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ORIGINAL RESEARCH

Synthesis, Characterization, Biological Evaluation and Molecular Docking of Schiff Base Derived from o-Vanillin and its Complexes

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ABSTRACT

This study highlights the synthesis and characterization of tetradentate ONNO donor Schiff base ligand and thereafter complex formation with Co(II), Cu(II) and Ni(II). The Schiff base ligand is synthesized from 3-Methoxysalicylaldehyde and 4-Nitro-1,2-phenylenediamine. Ligand and complexes were characterized by elemental analysis, FTIR, UV and^{1}HNMR spectroscopy and were screened for their *in-vitro* antimicrobial activity against two-gramnegative bacteria *Pseudomonas aeruginosa*, *Escherichia coli* and one-gram positive bacteria *Staphylococcus aureus* by agar well diffusion method. Further anticancer activity of ligand and complexes was screened with Humen breast cancer protein HER2(PDB ID: 3MZW) by molecular docking. The biological activity of complexes has been found greater than that of ligand.

KEY WORDS: Biological activity molecular docking, Metal complexes, Schiff base, Spectroscopy

INTRODUCTION

Over the past few decades, there has been prominent observation among modern era chemists about Schiff bases due to their manifold structural, physical and chemical properties. This triggered spark to academic researchers forinvestigations of various applications of these ligands (Muthukkumar *et al.,* 2017, Chen *et al.,* 2020, Naureen *et al.,* 2021). Schiff base ligands are versatile in structure and due to which these are used as asymmetric stabilizing agents for metal complexes in various oxidation numbers (Muthukkumar *et al*., 2017, Kargar *et al.,* 2022). Schiff base metal complexes have been reported as good catalysts in heterogeneous systems (Pui *et al.,* 2001) in liquid-liquid extraction (Al Zoubi *et al.,* 2011), in transport of metal ions through the liquid membrane (Bharti *et al.,* 2010). Schiff base transition metal complexes are also well known for their specific biological activities. These have been reported extensively explored in therapeutic applications and promising drugs such as antiviral (Bhandarkar *et al.,* 2023), antibacterial (Osowole *et al.,* 2012), antidiabetic (Creaven *et al.,* 2010) and antifungal (Smith *et al.,*1989). These are also used as contrast agent in MRI (Saghatforoush *et al.,* 2019) and in chemotherapy of cancer (Bozie *et al.,* 2007). It has been reported that Schiff bases synthesized from condensation of carbonyl compounds with diamines represent an important class of chelating ligands and are obtained by taking carbonyl compounds with diamines in a 2:1 M ratio (Jones *et al.,* 1979; Alleman *et al.,*1999; Laila *et al.,* 2021). The condensation of hydroxyl aldehydes with diamines in 2:1 M ratio form ONNO donor tetradentate ligands, the field of interest of recent researchers (Sah *et al.,* 2006) because these have been reported as oxygen carriers in biological systems (Valko *et al.,* 1995; Jeong *et al.,*1996; Datta *et al.,*2002; Blagus *et al.,* 2009; Yu *et al.,* 2009). The Schiff bases prepared in this way commonly behave as tetradentate chelating ligands. It has been reported that [2+1] (2:1 M ratio between hydroxyl aldehyde and diamine) Schiff bases contain two oxygen donor and two nitrogen donor atoms. Transition metal chelates with N, O donors have specific biological activities (Ashraf *et al.,* 2017). A small number of metal complexes with Schiff bases have been used in technology because of their energy-transfer and photophysical properties. Molecular modeling, docking and other

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developments in computational chemistry accelerated the chemistry of transition metals in recent past (Ganeshan *et al.,* 2022; Paularokiadoss *et al.,* 2022).

As a continuation, a novel Schiff base ligand was prepared by the reaction of 4-Nitro-1,2-phenylenediamine and 3-methoxy salicylaldehyde and complexed with Co(II), Cu(II), and Ni(II) ions. The structural characterization and antimicrobial activity of the ligand and its corresponding complexes have been rigorously examined. Furthermore, molecular docking studies of ligand H_2L and corresponding complexes with the human breast cancer-associated target protein HER2 is included.

