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ORIGINAL RESEARCH

Synthesis, Characterization Biological Activity and Molecular Docking of Some Trivalant Transition Metal Complexes with Schiff Bases Derived from o-Vanillin

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ABSTRACT

This study highlights the synthesis and characterization of tetradentate ONNO Schiff base ligands H_2L^1 (N, N-Bis(vanillinidene)-4-chloro-1,2-phenylenediamine), and H_2L^2 (N,N-Bis (vanillinidene)-4-nitro-1,2-phenylenediamine) and Fe(III), Co(III), Cr(III) complexes of H_2L^1 and H_2L^2. The Schiff base ligands H_2L_1 and H_2L_2 have been synthesized from o-vanillin and 4-chloro-o-phenylenediamine and 4-nitro-o-phenylenediamine by condensing them in 2:1 molar ratio respectively. Ligands and complexes have been characterized by microanalytical technique, FTIR, UV, NMR spectroscopy and magnetic susceptibility. On coordination to the metal centers, the ν(C=N) and ν(C-O) peaks shifted to lower frequencies and new peaks for (M-N) and (M-O) appears in the range 535-560 and 421-460 cm^{-1}, respectively. The Schiff base ligand and complexes have been screened for antimicrobial property against bacteria and fungi. Molecular docking has been also carried out against CPE(Clostridium perfringens enterotoxin) (PDB ID:2XH6). It has been observed that affinity of complex is greater than ligands.

KEY WORDS: Molecular docking, Schiff base, Spectral studies, Transition metal complex

INTRODUCTION

Schiff Bases, introduced by Hugo Schiff in 1864 also known as imine or azomethine have gained importance due to their ease of synthesis, relatively cheap starting material and their stability towards air oxidation. These Schiff bases having SH or OH moiety near the azomethyne group have amazing chelating ability (Bahron *et al.,* 2019). There are various acyclic and macrocyclic organic ligands, among which Schiff base ligands enrich modern coordination chemistry very much and play an important role in the development of coordination chemistry because they form stable complexes with various transition metals in different oxidation states (El Sherif *et al.,* 2011). Schiff base metal complexes are good catalysts in heterogeneous systems such as in stereoselective epoxidation of alkenes (Pui *et al.,* 2001; Pui *et al.,* 2002; Fiammengo *et al.,* 2002) in liquid-liquid extraction (Al Zoubi *et al.,* 2011,2013, 2014), in transport of metal ions through the liquid membrane (Bharti *et al.,* 2010) and in asymmetric addition of organometallic reagents to aldehydes and ketone. Schiff base complexes are also well known for their specific biological activities. These have been extensively explored in therapeutic applications and promising drugs such as antiviral (Ahmad *et al.,* 2019), antibacterial (Osowole *et al.,* 2012), antidiabetic (Creavenm *et al.,* 2010) and antifungal (Smith *et al.,* 1989). These are also used as contrast agent in MRI (Saghatforous, *et al.,* 2019) and in chemotherapy of cancer (Murata *et al.,* 2007).

Schiff bases are compounds with azomethine [-C=N-] group in their structure and are prepared from the condensation of an active carbonyl compound with primary amine (El-Wahab *et al.,* 2007). It has been reported that Schiff bases synthesized from carbonyl compounds with diamines represent an important class of chelating agents. They can be obtained by condensing carbonyl compounds with diamines in a 2:1 M ratio (Alleman *et al.,* 1999; Jones *et al.,* 1979; Laila *et al.,* 2021). The condensation of hydroxyl aldehydes with diamines is the

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field of interest of recent researchers. These Schiff bases contain nitrogen and oxygen donor atoms (Sah *et al.,* 2007). The Schiff bases prepared in this way commonly behave as bidentate and 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 atoms as well as two nitrogen donors. The structure of these Schiff bases provides an interesting mode of coordination (Blagus *et al.,* 2009). These tetradentate chelating Schiff base ligands are of great interest to modern researchers (Yu *et al.,* 2009). Metal chelates coordinated through ONNO donor atom of Schiff base have been reported as oxygen carriers and are useful model of bioinorganic processes (Datta *et al.,* 2002). Transition metal complexes with N, O donor atoms show noticeable biological activities (Ashraf *et al.,*2017). This enhanced biological activity may be explained by Overton's concept and chelation theory (Aly & Moustafa *et al.,* 2015) that are based on lipophilicity and penetration of the complexes through the lipid membrane. Metals like Cr(III), Fe(III), Co(III) have great affinity towards coordination because of their smaller size and higher nuclear charge.

