Mixed Ligand Complexes of Cu(II), Ni(II), and Zn(II) ions containing N-(4-methoxybenzylidene)isonicotinohydrazone Schiff base and 1,10-Phenanthroline : Synthesis, Characterization, Antimicrobial and Antioxidant properties

Abstract

N-(4-methoxybenzylidene) isonicotinohydrazone (La) Schiff base ligand was prepared by the condensation reaction of isonicotinic acid hydrazide (INH) and 4-methoxybenzaldehyde. A series of metal complexes of Cu(II), Ni(II), and Zn(II) was synthesized with Schiff base ligand (primary ligand, La) and 1, 10-phenanthroline (L1) as a secondary ligand in stoichiometry ratio (1:1:1). Moreover, the synthesized ligand and its complexes have been characterized by analytical and physical properties, conductivity, magnetic susceptibility measurements, FTIR-spectra, and UV-Visible spectra. Conductivity measurements indicated that all complexes were 1:2 electrolytes in nature. IR spectra recommended that the oxygen of the carbonyl group (=CO) and nitrogen of the azomethine group (-C=N) were coordinated with metal ions. The confirmation of a square planar structure for Cu(II) and Ni(II) complexes, as well as a tetrahedral structure for the Zn(II) ion complex, was supported by their respective magnetic moment values and UV-Visible spectra.The metal complexes of La with L1 were tested against *Escherichia coli* and *Pseudomonas sp.*Among the tested compounds, Zn(II)complex showed higher antibacterial activity over both bacterial strains against reference drug Kanamycin-30.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; DPPH

1. Introduction

Compounds with the formula of the azomethine group (-C=N-) are called Schiff bases, which are derived from the condensation reaction of primary amines and carbonyl compounds containing aldehydes or ketones [1-3]. Schiff bases are terrific coordinating ligands [4]. In the last decade, Schiff base ligands have gained more attention mainly by reason of their wide uses in the field of catalysis, biomimetic modeling as well as designing molecular magnet molecules and because of their antimicrobial and antifungal activity [5, 6].Moreover, they are an intriguing class of ligands that have played a significant role in coordination chemistry [7-10] and inorganic chemistry because they readily form stable complexes with most transition metal ions [11]. Furthermore, they have various applications in biological, clinical, analytical, electrochemistry, medicinal, and industrial studies in addition to they are used as liquid crystals in the field of analytical, medicinal, and polymer chemistry [12-14]. As-well, Schiff bases and their complexes exhibit biological activities including antibacterial, antifungal, anti-oxidative anti-inflammatory, anti-tumor, anti-cancer, and anti-HIV [15-18].Mixed ligand complexes having a significant role in the biological field as represented by several ways in which enzymes are known to be activated by metal ions.Schiff bases which derived from heterocyclic compounds for instance; P- anisaldehyde and furan- 2-carbaldehyde have fascinated an escalated interest in the field of bioinorganic chemistry[19-21]. Isoniazid which is known as isonicotinylhydrazide(INH) in addition to it is an organic compound that is one of the most powerful drugs and the first-line medication drugs for treating and preventing tuberculosis. It is considered as standard treatment material by the World Health Organization (WHO) against Mycobacterium tuberculosis bacteria due to its high antibacterial activity. It forms metal chelate compounds with diverse bivalent ions having moderate to better biological importance [22-25].

In view of the versatile importance of Schiff base ligands and their metal complexes, we hereindescribed thethe coordination behavior of a Schiff base (La) derived from the p-anisaldehydeand isoniazid, as well as their metal complexesspecifically; Cu(II), Ni(II) and Zn(II) in the presence of 1,10 phenanthroline(L1) as a secondary ligand.Some results of bioactivity tests such asantimicrobial and antioxidant activities for ligands and their metal complexes were also encompassed.

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 (La)

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 $CaCl_2$.

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, La

2.2.Synthesis of Mixed Ligand Complexes

The synthesizedSchiff base ligand (La) having 0.255 g(1mmol) was dissolved in methanol (10 mL) solution. Then, the hot methanolic solution of ligand andequimolar 1,10-phenanthroline hydrate (0.198 g, 1 mmol), which was used as a secondary ligand (L1) 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).

$[Cu(La)(L1](NO_3)_2$:

$[CuC_{14}H_{13}N_3O_2]$; F.wt.(g/mol): 498.55; Yield: 71%; Color:Munsell yellow solid, mp., 216 °C. Molar conductance (Ω^{-1} cm^2mol^{-1}): 145. μ_{eff}, B.M: 1.83. IR spectrum, ν, cm^{-1}: 528.51 (M–N), 598.53 (M=O), 1557.52 (C=N). 1607.25 (C=O). UV-Vis spectrum, λ_{max}, nm: 275, 323, 378. Elemental analysis for $CuC_{14}H_{13}N_3O_2$;Found, %: C, 50.10; H, 3.38; N, 15.74; O, 20.54; Cu, 10.18. Calculated, %: C, 50.08; H, 3.37; N, 15.73; O, 20.55; Cu, 10.20.

