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Design, Spectroscopic Characterization, and Cytotoxic Assessment of Schiff Base Metal Complexes Originating from Benzimidazole Derivative

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Abstract

A benzimidazole-based Schiff base ligand, (E)-2-(1H-benzo[d]imidazol-2-yl)-N-((pyridin-2-yl)methylene)benzenamine (L), was prepared through the condensation of 2-(o-aminophenyl)benzimidazole with pyridine-2-carboxaldehyde. This ligand was subsequently complexed with Co(II), Ni(II), Cu(II), Zn(II), Ru(II), and Pd(II) ions to produce a series of coordination compounds represented in Fig:1. The resulting complexes were isolated in good yields and showed stability under ambient conditions. Each compound underwent comprehensive characterization, including elemental analysis, FT-IR, UV–Vis, ^{1}H and ^{13}C NMR, EPR, ESI–MS, magnetic susceptibility, and thermogravimetric analysis. The collected data suggested octahedral coordination geometries for the Co(II) and Ru(II) derivatives, tetrahedral structures for the Ni(II) and Zn(II) complexes, and square-planar arrangements for the Cu(II) and Pd(II) species. Cytotoxic properties were evaluated against the MCF-7 human breast cancer cell line using the MTT assay. Metal coordination enhanced the biological activity of the ligand, with Zn(II), Pd(II), and Cu(II) complexes showing the greatest potency. Notably, the Zn(II) complex displayed the lowest IC_{50} value, making it a promising candidate for further study. These results indicate that Schiff base metal complexes incorporating benzimidazole may offer valuable leads in the development of new anticancer agents.

Keywords: *Benzimidazole; Schiff base; Metal complexes; Spectroscopic characterization; MCF-7 cell line; Cytotoxicity*

1. INTRODUCTION

Metal-based pharmaceuticals remain an important area in many fields including analytical[1], medicinal[2], organic[3] chemistry, as the coordination environment of a metal ion can be fine-tuned to influence both stability and biological performance. cancer is a disease characterized by abnormal and uncontrolled cell growth resulting from altered regulatory signaling pathways[4] and lung, liver, stomach, colorectal, ovarian and breast cancers being the leading causes of cancer related deaths globally[5]. Complexes derived from ligands with strong donor groups have been shown to exhibit a variety of pharmacological activities, particularly in oncology. The clinical success of platinum-based drugs such as cisplatin has reinforced interest in designing coordination compounds with improved therapeutic profiles, better selectivity, and reduced side effects[6]. Schiff bases, formed by condensing primary amines with carbonyl compounds, are highly valued for their structural diversity and ability to bind metal ions through multiple donor atoms. When aromatic heterocycles are incorporated into the ligand framework, the resulting complexes often display enhanced stability and biological potency.

Benzimidazole is a particularly attractive moiety for ligand design due to its resemblance to naturally occurring purines, enabling it to interact effectively with biomolecules through hydrogen bonding and π-stacking. Incorporating benzimidazole into Schiff bases not only increases chelating ability but can also modulate electronic and steric properties, which in turn affects the geometry and reactivity of the resulting metal complexes. Hence benzimidazole and its derivatives shows potential therapeutic activities like antiinflammatory [7], antihypertensive [8], antioxidant [9], antiulcer, antifungal [10], antimicrobial [11], anti-Hepatitis B [12], anti-HIV [13], anticancer [14] and antiviral [15]. . In addition benzimidazoles are used as PI3-Kinase inhibitors [16] and effective anti-staphylococcal drugs [17].

Previous studies have shown that transition metal complexes of benzimidazole-derived Schiff bases can possess greater cytotoxic effects than the ligands alone. Factors such as increased lipophilicity, improved membrane permeability, and the inherent reactivity of the metal ion are thought to contribute to these enhancements. Moreover, the coordination geometry and oxidation state of the metal center can significantly impact the biological pathway and target interactions.

