand and showed the charge transfer transitions from the ligand to metal (LMCT) and vice versa [31]

In the UV-region, the electronic spectra of the Cu(II), and Ni(II) complexes displayed two absorption bands in the region 269-272 nm, and 352-354 nm, attributed to π-π*, and charge transfer band(C.T) [37]. On the contrary, the spectra of Zn(II) complex showed three strong bands in the region 271 nm assigned to π-π, 326 nm assigned to n-π*, and 380 nm attributed to MLCT transitions, respectively [37-40]

Therefore, the effective magnetic moment values and electronic transitions complied with the square planar structure for Cu(II), and Ni(II) complexes as well as tetrahedral structure for Zn(II) ion complex.

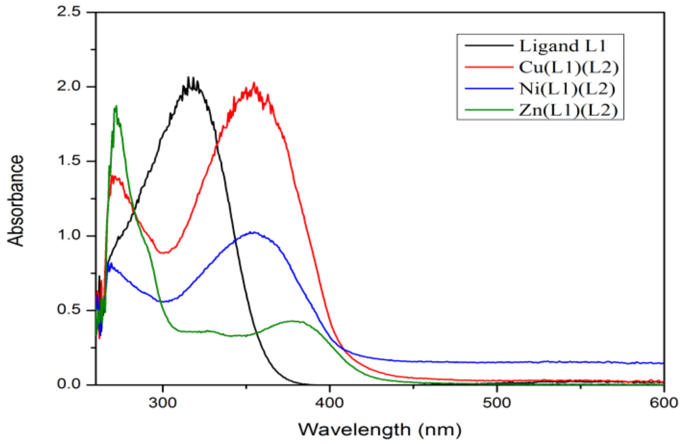

Figure 2:UV- Visible Spectra of the L1 and its Mixed Ligand Complexes with L2.

On the basis of the above characterizations, the probable structure of complexesisgiven below

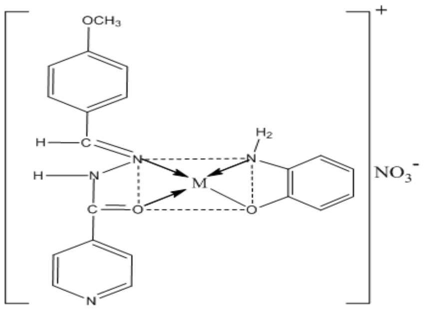

Figure 3: The proposed geometry of mixed ligand complexes for L1 and L2where, M=Cu(II), and Ni(II)

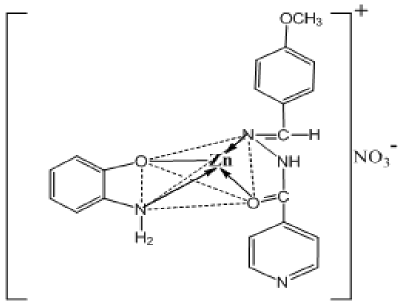

Figure 4: The proposed geometry of mixed ligand complexes for L1 and L2

4.Pharmacology

Antibacterial Activity

The antibacterial activity of Schiff base ligands and mixed ligand complexes against Escherichia coli and Pseudomonas sp. was studied at a concentration of 100 g/ 10L in DMF. The diameter of the inhibitory zone was measured in millimeters, and the results of their antibacterial activity are reported in **Table 1** and shown in **Fig. 5**. The Schiff base ligands did not exhibit any inhibitory zone against the tested bacterial strains. Furthermore, $[Cu(L1)(L2)]NO_3$ was found to have the best antibacterial activity, with a zone of inhibition extending from 6 to 6 mm against Pseudomonas sp. and Escherichia coli. E. coli was unaffected by the Zn(II) complex. In addition, the increased activity of the complexes may be understood by Overtone's idea and Tweedy's chelation hypothesis [41]. The considerable antibacterial activity of metal complexes is owing to their lipo-solubility nature derived from lipid-soluble components, which is a key control element in antibacterial activity. The polarity of metal ions is decreased during chelation owing to overlap and partial sharing of positive charge by the metal ion with the orbitals of the donor groups of the ligands. Metal ions may so readily be adsorbed on the surface of an organism's cell wall. As a result, it inhibits cell respiration and prevents protein synthesis. This, in turn, restricts the development of new organisms. Apart from that, the methyl group plays an important role in increasing the lipophilic nature of metal complexes, which is the reason for their remarkable antibacterial activity, with other factors such as solubility, coordinating sites, complex geometry, steric, concentration, and hydrophobicity having a significant impact on antibacterial potency [41-43].