The present work deals with the synthesis, structure elucidation and antimicrobial activity of Schiff bases derived by condensation of o-vanillin and 4-Chloro-o-phenylenediamine(H_2L^1) and o-vanillin and 4-Nitro-o-phenylenediamine(H_2L^2) and their Fe(III), Co(III), Cr(III) complexes. The structure of complexes was determined by using elemental analysis, FTIR, UV, ^{1}HNMR, ^{13}CNMR analytical techniques. Besides synthesis and characterization of complexes by physiochemical techniques, biological activities of prepared complexes were determined against some microbial strains for antibacterial and antifungal activities.

EXPERIMENTAL

Reagents and apparatus

All the chemicals and reagents used were of research grade. $Cr_3O(OAc)_6 \cdot 3H_2O$, $FeCl_3 \cdot 6H_2O$ and $CoCl_2 \cdot 6H_2O$ were provided by E. Merk. o-Vanillin, 4-chloro-o-phenylene diamine and 4-nitro-o-phenylenediamine were purchased from Sigma Aldrich. All the chemicals and solvents were used as purchased, without further purification. The electronic spectra of the complexes were taken on Hitachi Perkin Elmer Lambda Spectrometer range of 800-200 nm in DMF solvent. The IR Spectra of ligands and complexes was recorded in Perkin Elmer Spectrum IR Version 10.6.1. ^{1}HNMR spectra of ligands and complexes were recorded in DMSO-d_6 using Bruker-300 spectrometer. Melting points were recorded with an ambassador melting point apparatus by using thin capillaries. Molecular docking was performed by CB-Dock. Antimicrobial screening was performed at MRD Lifesciences at Lucknow.

Synthesis of ligand(H_2L^1)

0.02 moles (3.042g) of o-vanillin and 0.01 mole (1.426g)

Table 1: Physical Properties and analytical data of ligands H_2L^1, H_2L^2 and their Fe(III), Co(III) and Cr(III) complexes

Compound/ Empirical Formula	Stirring Time(hrs)	Colour	Decomposition Temp.(^{0}C)	Calc.(found) % C	H	N	Cl	O	M
H_2L^1 ($C_{22}H_{19}N_2O_4Cl$))	3-4	Saffron brown	224	64.31 (63.92)	4.66 (5.72)	6.82 (6.94)	8.63 (8.21)	15.58 (15.25)	-
H_2L^2 ($C_{22}H_{19}N_3O_6$)	3-4	Yellow	229	62.70 (61.92)	4.54 (4.72)	9.97 (10.11)	-	22.78 (23.29)	-
$[CrL^1(H_2O)_2]Cl$	3-4	Fade Saffron brown	229	51.85 (52.31)	4.38 (3.93)	5.04 (4.89)	6.38 (7.03)	23.02 (22.63)	9.35 (9.03)
$[FeL^1(H_2O)_2]Cl$	3-4	Yellowish brown	230	49.28 (49.01)	3.95 (4.31)	5.22 (5.42)	13.22 (12.93)	17.90 (18.33)	10.42 (9.93)
$[CoL^1(H_2O)_2]Cl$	3-4	Yellowish brown	233	49.00 (49.26)	3.39 (3.13)	5.19 (5.11)	13.15 (13.63)	17.80 (17.98)	10.93 (10.73)
$[CrL^2(H_2O)_2]OPc$	3-4	Dark brown	233	50.89 (51.03)	4.27 (4.01)	7.42 (7.65)	-	28.24 (28.11)	9.18 (9.28)
$[FeL^2(H_2O)_2]Cl$	3-4	Brown	234	48.33 (48.13)	3.87 (3.99)	7.69 (7.84)	6.48 (6.23)	23.41 (23.53)	10.21 (10.30)
$[CoL^2(H_2O)_2]Cl$	3-4	Brown	236	48.06 (49.91)	3.85 (3.71)	7.64 (7.43)	6.45 (6.63)	23.28 (23.24)	10.72 (10.63)