In this work, we report the synthesis of a benzimidazole-based Schiff base ligand and its complexes with Co(II), Ni(II), Cu(II), Zn(II), Ru(II), and Pd(II). These metals were selected for their pharmacological relevance and distinct coordination preferences. Anti tumor activity was shown by copper benzimidazole complexes[18-20]. Each compound was thoroughly characterized, and its cytotoxic potential was examined against MCF-7 breast cancer cells. The findings aim to provide deeper insight into the relationship between structure and anticancer activity, potentially guiding the design of future metallodrugs.

2. MATERIAL AND METHODS

All reagents were of analytical or spectroscopic grade and were used without further purification unless otherwise specified. The starting materials, 2-(o-aminophenyl)benzimidazole and pyridine-2-carboxaldehyde, were purchased from Sigma-Aldrich (USA). Cobalt(II) chloride hexahydrate, nickel(II) chloride hexahydrate, copper(II) chloride dihydrate, zinc(II) chloride, ruthenium(III) chloride hydrate, and palladium(II) chloride were obtained from Merck (Germany). Dimethyl sulfoxide (DMSO), ethanol, methanol, and other solvents were procured from local suppliers, and when needed, distilled before use. All aqueous solutions were prepared using double-distilled water.using double-distilled water.

Elemental composition (C, H, N) was determined on a PerkinElmer 2400 CHN analyzer. Infrared spectra were recorded as KBr pellets using a Shimadzu FTIR-8400S spectrometer over the range of 4000–400 cm^{-1}. UV–visible absorption spectra were measured on a Shimadzu UV-2600 spectrophotometer using 1 cm quartz cuvettes. ^1H and ^13C NMR spectra were obtained in DMSO-d_6 on a Bruker Avance III 400 MHz instrument, with tetramethylsilane (TMS) as an internal standard.

For paramagnetic complexes, electron paramagnetic resonance (EPR) spectra were recorded at room temperature in the X-band region using a JEOL JES-FA200 spectrometer. Mass spectra were acquired by electrospray ionization (ESI–MS) on a Bruker microTOF-Q II system. Magnetic susceptibility was measured with a Gouy balance using $Hg[Co(NCS)_4]$ as the reference. Thermogravimetric analysis (TGA) was performed under nitrogen on a PerkinElmer TGA 4000 instrument, heating samples from 30 °C to 800 °C at 10 °C/min.

2.1. Cytotoxicity Evaluation

The cytotoxic effects of the ligand and its complexes were determined against the MCF-7 human breast adenocarcinoma cell line using the MTT assay[21]. Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 U/mL penicillin and 100 μg/mL streptomycin), incubated at 37 °C in a 5% CO_2 humidified atmosphere.

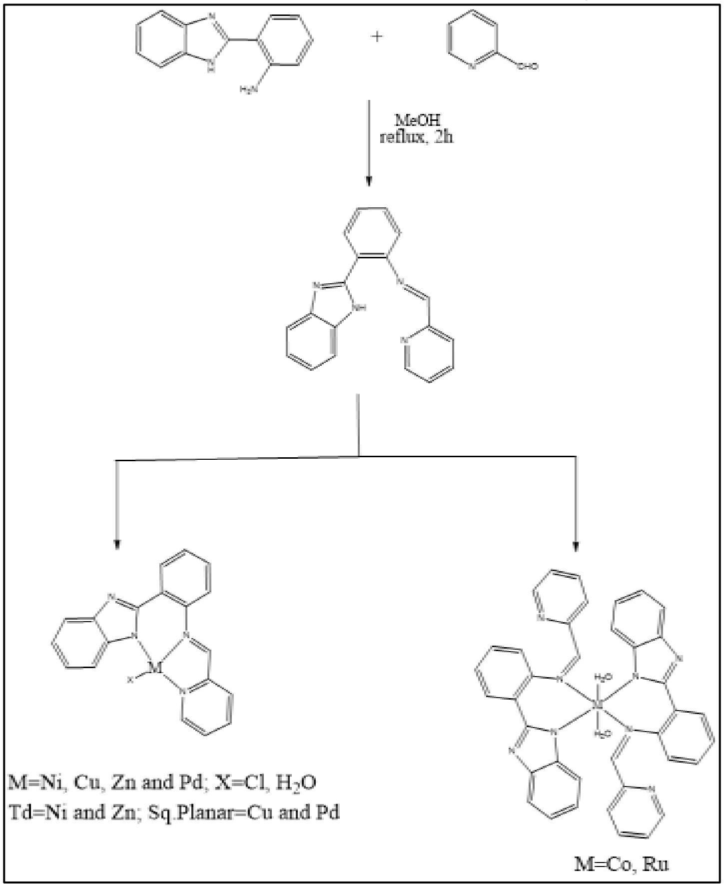
Cells were seeded in 96-well plates at a density of approximately 1×10^4 cells per well and allowed to attach for 24 h. Test compounds were dissolved in DMSO and diluted with culture medium to achieve the required concentrations (final DMSO concentration ≤0.5%). Treatments were applied for 48 h, after which 20 μL of MTT solution (5 mg/mL in PBS) was added to each well. After a 4 h incubation, the resulting formazan crystals were dissolved in 150 μL of DMSO, and absorbance was measured at 570 nm with a microplate reader. Cell viability was calculated relative to untreated controls, and IC_{50} values were obtained from dose–response curves[22].

