Mixed Ligand Complexes of Ni^{2+}, Cu^{2+} and Zn^{2+} 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 Ni^{2+}, Cu^{2+} and Zn^{2+} ions was synthesized with Schiff base ligand (primary ligand, L^1) and 1, 10-phenanthroline (L^2) 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 electrolytic 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 Ni^{2+} and Cu^{2+} complexes, as well as a tetrahedral structure for the Zn^{2+} ion complex, was supported by their respective magnetic moment values and UV-Visible spectra. The antimicrobial activity of the metal complexes formed by L1 and L2 was evaluated against Escherichia coli and Pseudomonas sp. The metal complexes formed by the combination of L^1 and L^2 were subjected to testing against *Escherichia coli* and *Pseudomonas sp*. The Zn(II) complex exhibited superior antibacterial activity compared to the reference drug Kanamycin-30 against both bacterial strains in the tested compounds. In addition, the synthesised metal complexes demonstrated a comparatively moderate level of antioxidant activity when compared to the Schiff base. The Cu^{2+}-complex exhibited the highest level of activity, while the Zn^{2+} -complex demonstrated the lowest antioxidant activity, which was comparable to that of BHT.

Keywords: Schiff base; Transition metals; Antibacterial; Antioxidant; DPPH

1. Introduction

“Compounds with the chemical formula of the azomethine group (-C=N-) are often referred to as Schiff bases. These compounds are formed by the condensation process between carbonyl compounds (i.e. aldehydes or ketones) and primary amines that include aldehydes or

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ketones" [1-3]. "Schiff bases are terrific coordinating ligands" [4]. Schiff base ligands have garnered increased interest over the last decade due to their extensive applications in biomimetic modeling, catalysis, molecular magnet molecule building, as well as their antifungal and antibacterial properties [5, 6]. Furthermore, this family of ligands has been of great interest in the field of coordination chemistry [7-10] and inorganic chemistry due to their ability to efficiently form stable complexes with a wide range of transition metal ions [11]. Moreover, these compounds possess many uses in the realms of biological, clinical, analytical, electrochemistry, pharmaceutical, and industrial investigations. Additionally, they find utility as liquid crystals within the domains of analytical, medicinal, and polymer chemistry [12-14]. "Moreover, Schiff bases and their complexes have been shown to possess many biological activities, such as antibacterial, antifungal, anti-oxidative, anti-inflammatory, anti-tumor, anti-cancer, and anti-HIV properties" [15-18]. "Mixed ligand complexes have a crucial function in the realm of biology, as seen by several instances when metal ions are known to activate enzymes.Schiff bases generated from heterocyclic molecules, such as P-anisaldehyde and furan-2-carbaldehyde, have garnered significant attention in the realm of bioinorganic chemistry" [19-21]. Isoniazid, sometimes referred to as isonicotinylhydrazide (INH), is an organic molecule well recognised for its potent therapeutic properties as a first-line therapy in the treatment and prevention of TB. Due to its significant antibacterial action, the World Health Organisation (WHO) recognises it as a standard therapy material against Mycobacterium TB germs. Metal chelate complexes are formed by this substance with various bivalent ions, which exhibit a range of biological significance from moderate to high [22-25].

In light of the multifaceted significance of Schiff base ligands and their metal complexes, we present a comprehensive account of the coordination characteristics exhibited by a Schiff base (L^1) synthesised from p-anisaldehyde and isoniazid. Additionally, we investigate the behaviour of its metal complexes, namely Cu(II), Ni(II), and Zn(II), in the presence of a secondary ligand, 1,10 phenanthroline (L^2). The study also included the incorporation of bioactivity assays, including antibacterial and antioxidant properties, to evaluate the ligands and their corresponding metal complexes.