EXPERIMENTAL

The compounds 4-Nitro-1,2-phenylenediamine and 3-methoxysalicylaldehyde were acquired from Sigma-Aldrich and used as purchased without any further purification. $NiCl_2·6H_2O$, $CoCl_2·6H_2O$, $Cu(OAc)_2·6H_2O$ and Triethylamine was purchased from Merk. The UV-visible spectra of the ligand and complexes were recorded on Hitachi Perkin Elmer Lambda Spectrometer with a range of 200-800 nm in DMSO. Molar conductance was measured by systronics digital conductivity meter type 307. Magnetic moments were measured by using calibrated $Hg[Co(SCN)_4]$ and a Gouy balance. Shimadzu FT-IR spectrometer with a range of 4000-400 cm^{-1} was used for FTIR spectra of ligand and complexes. ^1H NMR spectra of synthesized Schiff base ligand and corresponding complexes were recorded in DMSO-d_6 using Bruker-300 spectrometer. Melting points of ligand and synthesized complexes were determined with an ambassador melting point apparatus using thin capillaries. Molecular docking was performed by CB-Dock. Antimicrobial screening was performed at MRD Life sciences lab at Lucknow.

Synthesis of ligand (H_2L)

1.0 mole of 3-methoxysalicylaldehydeand 0.5 mole of 4-nitro-1,2-phenylenediamine (2:1 molar ratio) are dissolved separately in ethanol and then are mixed drop by drop with continuous stirring. The resulted reaction mixture with continuous stirring was refluxed for 3 hours at 60-70^{0}C (Gautam C.*et al.,* 2021). Golden yellow colored solid was separated, filtered and washed with ethanol, followed by diethyl ether.The solid obtained is dried over anhydrous calcium chloride. The progress of reaction was studied using TLC.

Synthesis of Co(II)complex

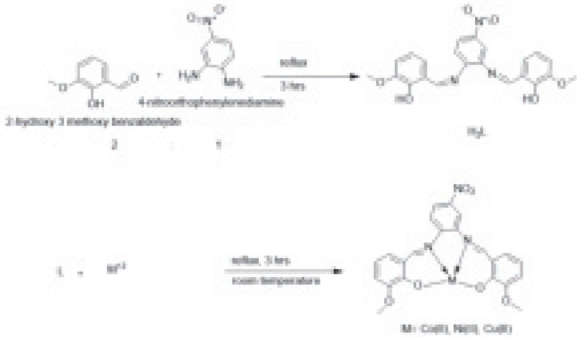
Complex was synthesized by refluxing ethanolic solutions of ligand and hydrated cobalt chloride ($CoCl_2·6H_2O$) in 1:1 molar ratio followed by addition of few drops of triethylamine, at 60^{0}C for 3-4 hours (Gautam C. *et al.,* 2021). After refluxing a brownish yellow solid was separated, which was filtered and washed with ethanol. Solid obtained was dried using anhydrous calcium chloride in vacuum.

Synthesis of Ni(II) complex

Complex was synthesized by refluxing ethanolic solutions of ligand and hydrated nickel chloride ($NiCl_2·6H_2O$) in 1:1 molar ratio followed by addition of few drops of triethylamine, at 60^{0}C for 3-4 hours (Gautam C. *et al.,* 2021). After refluxing a brownish black solid material was separated, filtered and washed with ethanol. The solid was dried using anhydrous calcium chloride in vacuum.

Synthesis of Cu(II) complex

Complex was synthesized by refluxing ethanolic solutions of ligand and hydrated cupric acetate $Cu(OAc)_2·6H_2O$) in 1:1 molar ratio followed by addition of few drops of triethylamine, at 60^{0}C for 3-4 hours (Gautam C. *et al.,* 2021). After refluxing a brownish black solid was separated, filtered and washed with ethanol.The solid dried using anhydrous calcium chloride in vacuum. The synthesis route of ligand and complex and their proposed structure is given in scheme 1.