$[Ni(La)(L1)](NO_3)_2$:

$[NiC_{14}H_{13}N_3O_2]$:F.wt.(g/mol): 493.69; Yield: 61%; Color:Dark green solid, mp., 276 °C. Molar conductance (Ω^{-1} cm^2mol^{-1}): 140. μ_{eff}, B.M: 1.31. IR spectrum, ν, cm^{-1}: 534.78 (M–N), 590.85 (M=O), 1530.18 (C=N), 1603.59 (C=O). UV-Vis spectrum, λ_{max}, nm: 263, 296, 386. Elemental analysis for $NiC_{14}H_{13}N_3O_2$;Found, %: C, 50.50; H, 3.42; N, 15.86; O, 20.72; Ni, 9.48. Calculated, %: C, 50.47; H, 3.40; N, 15.85; O, 20.71; Ni, 9.49.

[Zn(La)(L1)$(NO_3)_2$:

[$ZnC_{14}H_{13}N_3O_2$]: F.wt.(g/mol): 500.38; Yield: 79%; Color:White solid, mp., 266 °C. Molar conductance (Ω^{-1} cm^2mol^{-1}): 150. μ_{eff}, B.M: 0.75. IR spectrum, ν, cm^{-1}: 530.45 (M–N), 597.77 (M=O), 1552.12 (C=N), 1608.99 (C=O). UV-Vis spectrum, λ_{max}, nm: 270, 362. Elemental analysis for $ZnC_{14}H_{13}N_3O_2$;Found, %: C, 49.95; H, 3.39; N, 15.69; O, 20.46; Zn, 10.45. Calculated, %: C, 49.93; H, 3.36; N, 15.68; O, 20.48; Zn, 10.46

3. Resultsand Discussion

All complexes were insoluble in polar solvent but soluble in DMSO and DMF. In addition, allcomplexes were quite stable and may be stored without any noticeablechange.Conductivity of complexes was in the range 140-150ohm^{-1} cm^2 mol^{-1}which indicated 1:2 electrolytic in nature [26, 27].Magnetic susceptibility values revealed that the value of the magnetic moment in the case of Cu(II) complex was 1.83 B.M which indicates paramagnetic and also corresponds to a square planar geometry[28]. For the Ni(II) complex, the value of magnetic moment was 1.31 indicatingthe diamagnetic nature with square planar geometryand on the other hand, tetrahedral structure for Zn(II) ion complex with 0.75 B.M [29-33].

IR Spectral Studies

The IR spectrum of the free liganddisplayed typical bands at 1659cm^{-1}and 1594 cm^{-1} due to the ν(C=O) and ν(C=N) functional groups respectively (**Figure 1**) [34-36]. In IR spectra of metal complexes, the band of Schiff base ligand(1659 cm^{-1}), assigned to the ν(C=O) stretching vibration of the primary ligand wasshifted tolower frequencies ranging 1603–1609 cm^{-1} in theCu(II), Ni(II), and Zn(II) complexes which indicated the carbonyl oxygen of the Schiff base ligand coordinated to the metal ions (**Figure 1**). The new absorption bands at 597–628cm^{-1} in the IR spectra of complexes observed due to M–O stretching vibrations [37-39]. On complexation, the azomethine (-C=N) band (1594 cm^{-1}) of the free Schiff base was shifted to lower wavenumbers from 1552–1558 cm^{-1}region in the synthesized complexes containing Cu(II), Ni(II), and Zn(II) metal ions besides, it adaptsthe involvement of the azomethine nitrogen atom in the coordination of the metal ions. Moreover, the other bands emerged at 528–535 cm^{-1} in the IR spectra of these metalcomplexes because of ν(M–N) vibration [40-41]. The IR spectra of mixed ligand complexes showed a strong sharp band at1384 cm^{-1} that can be assigned to uncoordinatednitrate ion [27]. All of these IR data confirm two ligands coordinated in Cu(II), Ni(II), and Zn(II) metal complexes throughtheir O and N atoms respectively.

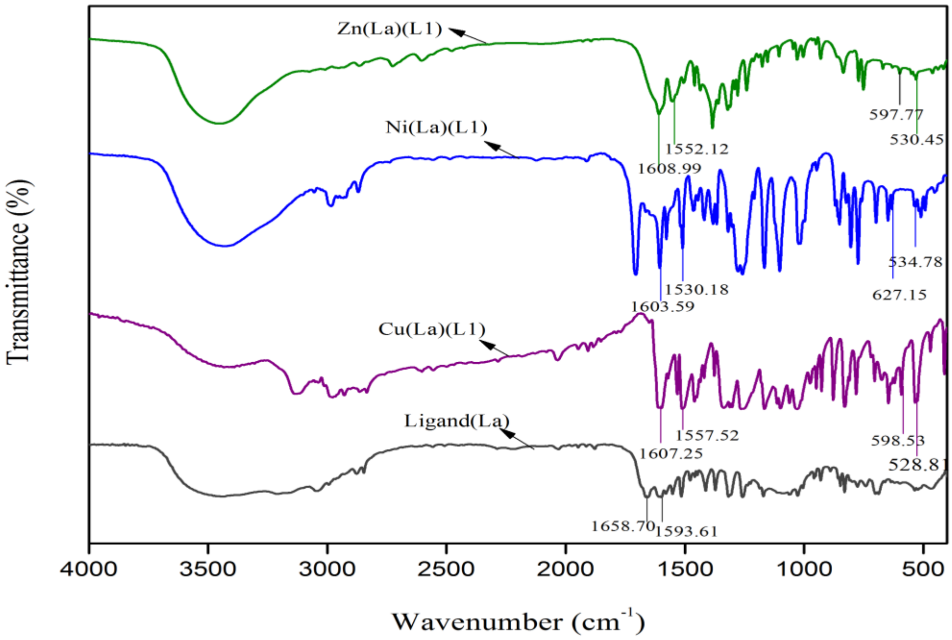

Figure 1:IR Spectra of the ligand La, and its Mixed Ligand Complexes with L1.