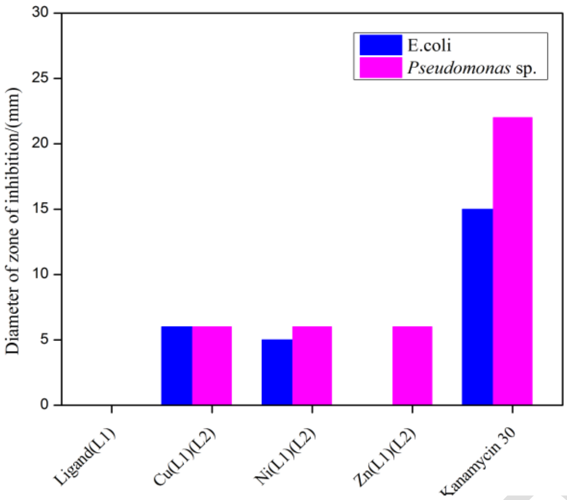

Fig 5: Graphical representation of antibacterial activity of ligand L1 and its metal complexes against *Escherichia coli* and *Pseudomonas* sp. with Kanamycin-30 standard.

Table 1: Antibacterial activities of ligand L1, L2, and its metal complexes

Diameter of Zone of Inhibition (mm) of tested compounds (100µg/disc)		
Compounds	Gram Negative	
	Escherichia coli	*Pseudomonas* sp.
Kanamycin (30 µg/disc)	15	22
Ligand (L1)	-	-
[Cu(L1)(L2)] NO_3	6	6
[Ni(L1)(L2)] NO_3	5	6
[Zn(L1)(L2)] NO_3	-	6

Antioxidant activity

Antioxidant activity of the prepared ligand and its mixed ligand complexes with metal ions was investigated using the free radical compound 2, 2-diphenyl-1-picryl hydrazyl (DPPH), and BHT(butylated hydroxytoluene) as a standard at different concentrations (20, 40, 60, 80, and 100 µg/mL). When DPPH was dissolved in DMF, it became pale red [44]. The percentage of DPPH radical scavenging activity as well as the IC50 values of BHT, ligands, and mixed ligand complexes are given in 2 and illustrated in Fig. 6-7. According to the findings, all of the metal complexes showed moderate DPPH radical scavenging activity, which was similar to BHT, when compared to Schiff base ligands. Cu(II) complexes outperformed Ni(II) and Zn(II) complexes in terms of antioxidant activity when compared to standard BHT. The variation in the antioxidant activity of the Schiff base metal complexes may be attributed to the coordination environment and redox properties. The redox properties of metal complexes are influenced by several factors, including axial ligation, chelate ring size, and chelate ring unsaturation [42, 43]. Cu(II) complexes have higher antioxidant activity than other synthesized complexes may be due to its reducing ability and proton donation characteristic, which allows Cu^{2+} to serve as a superoxide scavenging center [45]. The modest antioxidant activity of Ni(II) complexes may be attributed to steric hindrance caused by geometric structure, which prevents the radical approach of DPPH to active complex centers. Furthermore, since the Zn(II) ion is not a transition metal and therefore cannot participate in electron-transfer processes, its activity is reduced [45].

Table 2: % of Scavenging activity and IC_{50} values of BHT, ligand-L1, and its mixed ligand complexes with L2

Conc. (µg/mL)	% BHT	% L1	% $[Cu(L1)(L2)]NO_3$	% $[Ni(L1)(L2)]NO_3$	% $[Zn(L1)(L1)]NO_3$
20	10.61	1.00	12.70	12.30	2.69
40	23.06	1.70	22.91	25.00	3.54
60	30.96	3.20	25.13	26.18	5.09
80	34.23	5.38	27.56	25.26	7.50
100	38.76	7.12	28.77	25.78	9.34
IC_{50}	126.60	641.90	204.50	259.10	574.10