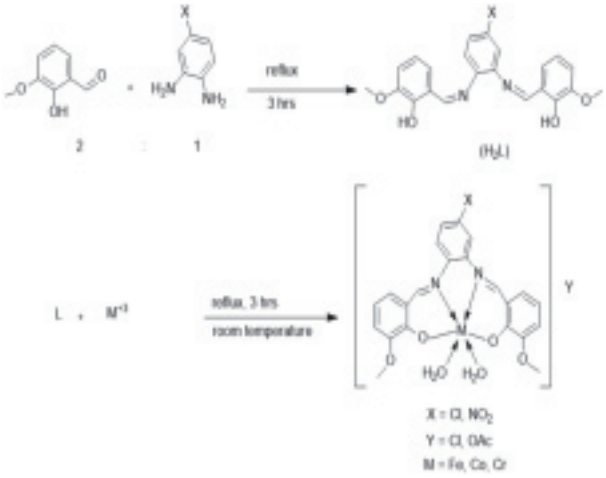

Fig. 1

of 4-Chloro-o-phenylenediamine (2:1 molar ratio) are dissolved separately in minimum amount of ethanol and then hot solutions are mixed dropwise. The resulted reaction mixture was refluxed for three hours at 60-80^{0}C (Trivedi *et al.,* 2022). Saffron brown coloured solid was separated, which was filtered and washed with ethanol, followed by diethyl ether, and dried over anhydrous calcium chloride.

Synthesis of ligand(H_2L^2)

0.020 moles (3.042g) of o-vanillin and 0.010 moles (1.531g) of 4-Nitro-o-phenylenediamine (2:1 molar ratio) are dissolved separately in minimum amount of ethanol and then hot solutions are mixed dropwise. The resulted reaction mixture was refluxed for 3 hours at 60-80^0 C (Trivedi *et al.,* 2022). Dark bright yellow coloured solid was separated, which was filtered and washed twice with 10mL of ethanol, followed by diethyl ether, and dried over anhydrous calcium chloride.

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

Ligand/Complex	$\nu(CH)_{arom.}$	$\nu(CH)_{aliph.}$	ν(C=N)	ν(C=C)	ν(C-O)
H_2L^1	3067	2947	1611	1575	1252
H_2L^2	3072	2976	1627	1581	1255
$[CrL^1(H_2O)_2]Cl$	3031	2913	1610	1548	1250
$[FeL^1(H_2O)_2]Cl$	3027	2933	1599	1575	1253, 1243
$[CoL^1(H_2O)_2]Cl$	3047	2936	1610	1581	1248
$[CrL^2(H_2O)_2]Cl$	3029	2956	1601	1545	1252
$[FeL^2(H_2O)_2]Cl$	3056	2922	1625	1567	1247
$[CoL^2(H_2O)_2]Cl$	3044	2933	1607	1515	1224