Step-1: General procedure for the synthesis of Schiff base ligand *(E)-2-(1H-benzo[d]imidazol-2-yl)-N-((pyridin-2-yl)methylene)benzenamine* (L) Shown in Scheme I

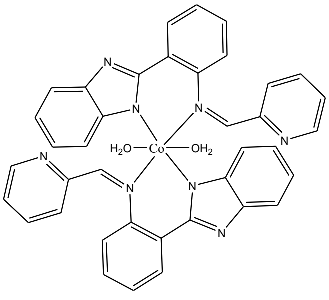
By combining equimolar amounts (1 mmol each) of 2-(o-aminophenyl)benzimidazole and pyridine-2-carboxaldehyde in ethanol (25 mL). A few drops of glacial acetic acid were added as a catalyst, and the mixture was refluxed for 4 h. Upon cooling to room temperature, the precipitate formed was collected by filtration, washed thoroughly with cold ethanol, and dried under reduced pressure. The product was recrystallized from ethanol to obtain pure L as crystalline material..

Step-2: General procedure for complex synthesis with Schiff base ligand (L)

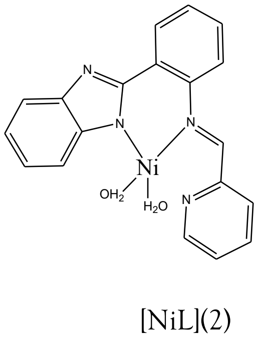
Each metal complex was prepared by dissolving 1 mmol of the Schiff base ligand in 20 mL of ethanol, followed by the addition of an ethanolic solution containing the corresponding metal salt (1 mmol). The reaction mixtures were refluxed for 5–6 h with continuous stirring. After cooling, the precipitated products were filtered, washed sequentially with ethanol and diethyl ether, and dried in a desiccator over anhydrous calcium chloride.



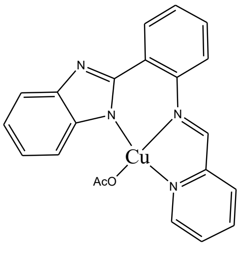
Scheme -I Schematic representation of Metal complexes Preparation