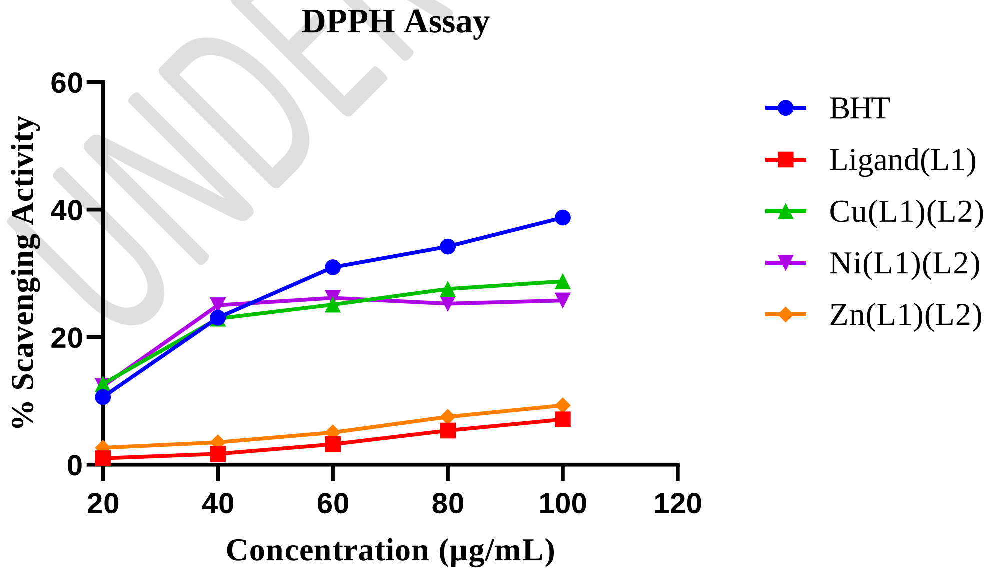

Fig. 6: DPPH radical scavenging activity of the mixed ligand complexes of ligand-L1, and L2 at different concentrations (20, 40, 60, 80, and 100 µg/mL with standard antioxidant BHT.

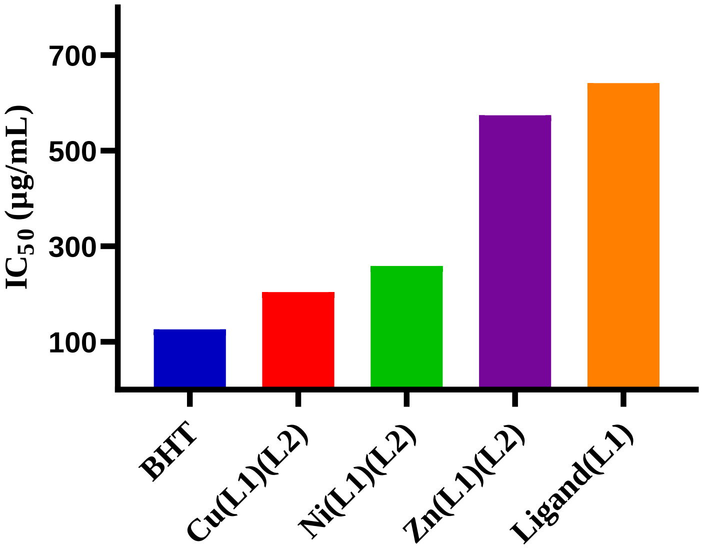

Fig. 7: IC_{50} value of the mixed ligand complexes of ligand-L1, and L2 at different concentrations (20, 40, 60, 80, and 100 µg/mL with standard antioxidant BHT.

CONCLUSIONS

A variety of novel Cu(II), Ni(II), and Zn(II) complexes generated from Schiff base ligand and 2-aminophenol have been successfully synthesized and spectroscopic and analytical techniques have been used to describe them. The ligands coordinated to central metals through N and O atoms, according to the IR spectrum study. On the basis of IR, UV-Vis, and magnetic susceptibility data, a square planar geometry for Cu(II) and Ni(II) complexes and a tetrahedral geometry for Zn(II) complexes may be suggested. In comparison to Schiff base ligand and other complexes, Cu(II) complexes have the most antibacterial activity. When compared to BHT, Zn(II) complexes had the lowest antioxidant activity than Cu(II) and Ni(II) complexes.

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