UV- VisibleSpectra

UV-Visible spectrum (**Figure 2**)of the ligand (La)exhibited two absorption bands at 267 and 318nm region which attributed to π-π* and n-π* transitions,respectively [42]. These transitions were checked out in case of the metal complexes(**Figure 2**), they shifted to longer and lower wavelength and it verifiedthe charge transfer transitions of the ligand to metal ions (LMCT) and vice versa [31]. The electronic spectra ofCu(II) complex displayed the absorption bands at 275, 323, and 378 nm respectively, which may be assigned to π-π*, n-π*, and charge transfer band(C.T) [43].Ni(II) complex showed three strong bands at 263, 296, and 386 nm. The peaks at 263 and 296 nm are attributed to π-π* and the absorption band at 386 nm may be assigned to metal-ligand charge transfer (MLCT). Two bands for Zn(II) complex at 270, and 362 nm are attributed to π-π* and charge transfer transitions, respectively [43-46].Therefore, the magnetic moment value coupled with UV-Vis spectrum data conformed square planar structure of Cu(II), and Ni(II) complexes and on the other hand, tetrahedral structure for Zn(II) ion complex.

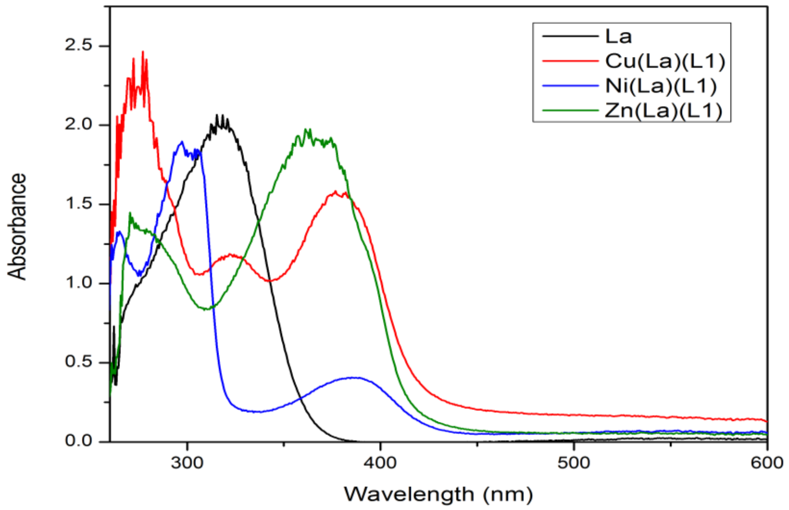

Figure 2:UV- Visible Spectra of the La and Its Mixed Ligand Complexes with L1.

On the basis of the above characterizations, the probable structure of complexes are given below

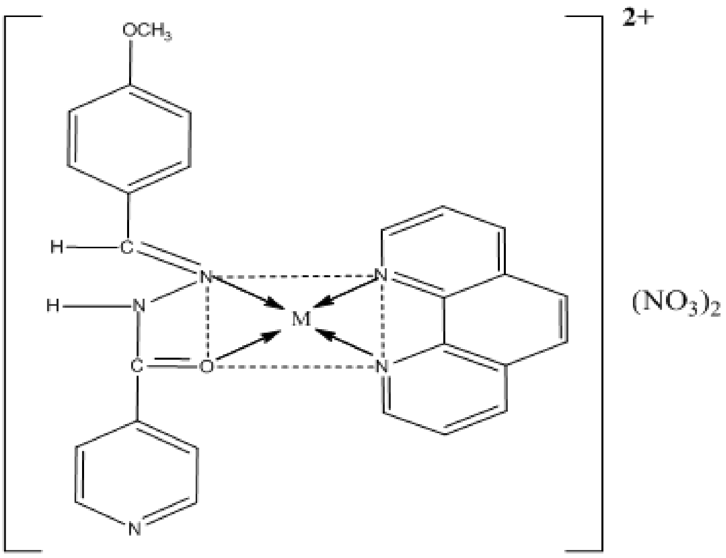

Figure3: Proposed structure of mixed ligand complexes, [MCu(La)(L1)]$(NO_3)_2$where,M=Cu(II), and Ni(II).

Figure 4: Proposed structureof[Zn(La)(L1)] $(NO_3)_2$

4. Pharmacology

Antibacterial Activity

The Schiff base ligand and its mixed ligand complexes were investigated for antibacterial activityagainst *Escherichia coli* and*Pseudomonas* sp. at the concentration (100 µg/ 10µL) in DMF. The values of inhibitory zone were measured in diameter (mm) and the result of their antibacterial activity has been listed in **Table 1**. The Schiff base ligands did not show any inhibition zone against the selected bacterial strains. Moreover, it was found that[Zn(La)(L1)]$(NO_3)_2$ exhibited the highest antibacterial activity with the zone of inhibition ranging between 16 and 17 mm against *Pseudomonas* sp., and *Escherichia coli*. In addition, Overtone's concept and Tweedy's chelation theory can explain the greater activity of the complexes [47]. The significant antibacterial activity of metal complexes is due to the fact that only lipid-soluble materials making lipo-solubility a main control factor in antibacterial activity. On chelation, due to overlap and the partial sharing of positive charge of the metal ion with the orbitals of the donor groups of the ligands, the polarity of metal ions is more reduced. The metal ions are therefore easily be adsorbed on the surface of the cell wall of the organisms. Thereby, it disrupts the respiratory process of the cells and blocks protein synthesis. This in turn limits additional organism growth. Besides this, the substituent methyl group plays a vital role to increase the lipophilic nature of the metal complexes that is the reason for remarkable antibacterial activity and other factors like solubility, coordinating sites, the geometry of complexes, steric, concentration, and hydrophobicity having considerable influence on the antibacterial potency [47-49].