2. Methodology

Various analytical methods were employed to characterize synthesized metal complexes. Their melting or decomposition temperatures were determined using an electro-thermal

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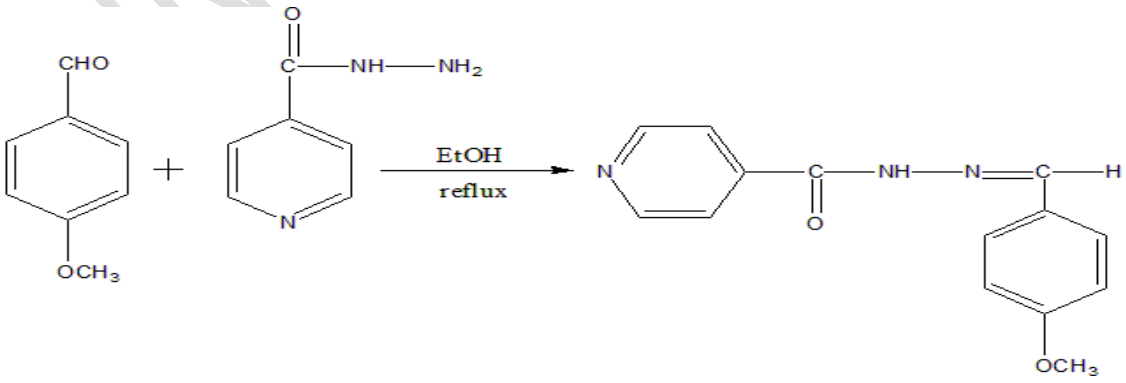
melting point instrument (model O.AZ6512). Infrared spectra (IR) of ligands and complexes were obtained with a SHIMADZU FTIR-8400 instrument. Electronic spectra were recorded with a Thermo-electron Nicolet evolution 300 UV-Vis spectrophotometer. Conductivity in N, N´-dimethylformamide (DMF) was measured using a Horiba conductivity meter B173. Magnetic moments were determined using the Sherwood Scientific Magnetic Susceptibility Balance. Elemental composition was assessed via the LECO (CHNS-932) elemental analyzer. Compound purity was evaluated by thin layer chromatography (TLC) using Silica gel-GF 254 (Merck) coated plates and various solvents (i.e. n-hexane, $CHCl_3$, and CCl_4).

2.1. Synthesis of N-(4-methoxybenzylidene) isonicotinohydrazone Schiff base Ligand (L^1)

Scheme 1 shows the condensation reaction between and P-anisaldehyde and Isoniazid (INH) in a 1:1 equimolar ratio to synthesize Schiff base ligand, L1. First, 1.374 g of INH (equivalent to 10.00 mmol) were dissolved in 15 mL of ethanol to make a homogenous solution, which was then transferred to a round-bottom flask with more ethanol. 1.22 mL of 4-methoxybenzaldehyde (equivalent to 10.00 mmol) was applied dropwise over 5 minutes and washed with 5 mL ethanol. Refluxing the resultant reaction mixture for 5 hours turned the yellow solution white. A white crystalline substance was filtered and dried in an anhydrous $CaCl_2$ desiccator after slow cooling and overnight repose.

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, L^1

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2.2. Synthesis of Mixed Ligand Complexes

The Schiff base ligand (L^1), weighing 0.255 g (1 mmol), was dissolved in a 10 mL methanol solution. Subsequently, an equimolar amount of 1,10-phenanthroline hydrate (L^2), used as a secondary ligand, was drop-wise added to the heated methanolic solution (10 mL, 1 mmol) containing metal nitrate salts (1 mmol) of metals such as Cu(II), Ni(II), and Zn(II). The reaction mixture was refluxed for 3 hours, cooled slowly, and allowed to stand overnight. The resulting precipitate was filtered, washed multiple times with methanol, and dried under vacuum using anhydrous CaCl2. The synthesized metal complexes displayed solubility in both DMSO and DMF solvents.

$[Cu(L^1)(L^2)](NO_3)_2$:

$[CuC_{14}H_{13}N_3O_2]$; 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.

$[Ni(L^1)(L^2)]NO_3)_2$:

$[NiC_{14}H_{13}N_3O_2]$: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.