Scheme 1: Synthesis of ligand H_2L and its complexes CoL, NiL and CuL.

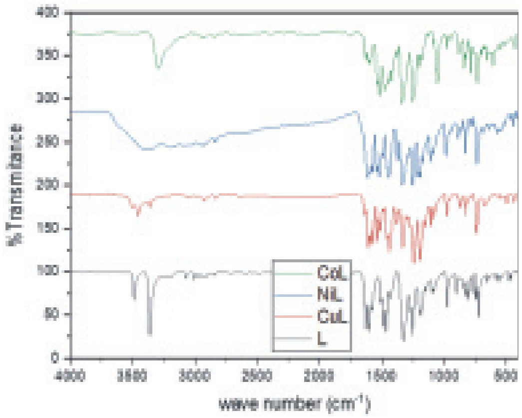


Fig.1. FTIR spectra of ligand and complexes

Table 1: Physical Properties, analytical data and molar conductance of ligand H_2L_2, and its Co(II) and Ni(II) Cu(II) complexes

Compound/ Empirical Formula	Stirring time (hrs)	Colour	Decomposition Temp.(^{0}C)	Λ_m(Ω^{-1}cm^2 mol^{-1})	% Calc. (found) C	 H	 N	 O	 M
H_2L ($C_{22}H_{19}N_3O_6$)	3-4	Yellow	229	-	62.70 (61.92)	4.54 (4.72)	9.97 (10.11)	22.78 (23.29	-
CoL ($C_{22}H_{17}CoN_3O_6$)	3-4	Fade Saffron brown	229	2.7	55.24 (54.42)	3.58 (3.93)	8.78 (8.89)	20.07 (19.93)	12.32 (12.83)
NiL ($C_{22}H_{17}NiN_3O_6$)	3-4	Yellowish brown	230	3.9	55.27 (54.98)	3.58 (3.61)	8.79 (8.53)	20.08 (19.93)	12.28 (12.95)
CuL ($C_{22}H_{17}CuN_3O_6$)	3-4	Yellowish brown	233	7.8	54.71 (54.02)	3.55 (3.93)	8.70 (8.15)	19.88 (20.18)	13.16 (13.73)

Table 2: Infrared spectral bands (cm^{-1}) of the ligand and complexes

Ligand/Complex	$\nu(CH)_{arom}$.	$\nu(CH)_{aliph}$.	ν(C=N)	ν(C=C)	ν(C-O)
H_2L	3072	2976	1627	1581	1255
CoL ($C_{22}H_{17}CoN_3O_6$)	3005	2943	1609	1536	1254
NiL ($C_{22}H_{17}NiN_3O_6$)	3086	2938	1612	1594	1251
CuL ($C_{22}H_{17}CuN_3O_6$)	3050	2927	1611	1592	1243

Table 3: Proton magnetic reonance spectral data (δ, ppm) of the Schiff bases

Ligands	δ(O-H) Protons	δ(CH=N) Proton	δ(Ar-H) Protons	δ(O-CH_3) Protons
H_2L	11.8, 11.2	9.0, 8.6	6.0-8.0	3.9

Antimicrobial assay

The *in vitro* screening of newly synthesized Schiff base ligand and corresponding complexes were performed against bacteria by using agar well diffusion method (Chah *et al.,* 2006) in DMSO. Erythromycin was used as standard drug for antibacterial activity. Antibacterial examinations were performed against the bacterial strains *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa.*

The biological activity was determined by measurement of diameter of inhibition zone (IZD) around the wells. The tests were performed at the MRD Life Sciences, Lucknow, UP.