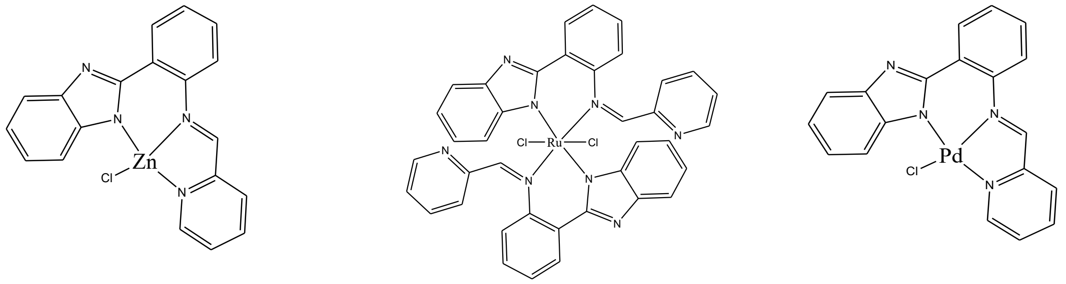
[CoL](1)



[NiL](2)



[CuL](3)



[ZnL](4) [RuL](5) [PdL](6)

Fig. 1. Structures of Schiff base metal complexes

3. RESULTS AND DISCUSSIONS

3.1 Elemental Analysis and Yields

The analytical results for the Schiff base ligand (L) and its metal complexes correspond well with the calculated values, verifying the expected compositions. All products were isolated in good purity, with yields ranging between 65% and 82%. These values are typical for coordination compounds formed via condensation reactions under reflux. The calculated and experimental values of CHNO for ligand and complexes were represented in table1

Table.1 Elemental Analysis of Schiff base Ligand(L) and metal complexes

Compound	Chemical formula	colour	Elemental analysis % found(calculated)		
			C	H	N
L	$C_{19}H_{14}N_4$	Brown	69.75(76.49)	4.49(4.73)	17.38(18.78)
$Co(H_2O)_2(L)_2]$	$C_{38}H_{30}N_8O_2Co$	Brown	56.69(66.18)	4.35(4.38)	13.14(16.25)
$[Ni(H_2O)_2(L)]$	$C_{19}H_{17}N_4O_2Ni$	yellow	51.65(58.21)	4.46(4.37)	12.98(14.29)
[Cu(AcO)(L)]	$C_{21}H_{16}N_4O_2Cu$	Brown	58.02(60.06)	3.71(3.84)	13.38(13.34)
[Zn(Cl)(L)]	$C_{19}H_{13}ClN_4Zn$	Yellow	57.31(57.31)	3.29(3.29)	14.07(14.07)
$Ru(H_2O)_2(L)_2]$	$C_{38}H_{30}N_8O_2Ru$	Black	62.37(62.37)	4.13(4.13)	15.31(15.31)
[Pd(Cl)(L)]	$C_{19}H_{13}ClN_4Pd$	Green	51.78(51.96)	3.85(2.98)	11.76(12.76)

3.2 NMR Spectroscopy

^1H NMR analysis of the ligand revealed a distinct signal for the azomethine proton at δ ~8.70 ppm. In the complexes, this resonance shifted slightly downfield, consistent with deshielding due to coordination. ^{13}C NMR spectra exhibited a similar downfield displacement for the imine carbon, further indicating its direct involvement in bonding to the metal ion. Other aromatic proton and carbon signals remained largely unchanged, confirming that coordination primarily occurs via the imine and benzimidazole nitrogen atoms. In addition the absence of peak at 5.36 ppm corresponding to imidazole N-H proton, confirms the coordination of imidazole Nitrogen to Zn meta[23].

^{1}H NMR ($CDCl_3$)-**(L)**: δ 8.6(d, 1H), 8.17(d,1H), 7.84(d, 1H), 7.45(t, 1H), 7.09-7.32(m, 5H), 6.93(t,1H), 6.82(d, 1H), 6.72(d, 1H), 6.57(d, 1H), 5.36(s, broad)

^{1}H NMR ($CDCl_3$-**ZnL(4)**): δ 8.67(s, 1H), 8.10(s, 1H), 7.75(s, 1H), 7.46(t, 1H), 7.11-7.24(m, 5H), 6.91(s, 1H), 6.71(d, 1H), 6.59(d, 1H).