$[Zn(L^1)(L^2)](NO_3)_2$:

$[ZnC_{14}H_{13}N_3O_2]$: 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. Results and Discussion

“All complexes were insoluble in polar solvents but demonstrated solubility in DMSO and DMF”. [53] Notably, they exhibited remarkable stability, implying suitability for long-term storage without observable changes. Conductivity values ranged from 140 to 150 ohm^{-1} cm^2

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mol-1, suggesting their 1:2 electrolytic in nature [26-27]. The Cu(II) complex possessed a magnetic moment of 1.83 B.M, signifying paramagnetic behavior and a square planar geometry, consistent with prior reports [28]. In contrast, the Ni(II) complex was diamagnetic with a magnetic moment of 1.31BM, in line with its square planar shape. The Zn(II) complex adopted a tetrahedral configuration with a magnetic moment of 0.75 B.M [29-33].

IR Spectral Studies

The infrared (IR) spectra of the unbound ligand exhibited characteristic peaks at 1659 cm^{-1} and 1594 cm^{-1}, which may be ascribed to the vibrations of the ν(C=O) and ν(C=N) functional groups, respectively (**Figure 1**) [34-36]. The infrared spectra of metal complexes exhibit a notable shift in the band associated with the Schiff base ligand. Specifically, the ν(C=O) stretching vibration of the primary ligand, originally observed at 1659 cm^{-1}, undergoes a downward shift to frequencies ranging from 1603 to 1609 cm^{-1} in the Ni^{2+}, Cu^{2+} and Zn^{2+}-complexes. This shift provides evidence that the carbonyl oxygen of the Schiff base ligand coordinates with the metal ions (**Figure 1**). The appearance of additional absorption bands within the range of 597-628 cm^{-1} in the infrared spectra of the complexes may be attributed to the stretching vibrations of M-O bonds [37-39]. Upon complexation, the azomethine (-C=N) band at 1594 cm^{-1} in the free Schiff base observed a shift towards lower wavenumbers, namely within the range of 1552-1558 cm^{-1}, in the produced complexes that included Zn^{2+}, Cu^{2+}, and Ni^{2+} metal ions. Moreover, this observation illustrates the use of the azomethine nitrogen atom for coordinating the metal ions. Furthermore, additional bands were seen in the infrared spectra of these metal complexes at the wavenumbers of 528–535 cm^{-1}, which may be attributed to the vibrational mode of ν(M–N) [40-41]. In the infrared spectra of the mixed ligand complexes, a prominent peak at 1384 cm^{-1} was observed which could possibly be attributed to the presence of the uncoordinated nitrate ion [27]. The IR results obtained in this investigation affirm the coordination of both ligands to divalent central metal ions (Ni^{2+}, Cu^{2+} and Zn^{2+}) in metal complexes. These ligands coordinate to the metal ions through their N(nitrogen) and O(oxygen (O) atoms, respectively. The acquired observations have been documented and presented in **Table 1**.

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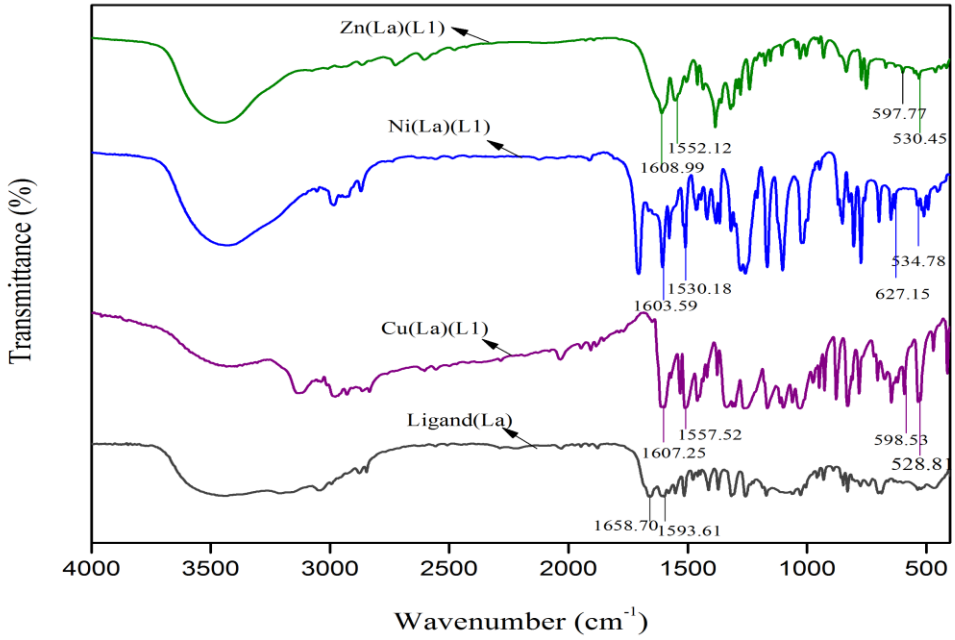