Table 1: Antibacterial activities of ligand La, L1, 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 (La)	-	-
$[Cu(La)(L1)]\ (NO_3)_2$	6	8
$[Ni(La)(L1)]\ (NO_3)_2$	-	-
$[Zn(La)(L1)]\ (NO_3)_2$	16	17

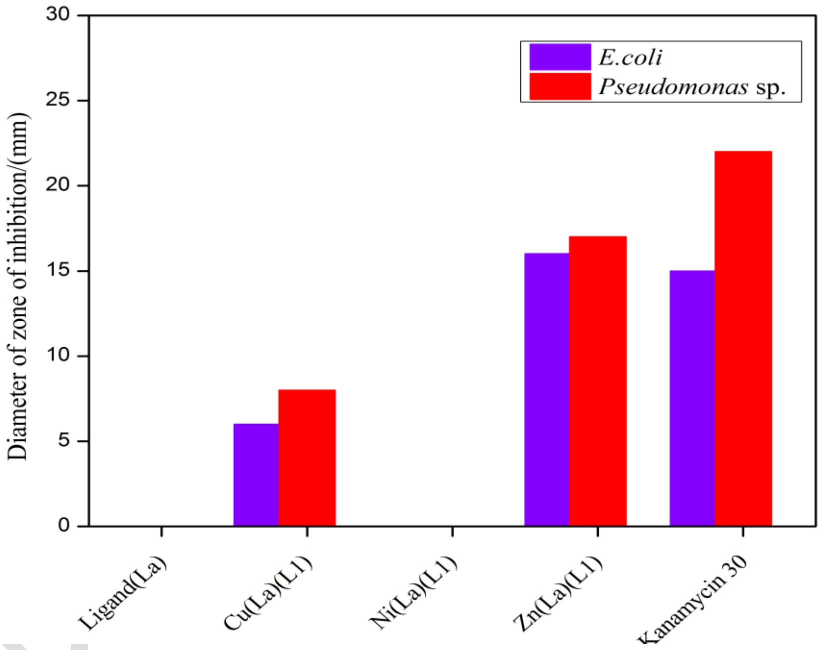

Figure 5: Graphical representation of antibacterial activity of La and its metal complexes with L1 against *Escherichia coli* and *Pseudomonas* sp.with standard Kanamycin-30.

Antioxidant activity

Antioxidant activity of the synthesized ligands and its mixed ligand complexes with was investigated by the free radical compound 2, 2-diphenyl-1-picryl hydrazyl (DPPH), and BHT(butylatedhydroxytoluene) as a standard at different concentrations (20, 40, 60, 80, and 100 µg/mL). DPPH having a violet color when dissolved in DMF, it became pale red [50]. The percentage of DPPH radical scavenging activity and IC_{50} values of BHT, ligands, and its mixed ligand complexes has been listed in Table 2and shown in **Fig. 3-4**. From the results, it is found that all the metal complexes displayed moderate DPPH radical scavenging activity than the Schiff base ligands comparable with BHT. Among all the tested compounds, Cu(II) complexes exhibited the highest antioxidant activity than Ni(II) and Zn(II) complexes as compared with the standard BHT. Due to the coordination environment and redox properties, the difference in the antioxidant activity of the Schiff base metal complexes can be ascribed. Generally, the redox properties of the metal complexes depend on some factors including axial ligation, chelate ring size, and degree of unsaturation in the chelate ring [49, 51]. The high antioxidant activity of Cu(II) complexes compared to other prepared complexes is assigned to the high reducing ability of Cu^{2+} and its proton donation property where Cu^{2+} act as a superoxide scavenging center [52]. Ni(II) complexes showed low antioxidant activity, it could be due to steric hindrance by geometric structure, hindering the radical approach of DPPH to active complex centers. Furthermore, Zn(II) having lower activity because probably, Zn(II) ion is not a transition metal and therefore cannot participate in electron-transfer reactions [52].