3.3 Infrared Spectroscopy

In the FT-IR spectrum of the free ligand, a strong absorption at approximately 1621 cm^{-1} was assigned to the azomethine (C=N) stretching vibration, confirming Schiff base. The IR spectrum of Schiff base ligand(**L**) clearly shows the disappearance of peaks at 1680-1695 for –CHO and 3400 cm^{-1} for $–NH_2$ of precursors and a characteristic band in the range of 1611-1636 cm^{-1} confirms the formation of azomethine(-HC=N) bond [24]. Formation Coordination to metal centers resulted in a noticeable shift of this band toward lower wavenumbers (by 8–15 cm^{-1}), which is consistent with the participation of the imine nitrogen in complexation. The N–H stretching band of the benzimidazole unit, observed near 3120 cm^{-1} in the free ligand, showed minor changes or reduced intensity upon complex formation[25]. In case of **CoL** and **NiL** metal Complex a weak intensity band appeared at 502-545 supports the (M-O) stretching frequency [26]. A broad absorption band appearing in the 2970-3577 cm-1 region indicates the presence of coordinated water in the complex, bands in the region 809 and 730-772 cm^{-1} ν(–OH) rocking and wagging mode of vibrations, respectively [27]. corresponds to while New absorptions in the 480–520 cm^{-1} region were attributed to metal–nitrogen (M–N) vibrations, providing additional evidence for coordination through nitrogen atoms. The characteristic infrared spectral bands of Schiff base ligand (L) and its corresponding bivalent CoL(1), NiL(2), CuL(3), ZnL(4), RuL(5) and PdL(6) complexes were shown in Table.2

Table2. Important infrared frequencies of Schiff base ligand(L) and its metal complexes

compound	ν(C=N)	ν(N-H)	ν(M-N)	ν(M-O)	ν(M-Cl)	ν(M-OH$_2$)
L	1611-1634	3225	-	-	-	-
Co(H_2O)$_2$(L)$_2$]	1606	3050	427	508	-	3050-3652
[Ni(H_2O)$_2$(L)]	1591-1603	3175	424	515	-	3251-3686
[Cu(AcO)(L)]	1566-1589	3182	427	508	-	-
[Zn(Cl)(L)]	1592	3066	464	-	288	-
Ru(H_2O)$_2$(L)$_2$]	1596	3204	474	519	-	3302-3475
[Pd(Cl)(L)]	1589	3024	468	-	341	-

3.4 Electronic Spectra and Magnetic Properties

The UV–Vis spectrum of the ligand displayed intense π–π* and n–π* transitions in the 250–320 nm range. Complex formation introduced additional absorption bands, corresponding to d–d transitions, whose positions were characteristic of the geometries adopted by each complex. Electronic spectra of **CoL** complex exhibits three d–d transition bands at 299, 358 and 670 attributed to $^4T_1g(F)\rightarrow{}^4T_2g(F)$, $^4T_1g(F)\rightarrow{}^4T_1g(P)$ and $^4T_1g(F)\rightarrow{}^4A_2g(P)$ transitions, respectively and suggests an octahedral geometry[24b]. The UV-Vis spectra of **NiL** complex has three absorption bands at 291, 301 and 352 which might be assigned to $^3T_1(F)\rightarrow{}^3T_2(F)$; $^3T_1(F)\rightarrow{}^3A_2(F)$ and $^3T_1(F)\rightarrow{}^3T_2(P)$ transitions, respectively and characteristic of tetrahedral geometry[28]. The electronic spectra of **CuL** complex shows three bands at 264, 299 and 691 assigned to $^2B_1g\rightarrow{}^2A_1g$, $^2B_1g\rightarrow{}^2B_2g$ and $^2B_1g\rightarrow{}^2Eg$ transitions, respectively. A broad absorption band at 691 was appeared due to John-Teller distortion and suggests the square planar structure for Cu(II) complex[29]. The electronic spectra of **ZnL** complex exhibited absorption bands at 289, 301 due to π–π* transitions and one more band at 356 due to charge transfer transitions[30]. The UV-vis spectra of **RuL** complex gives four d-d bands corresponds to $^1A_1g\rightarrow{}^3T_1g$, $^1A_1g\rightarrow{}^3T_2g$, $^1A_1g\rightarrow{}^1T_1g$ and $^1A_1g\rightarrow{}^1T_2g$ transitions, respectively and characteristic of an octahedral geometry for Ru(II) complex[31]. The **PdL** complex shows a broad band in the region of 420-470 nm due to $^1A_1g\rightarrow{}^1B_1g$ d-d transition. In addition, a charge transfer band appeared in the range of 270-325 nm, which indicates the square planar structure around Pd(II) ion[32].Electronic absorption spectra of the Schiff base ligand(L) and its corresponding bivalent complexes CoL(1), NiL(2), CuL(3), ZnL(4), RuL(5) and PdL(6), recorded as shown in table 3