Figure 1: IR Spectra of the ligand L^1, and its Mixed Ligand Complexes with L^2

Table 1: Key Infrared Bands (cm^{-1}) of Ligand L^1 and its Mixed Ligand Complexes with L^2

Symbol of Compounds	Compounds	ν (C=O)	ν (C=N)	V (M-O)	ν (M-N)
Ligand (L^1)	$C_{14}H_{13}N_3O_2$	1658.70	1593.61		
Ligand (L^2)	$C_{12}H_8N_2$		1587		
$[Cu(L^1)(L^2)](NO_3)_2$	$[Cu(C_{14}H_{13}N_3O_2)(C_{12}H_8N_2)](NO_3)_2$	1607.25	1557.52	598.53	528.51
$[Ni(L^1)(L^2)](NO_3)_2$	$[Ni(C_{14}H_{13}N_3O_2)(C_{12}H_8N_2)](NO_3)_2$	1603.59	1530.18	627.15	534.78
$[Zn(L^1)(L^2)](NO_3)_2$	$[Zn(C_{14}H_{13}N_3O_2)(C_{12}H_8N_2)](NO_3)_2$	1608.99	1552.12	597.77	530.45

UV- Visible Spectra

Analysis of the UV-Visible spectrum shown in **Figure 2** for the ligand (L^1) revealed the existence of two absorption bands at 267 and 318 nm, corresponding to π-π* and n-π* transitions, respectively [42]. "The electronic spectra of the Cu(II) complex exhibited absorption bands at 275, 323, and 378 nm, attributed to π-π*, n-π*, and charge transfer (C.T) transitions, respectively" [43]. "In a similar manner, the Ni(II) complex exhibited three distinct peaks at wavelengths of 263, 296, and 386 nm. The absorption peaks at 263 and 296 nm were attributed to π-π* transitions, while the absorption band at 386 nm suggested a metal-ligand charge transfer (MLCT) process. The Zn^{2+}-complex exhibited two distinctive bands at 270 and 362 nm, signifying π-π* and charge transfer transitions, respectively" [43-46]. Therefore, the magnetic moment values, in conjunction with the UV-Vis spectrum data, supported the conclusion of a square planar structure for the Ni^{2+} and Cu^{2+}-complexes, while the Zn^{2+}- complex was established to adopt a tetrahedral structure. **Table 2** displays the UV-Vis spectra of both L^1 and its mixed ligand complexes with L^2.