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

Conc. (µg/mL)	% BHT	% La	% $[Cu(La)(L1)](NO_3)_2$	% $[Ni(La)(L1)] (NO_3)_2$	% $[Zn(La)(L1)] (NO_3)_2$
20	10.61	1.00	39.60	7.21	1.82
40	23.06	1.70	71.43	12.31	6.21
60	30.96	3.20	81.61	17.82	7.25
80	34.23	5.38	86.28	22.91	8.76
100	38.76	7.12	87.13	28.29	9.34
IC_{50}	126.60	641.90	17.77	182.40	552.60

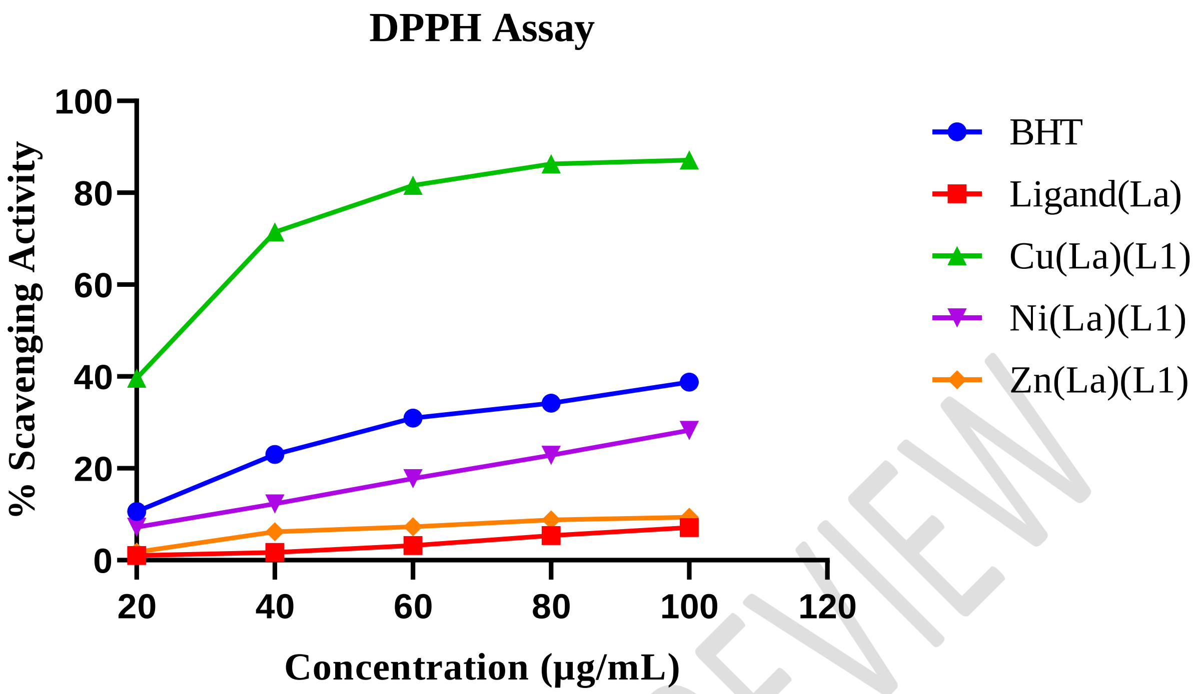

Figure6: DPPH radical scavenging activity of the mixed ligand complexes of ligand-La, and L1 at different concentrations (20, 40, 60, 80, and 100 µg/mL) with standard antioxidant BHT.

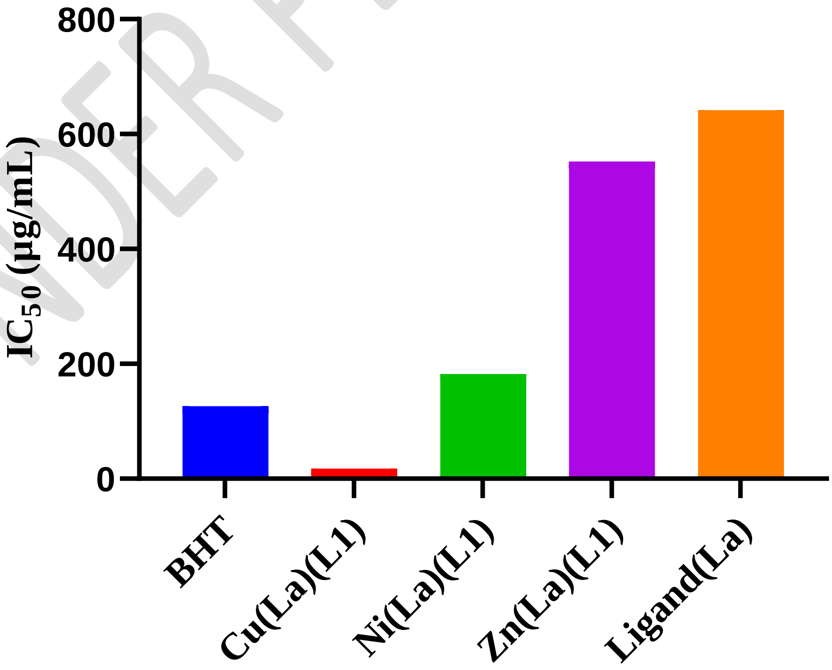

Figure7: IC_{50} value of the mixed ligand complexes of ligand-La, and L1 at different concentrations (20, 40, 60, 80, and 100 µg/mL with standard antioxidant BHT.

Conclusions

The Schiff base ligand, La and itsCu(II), Ni(II), and Zn(II) mixed ligand complexes with 1,10-phenanthroline (as L1) have been synthesized and well characterized. The value of conductivity revealed that the complexes were electrolytic in nature.IR spectral analysis indicated that the primary ligand(La) and 1,10-phenanthroline (L1) arecoordinated to central metal ions through N and O atoms. Therefore,based on UV-Vis spectra and magnetic moment data, the synthesizedCu(II) and Ni(II) complexes validated the square planar structure, whereas the Zn(II) ion complex confirmed the tetrahedral structure.Zn(II) complexes showed maximum antibacterial activity compared to Schiff base and other complexes but itshowed the lowest antioxidant activity among all synthesized complexes.