RESULT AND DISCUSSION

The physical properties and elemental analyses data for the Schiff base ligand H_2L and coressponding complexes are provided in Table 1. Elemental percentage of C, H, N, O were in close accordence with the theoratical values, indicating that the desired compounds were formed. The newly prepared complexes have higher melting point than the ligand, likely due to increase in molecular masses and stronger dative covalent and ionic bonds.

Infrared spectroscopy

The infrared bands of the ligand and coresponding metal complexes are provided in Table 2. The spectra of ligand and coresponding complexes are given in Fig. 1. The spectra of free schiff base show weak intensity stretching band at 3067, 3002 cm^{-1} for C-H stretching.The IR bands at 2976, 2938 cm^{-1} represent asymetric and symetric streching modes in H_2L. The spectra of Schiff base ligand H_2L with high intensity band at 1627 cm^{-1}, represents to ν(C=N) stretching (Ghani *et al.*, 2014; Kangavalli *et al.,*2023). This band were shifted towards lower frequency region in the complexes (1605-1625 cm^{-1}). This is due to coordination of imine nitrogen to metal ion. The decrease in stretching frequency indicates that the decrese in π electron density of the C=N bond on coordination to the metal center which weakened the bond.

The phenolic oxygen of o-vanillin were involved in chelation in deprotonated form. It was concluded by the shifting of ν(C-O) frequencies of phenolic peak towards lower region. The ν(C-O) phenolic band with medium intensity was observed at 1255 cm^{-1} in free ligand, which was slightly shifted towards lower side at 1243 to1248 cm^{-1} . There are two additional bands at 1488 and at 1544 cm^{-1} appeared in spectra of complexes which are not observed in ligand spectra may be assigned to coupled ν(C=N) and ν(C=C) modes. Weak bands at 526-543 cm^{-1} and 456-462 cm^{-1} represent to ν(M-N) and ν(M-O) which supports coordination of imine N and phenolic-O with central metal ion (Boharan *et al.,* 2019).

NMR Spectroscopy

The PMR data of ligand was recorded in DMSO-d_6 (Fig. 2). In the ^{1}HNMR spectra of H_2L, the peaks at δ 11.9 ppm (2H) represent the signal for phenolic protons, at δ 9.0 ppm(2H) for azomethyne protons, at δ 6.8-7.9 ppm for aromatic protons and peak at δ 3.9 ppm for $-OCH_3$ protons. The peaks at δ 3.4 and δ 2.5 ppm represent water and DMSO(solvent peaks).

Molar conductance

The molar conductance of metal complexes were obseved with 1×10^{-3} M DMSO solutions and are listed in Table 1. The recorded data shows that the complexes are non electrolytes with very low (2-8 mho cm^2 mol $^{-1}$) molar conductance.

UV-Visible spectra and magnetic moment

The UV-Visible spectra were recorded in DMF solvent in the range between 200-800 nm and are listed in Table 3 (Fig. 3). The bands corresponding to -CH=N are observed due to transfer of charge during interaction between metal and ligand. The ligand and their complexes have a band in the region 250-298 nm with high intensity, assigned for π→π* (C=C) of benzene ring and π→π*(C=N). The bands in the region 300-350 nm attributed to n→π* transitions. The peaks attributed to n→π* transitions between 300-350 nm in ligands show hyperchromic shift in Co(II)and Cu(II) complexes. All the complexes have weak band between 390-440 nm which represents to LMCT transitions.

The UV-vissible peaks at 310 and 392 nm may be allocated to the π→π* and n→π* and d-d transitions, suggest a square planar geometry around the cobalt(II) ion. The magnetic moment of the Co(II) complex was