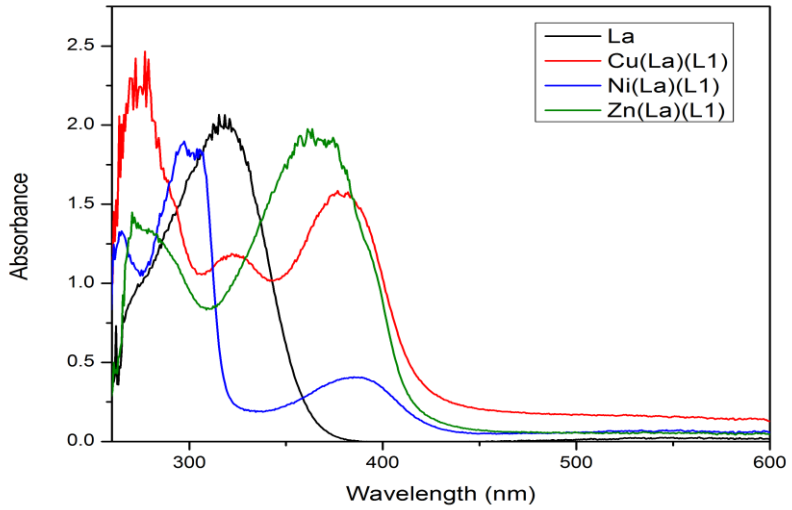

Figure 2: UV- Visible Spectra of the L^1 and Its Mixed Ligand Complexes with L^2

Table 2: UV- Visible Spectra of L^1 and Its Mixed Ligand Complexes with L^2

Symbol of Compounds	**Compounds**		**Assignment**
Ligand (L^1)	$C_{14}H_{13}N_3O_2$	267 318	π-π* n-π*

$[Cu(L^1)(L^2](NO_3)_2$	$[Cu(C_{14}H_{13}N_3O_2)$ $(C_{12}H_8N_2)]$ $(NO_3)_2$	275 323 378	π-π* n-π* C.T transition
$[Ni(L^1)(L^2](NO_3)_2$	$[Ni(C_{14}H_{13}N_3O_2)$ $(C_{12}H_8N_2)]$ $(NO_3)_2$	263 296 386	π-π* π-π* C.T transition
$[Zn(L^1)(L^2](NO_3)_2$	$[Zn(C_{14}H_{13}N_3O_2)$ $(C_{12}H_8N_2)]$ $(NO_3)_2$	270 362	π-π* C.T transition

Based on the aforementioned characterizations, the anticipated structures of the complexes are provided below:

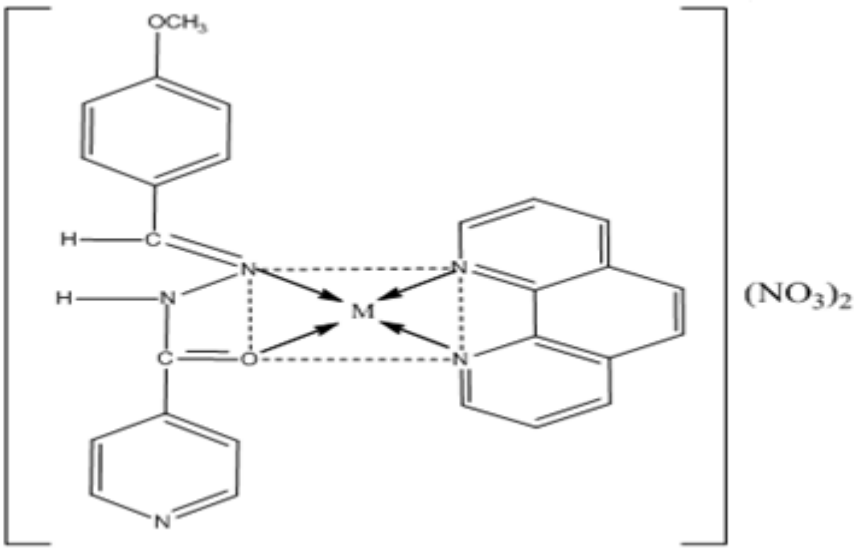

Figure 3: Proposed structure of mixed ligand complexes, $[M(L^1)(L^2)]NO_3)_2$ where, M=Cu(II), and Ni(II)