5. References

1. Thorat BR, Kamat P, Khandekar D, Lele S, Mustapha M, Sawant S, Jadhav R, Kolekar S, Yamgar R, Atram RG, “Synthesis and Fluorescence study of Novel Schiff Bases of Isoniazide”. J. Chem. Pharm. Res., 2011, 3(6):1109-1117.

2. Gadada N, Reinout M, Amorn P, “Synthesis and Antimicrobial Activity of New Schiff Base Compounds Containing 2-Hydroxy-4-pentadecylbenzaldehyde Moiety”. Advan. Chem., 2014, 1-9.

3. Omoruyi GI, Eric CH, “Spectroscopy, Crystal and Molecular Structures of New 4-Acylpyrazolone Dinitrophenylhydrazones”. Crystals 2016, 6, 127.

4. Ndahi NP, Nasiru YP, “Complexes of cobalt(II), nickel(II) and zinc(II) with schiff bases derived from 4-anisaldehyde”. Inter. J. Pharma. Sci. Res, 2012, 3(12): 5116-5120

5. Shubhangi NK, Harjeet DJ, “Synthesis, Characterization, and Antimicrobial Studies of N, O Donor Schiff Base Polymeric Complexes”. J. Chem., 2013; 1-5

6. Riyadh MA, Enaam IY, Mohamad JAJ, “Co(II) and Cd(II) Complexes Derived from Heterocyclic Schiff-Bases: Synthesis, Structural Characterisation, and Biological Activity”. The Sci. World J., 2013; 1-7

7. Gupta B, Fahmi N, “Co(II) and Ni(II) Complexes with Schiff Base Ligands: Synthesis, Characterization, and Biological Activity”. Russian J. Gen. Chem, 2016; 86(5):1182–1190

8. Ashok NP,Uttam MY, Pratik AD, Pravin US, “Synthesis of some Novel Halogenated Platinum (II) Complexes of Active Schiff’s Base Ligand Derived from 5-Bromo Isatin and Evaluation of their Antibacterial Activity”. World Sci. News, 2015; 10:32-43.

9. Rosenberg B, Vancamp L, Krigas T, “Inhibition of Cell Division in Escherichia coli by Electrolysis Products from a Platinum Electrode”. Nature, 1965; 205:698-699.

10. Ashok NP, Uttam MY, Pratik AD, Pravin US, “Synthesis and Antimicrobial Activities of Novel Palladium (II) Complexes of Active Schiff’s Base Ligand Derived from 5-Bromo Isatin”. Inter. Letters Chem. Phy. Astro., 2015; 52: 22-27

11. Lucica VA, Angela K, Cristian A, Adina MM, “Synthesis and characterization of new complexes of some divalent transition metals with 2-acetyl-pyridyl-isonicotinoylhydrazone”. J. Therm. Anal.Calorim., 2012; 107: 573–584

12. Rafeye R, Anita A,“Synthesis and Characterization of New Schiff Bases of Ethylenediamine and Benzaldehyde Derivatives, Along with Their Iron Complexes”.J. Appli. Chem. Res., 2015; 9(2): 59-65

13. Obasuyi EI, Iyekowa O, “Synthesis, Characterization and Antimicrobial of Schfiff Base from 5-Bromo –Salicylaldehyde and P-Toluidine”. J. Appl. Sci. Environ. Manage., 2018; 22 (11): 1733–1736

14. Koteswara RV, Subba RS, Satheesh KB, Reddi MNK, Naga RC, Ghosh SK, “Synthesis of Schiff's bases in aqueous medium: a green alternative approach with effective mass yield and high reaction rates”. Green Chem. Let. Rev., 2010; 3(3): 217-223.

15. Haythem AS, Eman AAS, Ibrahim MM, Amal GAB, Mohammad SM, “Synthesis, characterization and biological activity of Schiff bases derived from metronidazole”. Med. Chem. Res., 2012: 21:2969–2974.

16. Violet DV, Daniel PT, Renganathan R, Elsa F, Detlef WB, “Novel Bioactive Co(II), Cu(II), Ni(II) and Zn(II) Complexes with Schiff Base Ligand Derived from Histidine and 1,3-Indandione: Synthesis, Structural Elucidation, Biological Investigation and Docking Analysis J. Fluoresc., 2016

17. Laila HAR, Rafat MEK, Lobna AEN, Ahmed MAD, “DNA binding ability mode, spectroscopic studies, hydrophobicity, and in vitro antibacterial evaluation of some new Fe(II) complexes bearing ONO donors amino acid Schiff bases”. Arabian J. Chem., 2013

18. Prashanthi YK, Kiranmai, Ira, Sathish KK, Vijay KC, Shivaraj, “Spectroscopic Characterization and Biological Activity of Mixed Ligand Complexes of Ni(II) with 1,10 Phenanthroline and Heterocyclic Schiff Bases”. Bioinorg. Chem. Appli., 2012; 1-9.