Table.3 Important absorption wavelengths of Schiff base Ligand(L) and its metal complexes

Compound	Electronic transitions
L	290, 302, 358
$Co(H_2O)_2(L)_2]$	289, 299, 358, 670
$[Ni(H_2O)_2(L)]$	264, 291, 301, 352
[Cu(AcO)(L)]	264, 299, 691
[Zn(Cl)(L)]	289, 301, 356
$Ru(H_2O)_2(L)_2]$	265, 299, 421, 584
[Pd(Cl)(L)]	267, 297, 421

Magnetic susceptibility measurements supported these spectral observations. Co(II) and Ru(II) complexes exhibited magnetic moments consistent with octahedral coordination, while Ni(II) and Zn(II) complexes showed properties in line with tetrahedral geometries. The Cu(II) and Pd(II) derivatives exhibited features typical of square-planar arrangements. Diamagnetism in Zn(II) and Pd(II) complexes, and paramagnetic values for Co(II), Ni(II), Cu(II), and Ru(II), matched expectations for these assignments.

3.5 EPR and Mass Spectrometry

The Cu(II) complex displayed an axial EPR signal pattern with $g_\parallel > g_\perp$, characteristic of a square-planar environment with a $dx^2–y^2$ ground state[33]. ESI–MS spectra of selected complexes displayed molecular ion peaks matching the theoretical molecular weights, confirming their proposed structures.

3.6 Thermal Analysis

TGA profiles indicated that the complexes were thermally stable up to ~220 °C. For some derivatives, a minor weight loss was observed below 150 °C, which corresponded to the removal of coordinated or lattice water. Decomposition of the organic ligand framework occurred at higher temperatures, leaving behind metal oxide residues.

4. CYTOTOXIC ACTIVITY

The MTT assay demonstrated that the free ligand possessed moderate cytotoxicity against MCF-7 cells. Upon metal coordination, cytotoxic effects increased substantially. Zn(II), Pd(II), and Cu(II) complexes showed the strongest inhibitory effects, with the Zn(II) complex producing the lowest IC_{50} value among all tested samples. The enhanced activity of these complexes may arise from improved lipophilicity, facilitating cell membrane penetration, along with potential interactions of the metal centers with intracellular targets such as DNA or enzymes involved in cell proliferation. The synergistic contribution of both the benzimidazole-based ligand and the coordinated metal ion likely underpins the observed increase in potency. The IC50 values of Schiff base ligand (L) and metal complexes are given in and fig 2 and fig:3