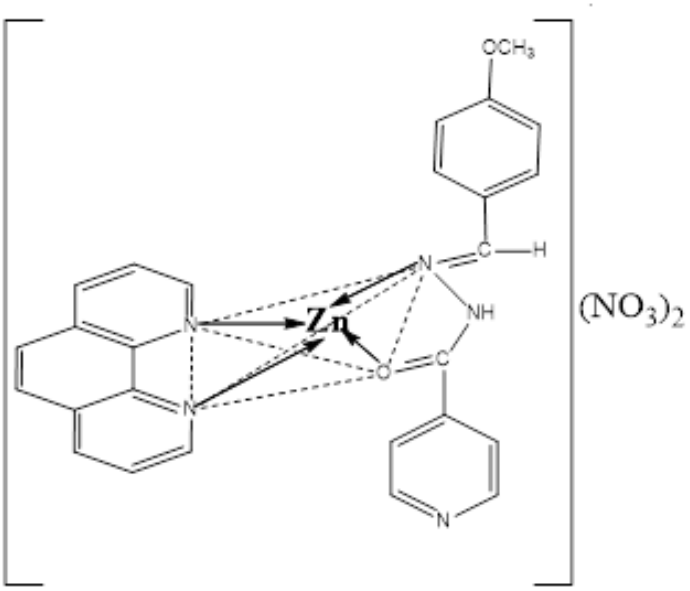

Figure 4: Proposed structure of [Zn(L^1)(L^2)] $(NO_3)_2$

4. Pharmacology

Antibacterial Activity

The antibacterial activity of the ligand, L^1 and its mixed metal complexes with L^2 in DMF at 100 µg/ 10µL was evaluated against *Escherichia coli* and *Pseudomonas sp*. The inhibitory zone width (mm) and antibacterial activity are given in **Table 3**. The Schiff base ligand, L1, did not demonstrate any discernible inhibitory zones when subjected to testing against the selected bacterial strains. Furthermore, it was found that [Zn(L^1)(L^2)]$(NO_3)_2$ had the greatest antibacterial efficacy in comparison to all other synthesized compounds in the presence of Kanamycin-30. It is possible to understand the improved performance of these complexes by taking Tweedy's chelation theory and Overtone's idea into consideration [47]. The metal complexes have significant antibacterial activity, which is probably related to their solubility in lipids. The degree of lipid solubility plays a critical role in determining the antibacterial efficacy of these complexes. Furthermore, it has been shown that a number of variables, including as solubility, concentration, hydrophobicity, complex geometry, coordinating sites, and steric effects significantly affect their antibacterial activity [47–49].

Table 3: Antibacterial activities of ligand L^1 and its metal complexes with L^2

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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 (L^1)	-	-
$[Cu(L^1)(L^2)]$ $(NO_3)_2$	6	8
$[Ni(L^1)(L^2)]]$ $(NO_3)_2$	-	-
$[Zn(L^1)(L^2)]]$ $(NO_3)_2$	16	17