19. Chaviara AT, Cox PJ, Repana KH, Papi RM, Papazisis KT, Zambouli D, Kortsaris AH, Kyriakidis DA, Bolos CA, “Copper(II) Schiff base coordination compounds of dien with heterocyclic aldehydes and 2-amino-5-methyl-thiazole: synthesis, characterization, antiproliferative and antibacterial studies. Crystal structure of CudienOOCl$_2$”. J. Inorg. Biochem., 2004; 98: 1271

20. Ciller JA, Seoane C, Soto JL, Yruretagoyena B, “Synthesis of heterocyclic compounds. LI. Schiff bases of ethyl 2-aminofurancarboxylates”. J. Heterocycl. Chem., 1986; 23: 1583

21. Omyma AMA, “Palladium(II) and zinc(II) complexes of neutral [N2O2] donor Schiff bases derived from furfuraldehyde: Synthesis, characterization, fluorescence and corrosion inhibitors of ligands”. Spectrochimica Acta Part A: Molec. Biomolec. Spect., 2014; 132: 52-60

22. Anoop KP, Abhishek B, Vikas B, Apoorva D, “Structural, Electronic, and Vibrational Properties of Isoniazid and Its Derivative N-Cyclopentylidenepyridine-4-carbohydrazide: A Quantum Chemical Study”. J. Theoret. Chem., 2014; 1-15

23. Garner RN, Pierce CG, Reed CR, Brennessel WW, “Photoinitiated Treatment of *Mycobacterium* using Ru(II) Isoniazid Complexes”. norganicaChimi. Acta, 2017. DOI: 10.1016/j.ica.2017.02.031

24. Zubatyuk RI, Kucherenko LI, Mazur IA, Khromyleva OV, Shishkin O V, “A theoretical structural study of isoniazid complexes with thiotriazoline”. Chem. Hetero. Comp.2014; 50 (3):476-482.

25. Guilian L, Jingrui Z, Yi J, Li-li Z, Haican L, Machao L, Xiuqin Z, Kanglin W, “Cross-resistance of isoniazid, para-aminosalicylic acid and pasiniazid against isoniazid-resistant Mycobacterium tuberculosis isolates in China”.J. Glob. Antimicr. Resis., 2020; 20: 275–281.

26. Imran A, Waseem AW, Kishwar S, “Empirical Formulae to Molecular Structures of Metal Complexes by Molar Conductance”, Syn. React. Inorg. Metal-Org., Nano-Metal Chem.,T.F. G., 2013; 43(9); 1162-1170

27. Mariana LD, Angela K, Nicoale S, Adin MM, “Transition metal M(II) complexes with isonicotinic acid 2-(9-anthrylmethylene)-hydrazide”. J. Serb. Chem. Soc., 2010; 75: 1515.

28. Raman N, Dhaveethu RJ, Sakthivel A, “Synthesis, spectral characterization of Schiff base transition metal complexes: DNA cleavage and antimicrobial activity studies”. J. Chem. Sci., 2007; 119 (40): 303–310.

29. Sulekh C, Lokesh KG, Deepali J, “Spectroscopic studies on Mn(II), Co(II), Ni(II), and Cu(II) complexes with N-donor tetradentate (N4) macrocyclic ligand derived from ethylcinnamate moiety”. Spectrochimi. Acta Part A, 2004; 60 : 2411–2417

30. Mitu L, Mohamed N, Iqbal S, Raman N, Muhammad I, Sharma SK, “Template Synthesis, Characterization and Biological Activity of Cu(II), Ni(II), Co(II), Zn(II) Complexes with Isonicotinoylhydra”. E-J. Chem., 2010; 7(1): 227-233

31. Farhana A, Sadia AD, Saddam H, Shaheen S, Kudrat E-Z, "Synthesis, Spectral and Thermal Characterization of Selected Metal Complexes Containing Schiff Base Ligands with Antimicrobial Activities".Asian J. Chem. Sci., 2018; 4(3): 1-19

32. Saud IAR, Mohammad S, Ambreen A, Yusuf AKM, Abdul L, "Synthesis, spectroscopic characterization and biological activities of N_4O_2 Schiff base ligand and its metal complexes of Co(II), Ni(II), Cu(II) and Zn(II)". Spectromica. Acta Part A, 2012; 93: 86-94

33. Arun V, Sridevi N, Robinson PP, Manju S, Yusuff KKM, Ni(II) and Ru(II) Schiff base complexes as catalysts for the reduction of benzene". J. Mol. Catal. A : Chem., 2009; 304: 191-198.

34. Kirza A, Mitu L, Stanica N, "Complex combinations of transition metals d with the isonicotinoylhydrazone ligand -2-hidroxi-1-naftaldehid". Rev. Chim. Bucharest, 2005;2:137

35. Riyadh MA, Enaam IY, Mohamad JAJ, "Co(II) and Cd(II) Complexes Derived from Heterocyclic Schiff-Bases: Synthesis, Structural Characterisation, and Biological Activity". The Sci. World J., 2013; 1-6
36. Kehinde OO, Joseph AA, Cyril EE, Olayinka OA, Akinlolu K, Tadigoppula N, "*(E)-N'*-(2, 4-dihydroxybenzylidene)nicotinohydrazide and its Metal Complexes: Synthesis, Characterisation and Antitubercular Activity". Pak. j. sci. ind. res. Ser. A: phys. sci., 2016; 59(2): 63-75

37. Kehinde OO, Joseph AA, Cyril OEE, Tolutope OS, Akinlolu K, Micheal AM, Tadigoppula N, "Transition Metal Complexes of (*E*)-N'-(4 cyanobenzylidene)nicotinohydrazide): Synthesis, Structural and Anti-Mycobacterial Activity Study". J. Appli. Sci., 2015; 15 (10): 1210-1222