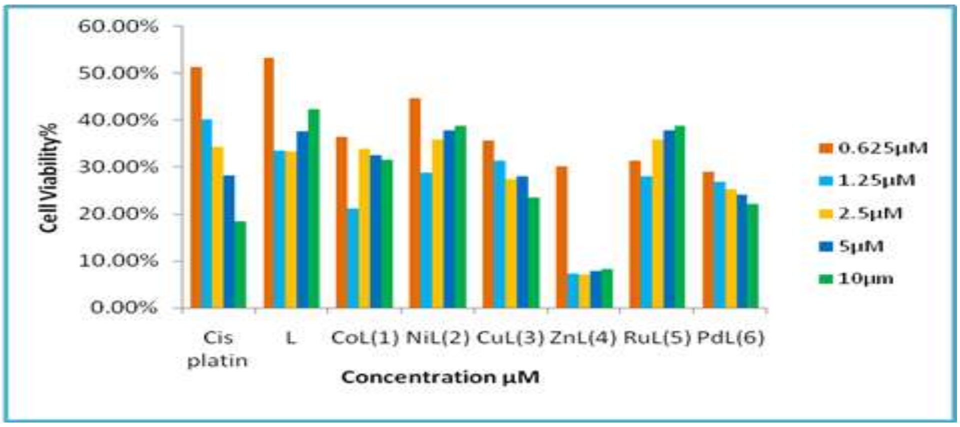


Fig.2 Cytotoxicity of Schiff base Ligand(L) and Metal Complexes

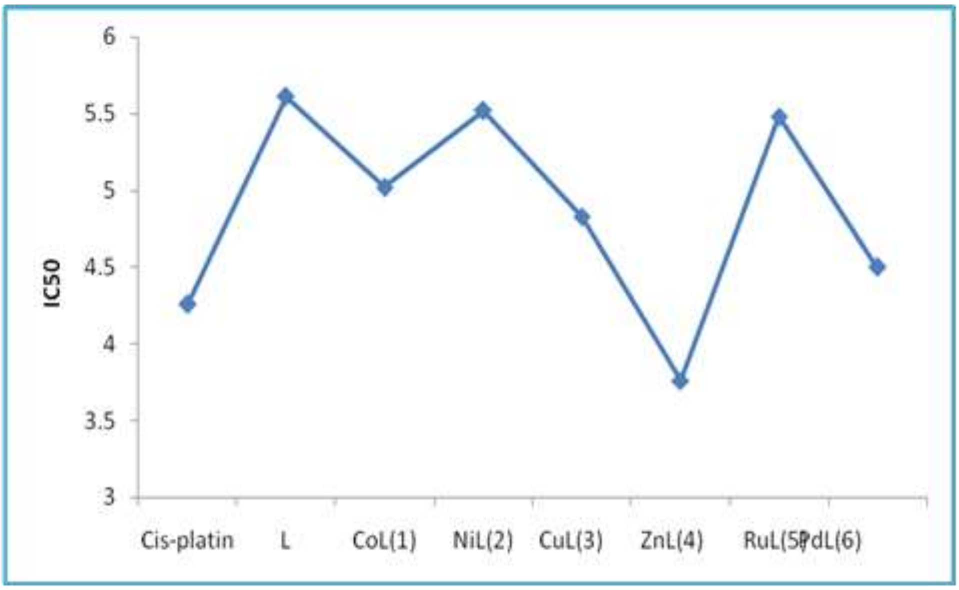


Fig.3 IC_{50} values of Schiff base ligand(L) and Metal Complexes

5. CONCLUSION

This work reports the synthesis and characterization of a benzimidazole-based Schiff base, *(E)-2-(1H-benzo[d]imidazol-2-yl)-N-((pyridin-2-yl)methylene)benzenamine*, and its Co(II), Ni(II), Cu(II), Zn(II), Ru(II), and Pd(II) coordination complexes. A combination of spectroscopic techniques, elemental analysis, magnetic studies, and thermal data confirmed the formation of stable complexes with well-defined geometries: octahedral for Co(II) and Ru(II), tetrahedral for Ni(II) and Zn(II), and square-planar for Cu(II) and Pd(II). Biological testing revealed that coordination significantly enhanced the cytotoxic potential of the ligand against the MCF-7 human breast cancer cell line. Among the series, the Zn(II) complex demonstrated the greatest potency, suggesting it could serve as a valuable lead for the development of new metal-based anticancer agents. These findings underline the importance of ligand design and metal selection in modulating bioactivity, and they open avenues for further mechanistic studies to understand how these compounds interact with cellular targets.

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