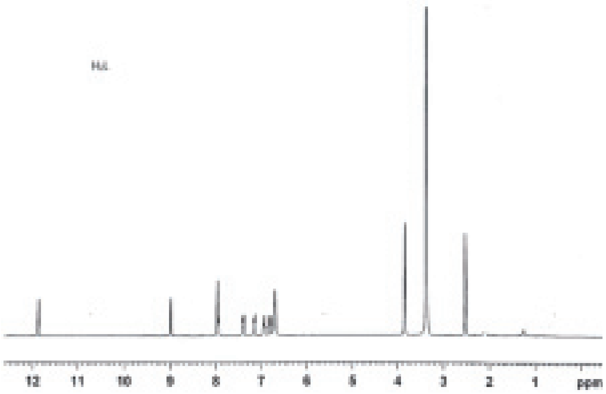


Fig.2. NMR spectra of H_2L

Table 4: UV-visible spectra and magnetic moment data of Ligand and complexes

Ligands/ Complexes	Absorbance (nm)	Assignments	Magnetic Moment μ_{eff} Exp.(Cal.)
H_2L	278	π→π*	-
	386	n→π*	
CoL	266	π→π*	4.23(3.86)
	310	n→π*	
	392	LMCT	
NiL	266	π→π*	2.38(2.82)
	334	n→π*	
	456	LMCT	
CuL	294	π→π*	1.38(1.72)
	356	n→π*	
	404	LMCT	

Table 5: Vina score with humen breast cancer protein HER2 (PDB: 3mzw)

Ligands/Complex	Binding energy/vina score (Kcal)
H_2L	-7.7
CoL	-9.2
NiL	-8.5
CuL	-8.5

Table 6: Antimicrobial activity

Pathogens	Inhibition zone diameter (IZD mm)				
	H_2L	CoL	NiL	CuL	Positive control
E. coli	22.4	22.6	16.3	23.7	12.66 mm
P. aeruginosa	21.33	22.6	18.9	22.1	15.09 mm
S. aureus	20.4	21.6	15.6	21.9	17.68 mmn

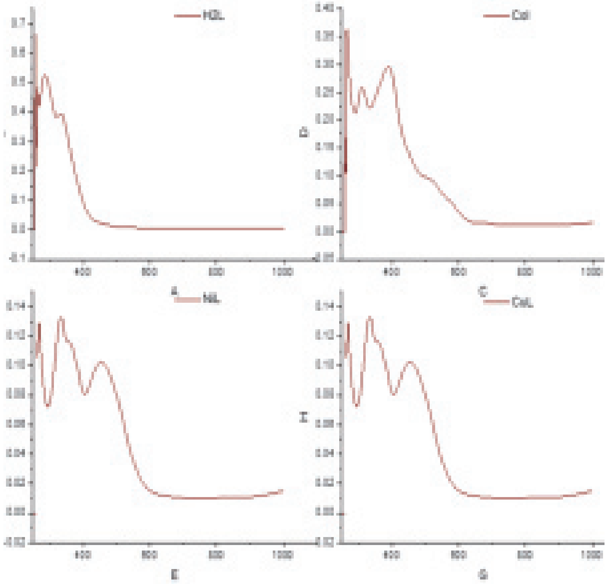


Fig.3. UV Spectra of ligand and complexes

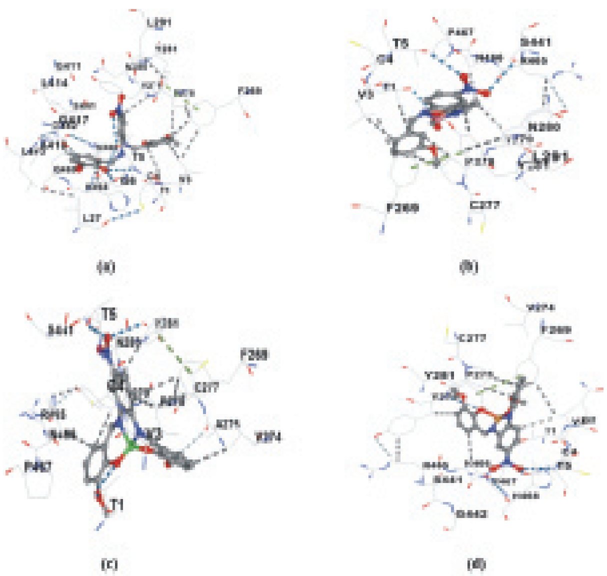


Fig.4. Lowest energy docked pose of (a) H_2L (b) CoL (c) NiL (d) CuL with humen breast cancer protein HER2