38. Kehinde OO, Micheal AM, Raju KVSN , Tadigoppula N, "Structural and in vitro anti-tubercular activity study of (*E*)-*N*'-(2,6-dihydroxybenzylidene)nicotinohydrazide and some transition metal complexes". J. Iran Chem. Soc., 2015; 12: 815–829

39. Gehad GM, Omar MM, Amr AI, "Biological activity studies on metal complexes of novel tridentate Schiff base ligand. Spectroscopic and thermal characterization". European J. Medi. Chem., 2009; 44: 4801–4812

40. Lawal M, Obaleye JA, Bamigboye MO, Nnabuike GG, Ayinla SO, Rajee AO, Babamale HF, Ajibola AA,"Mixed Metal Complexes of Isoniazid and Ascorbic Acid: Chelation, Characterization and Antimicrobial Activities". Nigerian J. Chem. Res., 2017; 22(1)

41. M. A. Latifa, Tania Tofaza, B. M. Chakia, H. M. Tariqul Islama, Md. Saddam Hossaina, and Md. Kudrat-E-Zahan,"Synthesis, Characterization, and Biological Activity of the

Schiff Base and Its Ni(II), Cu(II), and Zn(II) Complexes Derived from 4-(Dimethylamino)benzaldehyde and S-Benzyldithiocarbazate",Russian Journal of General Chemistry, 2019, 89(6): 1197-1201

42. Rehab KAS, Ahmed TN, Eman MA, “Synthesis, characterization and antimicrobial Evaluation of mixed ligand complexes of Manganese(II), cobalt(II), copper(II), nickel(II) and Mercury(ii) with 1,10 phenanthroline and a Bidentateschiff base”. Eur. Chem. Bull., 2016; 5(8): 335-338
43. Kechukwu PE, Peter AA, “Synthesis, Characterization and Biological Studies of Metal(II)Complexes of (3*E*)-3-[(2-{(*E*)-[1-(2,4 Dihydroxyphenyl)ethylidene]amino}ethyl)imino]-1-phenylbutan-1-one Schiff Base”. Molecules, 2015; 20: 9788-9802 doi:10.3390/molecules20069788.
44. Saddam HM, Shaheed ASME, Haque MM, Ranjan KM, Zakaria CM, Kudrat EZM, “Synthesis and Characterization of Cu(II) and Co(II) complexes containing Schiff base ligands towards potential biological application”. J. Chem. Bio. Phy. Sci. Sec. A.,2018; 8(4):654-668
45. Gondia NK, Priya J, Sharma SK, “Synthesis and physico-chemical characterization of a Schiff base and its zinc complex”. Res. Chem. Intermed. 2017; 43: 1165–11783.
46. Kismat AE, Saddam HM, Nur ABM, Zahid AASM , Ranjan KM, Mannan MA, Zakaria CM, Kudrat EZM, “Synthesis, Spectral and Thermal Characterization on Bioactive Complexes of Mg(II), Zn(II), Sn(II), VO(II) and Bi(III) Ions Containing Schiff Base Ligand”. J. Chem. Bio. Phy. Sci., 2019; 9(4): 201-218
47. Patel MN, Pansuriya PB, Parmar PA, Gandhi DS, “Synthesis, characterization, and thermal and biocidal aspects of drug-based metal complexes”. Pharma. Chem. J., 2008; 42(12): 687-692
48. Kadtala V, Nirmala G, Sreenu D, Kumar K, Krishnan R, Shivaraj, “Crystal structure, DNA interactions, antioxidant and antitumor activity of thermally stable Cu(II), Ni(II) and Co(III) complexes of an N,O donor Schiff base ligand”. Poly., 2019: 171: 86–97
49. Sumalatha V, Aveli R, Narendrula V, Nirmala G, Sreenu D, Shivaraj, “Synthesis, characterization, DNA binding propensity, nuclease efficacy, antioxidant and antimicrobial activities of Cu(II), Co(II) and Ni(II) complexes derived from 4-(trifluoromethoxy)aniline Schiffbases”.Chem. Data Collect., 2019; 20:1-12
50. Nighat N, Irshad A, Nizam D, Amjad W, Sadeeq U-R, Abdul S, Farhan K, Sher K, Simon P, Kamal U, “Synthesis, Characterization and Antioxidant Activity of Nickel(II) Schiff Base Complexes Derived from 4-(Dimethylamino)benzaldehyde”. J. Chem. Soc. Pak. Chem. Soc. Pak., 2020; 42(2): 238-242
51. Kadtala V, Nirmala G, Sreenu D, Kumar K, Krishnan R,Shivaraj, “Crystal structure, DNA interactions, antioxidant and antitumor activityof thermally stable Cu(II), Ni(II) and Co(III) complexes of an N,O donor Schiff base ligand”. Poly., 2019; 171: 86–97

52. Saif M, Hoda FE-S, Mahmoud MM, Mohamed FE, Nabeel AI, Fouad R. “Synthesis, characterization, and antioxidant/cytotoxic activity of new chromone Schiff base nanocomplexes of Zn(II), Cu(II), Ni(II) and Co(II)”. J. Molec. Struct., 2016.doi: 10.1016/j.molstruc.2016.03.060.