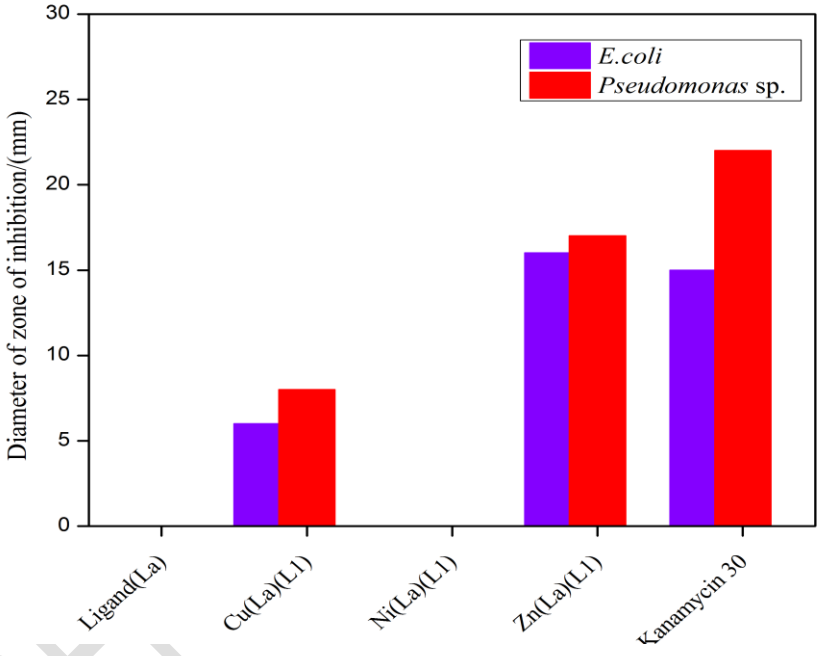

Figure 5: Graphical representation of antibacterial activity of L^1 and its metal complexes with L^2 against *Escherichia coli* and *Pseudomonas* sp. with standard Kanamycin-30.

Antioxidant activity

Antioxidant activity evaluation was conducted on both the synthesized ligand and its mixed ligand complexes, employing 2,2-diphenyl-1-picryl hydrazyl (DPPH), with butylated hydroxytoluene (BHT) as the standard of reference at different concentrations (ranging from 20 to 100 µg/mL). In **Table 4**, we have compiled the data pertaining to DPPH radical scavenging activity (expressed as a percentage) and IC_{50} values for L^1, its mixed ligand complexes with L^2, and BHT. The aforementioned results have been visually represented in Figures 6 and 7 to enhance comprehensibility. "Among all the tested compounds, Cu^{2+}-

complex exhibited the highest antioxidant activity than other complexes as compared with the standard BHTThe variation in the antioxidant activity of the Schiff base metal complexes may be attributed to their coordination environment and redox characteristics. The redox characteristics of metal complexes are influenced by several parameters, such as axial ligation, chelate ring size, and the level of unsaturation inside the chelate ring" [49-51]. "The high antioxidant activity of Cu^{2+}- complex compared to other prepared complexes is assigned to the high reducing ability of Cu^{2+} and its proton donation property where Cu^{2+} ion act as a superoxide scavenging center" [52]. "Ni^{2+}-complex 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-complex having lower activity because probably, Zn^{2+} ion (d^{10} configuration) is not a transition metal and therefore cannot participate in electron-transfer reactions" [52].

Table 4: Percentage of Scavenging activity and IC_{50} values of L^1, its mixed ligand complexes with L^2 and BHT

Conc. (µg/mL)	% BHT	% L^1	% $[Cu(L^1)(L^2)](NO_3)_2$	% $[Ni(L^1)(L^2)](NO_3)_2$	% $[Zn(L^1)(L1)](NO_3)_2$
20	10.61	1.00	8.02	7.21	1.82
40	23.06	1.70	13.57	12.31	6.21
60	30.96	3.20	18.74	17.82	7.25
80	34.23	5.38	24.30	22.91	8.76
100	38.76	7.12	33.02	28.29	9.34
IC_{50}	**126.60**	**641.90**	**160.34**	**182.40**	**552.60**

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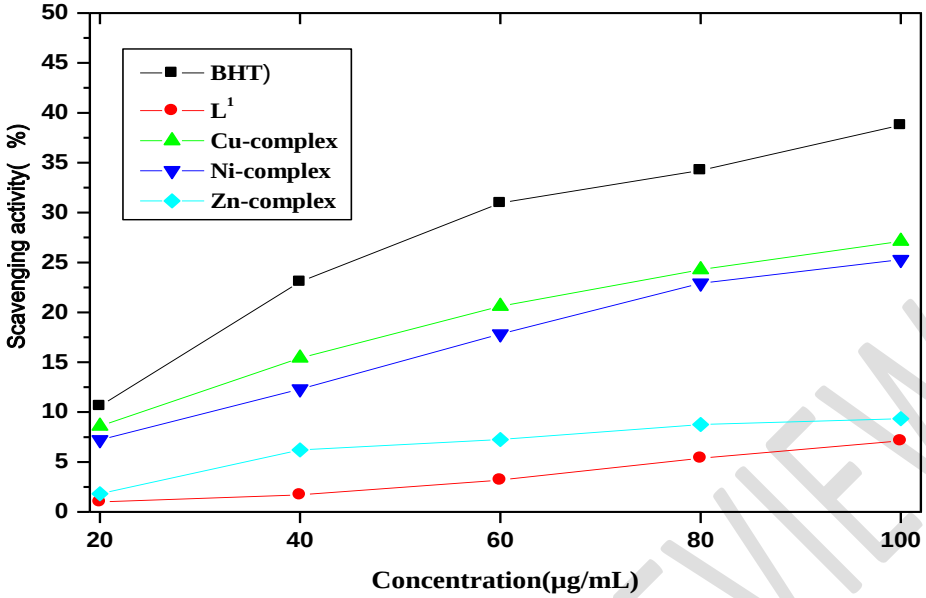