observed as 4.23 $\mu_B$which is in good agreement with expected squre planar geometry.The bands at 344 and 456 nm with medium intensity in UV-vissible spectra of Ni(II) complex are assigned to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions. The diamagnetic nature of Ni(II) complex atrributed to squre planar geometry (Ganesan *et al*., 2022). The bands at 356 and 404 nm with medium intensityin the electronic spectra of the Cu(II) complex represent to $\pi \rightarrow \pi^*$ and LMCT and d-d transitions, the magnetic moment values was determined as 1.38 μ_B, indicating the distorted tetrahedral geometry of Cu(II) complex.

Molecular docking

Molecular docking predicts the interaction between ligand or complex molecule and a known target protein. It provides molecular interaction behaviour with binding sites of target protein and also illustrates key biochemical processes (Prihantono *et al.*, 2020). Over the past few years H_2L based complexes displayed expressive anticancer activity against various types of cancers, and also exhibited biological activity against various bacteria. In this case H_2L, and their complexes CoL, NiL and CuLwere allowed to make interactions through molecular docking with anticancer protien HER2(PDB: 3MZW). Fig. 4. describes docking pose with lowest energy of H_2L and their CoL, NiL and CuL complexes with HER2.

The aminoacid in the target protein molecule participating in H bond formation with length of H bonds is also described in Fig. 4. The docking parameter (binding energies/vina score) are documented in Table-5. These results indicates that Co(II) complex of H_2L has lowest binding energy(-9.2 Kcal/mol) in comparision with ligand (-7.7 Kcal/mol), Ni(II) complex (-8.5 Kcal/mol) and Cu(II) complex (-8.5 Kcal/mol). This indicates that the complex Co(II)L shows highest anticancer activity towards humen Breast cancer protien among free ligand and Cu(II)L and Ni(II)L complexes HER2(PDB: 3MZW).

Antimicrobial Screening

Table 6 shows the results of antimicrobial activity of ligands and their compounds. The ligand show good control against tested bacteria but are inactive towards tested fungal cultures, where as their complexes exhibit greater activity towards bacteria and fungi. Ligand H_2L was found to be very active towards bacteria *E. coli* (IZD=22.4mm), *P. aeruginosa* (IZD=21.33mm) and *S. aureus* (IZD=20.4mm) and the values for CoL(IZD values are 22.6mm, 22.6mm, 21.6mm respectively. NiL(IZD values are 16.3mm, 16.9mm, 15.6mm respectively and for CuL These values are23.7mm, 22.1mm, 21.9mm respectively. These values are much greater than the used standard drug Erythromycin. These results showed that ligandCuL has good antibacterial property. It is observed that the biological activity of complexes is greater than that of free ligand.

CONCLUSION

Ligand H_2L acts as a tetradentate ligand and coordinated to central metal centers through their phenolic oxygen and azomethyne nitrogen donor atoms. Ligand and complexes are characterised by FTIR, NMR and UV-Visible spectroscopy. Magnetic moment measurement and spectocopic anlysis of molecules insights the tetrahedral geometry of Co(II) complexe having three unpaired electrons, Square planer geometry of Ni(II) having no unpaired electron and distorted tetrahedral geometry of Cu(II) complex with one unpaired-e. The comperative antimicrobial screening exhibits that complexes are more active against tested bacterial strains than free ligand.

The docking process involved $H_2L$and their CoL, NiL and CuL complexes interacting with the target protien HER2(PDB:3MZW) which is associated with humen breast cancer. The results support that the CoL complex has best inhibition property towards HER2. The *in vitro* antimicrobial screening reveals that CuL is most active towards bacteria.

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