Figure 6: DPPH radical scavenging activity of the mixed ligand complexes of L^1 and L^2 at different concentrations (ranging from 20 to 100 µg/mL) with standard antioxidant BHT.

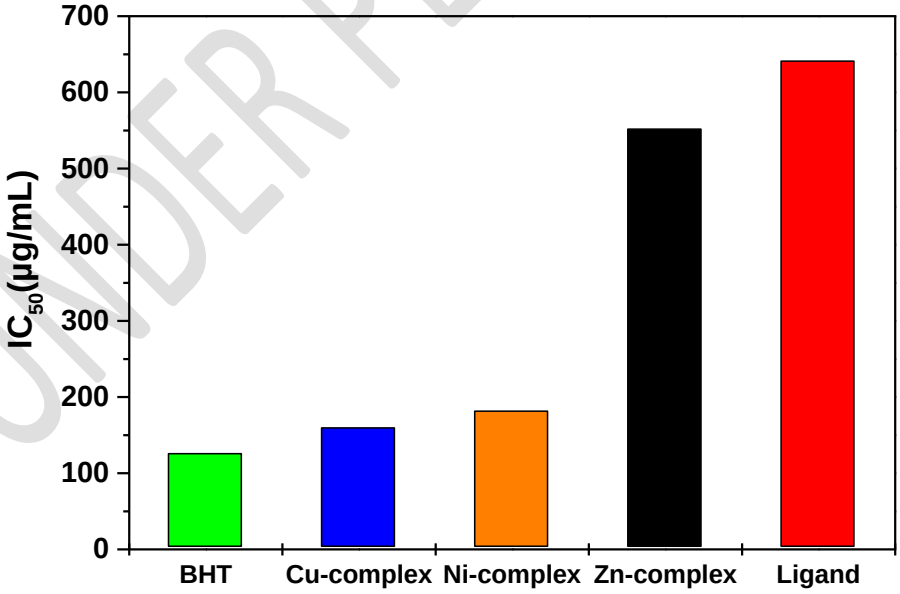

Figure 7: IC_{50} value of the mixed ligand complexes of ligand-La, and L1 at different concentrations (ranging from 20 to100 µg/mL) with standard antioxidant BHT.

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Conclusions

The Schiff base ligand, L^1 and its Ni^{2+},Cu^{2+} and Zn^{2+} mixed ligand complexes with 1,10-phenanthroline (as L^2) have been synthesized and well characterized. The complexes demonstrate electrolytic characteristics as confirmed by conductivity measurements. Infrared spectral analysis indicates coordination of the central metal ions with the primary ligand (L^1) and 1,10-phenanthroline (L^2) through nitrogen and oxygen atoms. UV-Vis spectra and magnetic moment data support the presence of square planar structures in Cu^{2+} and Ni^{2+} complexes, while the Zn^{2+}-complex assumes a tetrahedral configuration. Among these complexes, Zn-complex displays the highest antibacterial activity, albeit exhibiting the lowest antioxidant activity compared to the Schiff base and other 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.

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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

UNDER PEER REVIEW

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

UNDER PEER REVIEW

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 Bidentate schiff base". Eur. Chem. Bull., 2016; 5(8): 335-338

UNDER PEER REVIEW

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 Schiff bases". 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 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

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.

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