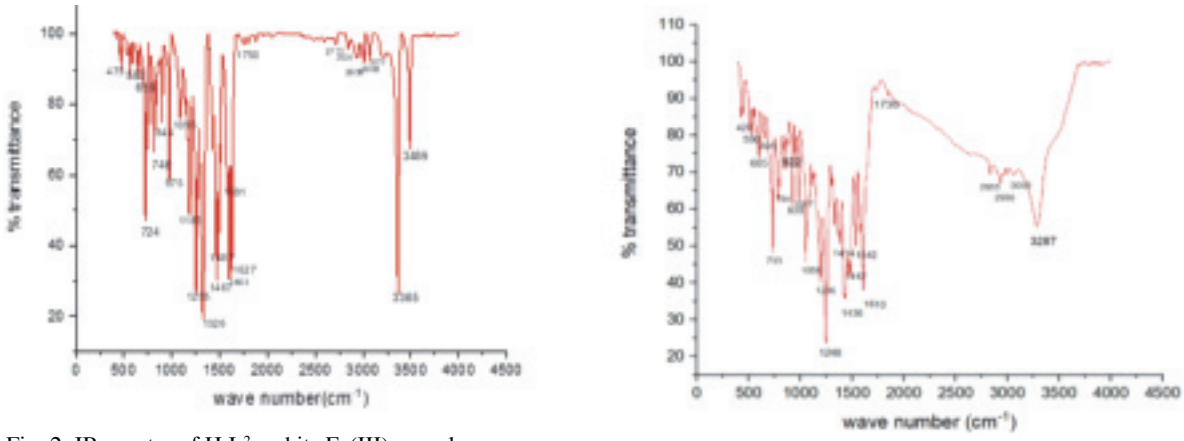

Fig. 2: IR spectra of H_2L^2 and its Fe(III) complex

Table 3: Proton magnetic resonance 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^1	12.8, 12.7	8.9, 8.8	6.8-7.7	3.9
H_2L^2	11.8, 11.2	9.0, 8.6	6.0-8.0	3.9

Table 4: UV spectra and magnetic moment of complexes

Ligands/ Complexes	Absorbance (nm)	Assignments	μ_{eff}(BM)
H_2L^1	290	π→π*	-
	340	n→π*	
H_2L^2	278	π→π*	-
	386	n→π*	
$[CrL^1(H_2O)_2]Cl$	296	π→π*	3.79
	338	n→π*	
$[FeL^1(H_2O)_2]Cl$	298	π→π*	5.84
	440	n→π*	
$[CoL^1(H_2O)_2]Cl$	272	π→π*	
	308	n→π*	dia.
	324	LMCT	
$[CrL^2(H_2O)_2]OAc$	278	π→π*	3.87
	392	n→π*	
$[FeL^2(H_2O)_2]Cl$	280	π→π*	5.89
	390	n→π*	
$[CoL^2(H_2O)_2]Cl$	270	π→π*	
	310	n→π*	dia.
	440	LMCT	

Table 5: Vina score with food poisoning protein CPE (PDB: 2XH6)

Ligand/ complex	Binding energy/vina score (Kcal.)
H_2L^1	-7.4
H_2L^2	-6.9
$[FeL^1(H_2O)_2]Cl$	-7.8
$[CoL^1(H_2O)_2]Cl$	-7.4
$[FeL^2(H_2O)_2]Cl$	-7.4
$[CoL^2(H_2O)_2]Cl$	-9.0

Synthesis of Fe(III)complexes

To a hot solution of ligands viz. H_2L^1 (1 mmol, 0.412 g) and H_2L^2 (1 mmol, 0.421 g) in ethanol, ethanolic solution of $FeCl_3 \cdot 6H_2O$(1mmol, 0.269 g) was added dropwise. After stirring the solution for 10 min triethylamine (0.2 mL) was added dropwise and mixture was stirred followed by refluxing for 3 h. (Gautam *et al.,* 2021). The colour of reaction mixture was changed from saffron brown to yellowish brown for H_2L^1 and from deep bright yellow to pale muddy for H_2L^2. The precipitate was filtered and washed with ethanol followed by diethyl ether. The precipitate was vacuum dried over anhydrous calcium chloride.

Synthesis of Co(III) complexes

To a hot solution of ligands viz. H_2L^1 (1 mmol, 0.412 g) and H_2L^2 (1mmol, 0.421 g) in ethanol, ethanolic solution of $CoCl_2 \cdot 6H_2O$ (1mmol, 0.237 g) was added dropwise. After stirring the solution for 10 min triethylamine (0.2mL) was added dropwise and mixture was stirred (Gautam *et al.,* 2021), followed by addition of 30% aq.H_2O_2 solution to convert Co(II) into Co(III) (Gupta *et al.,* 2019). Then reaction mixture was refluxing for 3h (Gautam *et al.,* 2021). The colour of reaction mixture was changed from saffron brown to yellowish brown for H_2L^1 and from deep bright yellow to pale muddy for H_2L^2. The precipitate was filtered and washed with ethanol followed by diethyl ether. The precipitate was vacuum dried over anhydrous calcium chloride.

Synthesis of Cr(III)complexes

To a hot solution of ligands viz. H_2L^1 (1 mmol, 0.412g) and H_2L^2 (1 mmol, 0.421g) in ethanol, ethanolic solution of $Cr_3O(OAc)_6 \cdot 3H2O$ (1 mmol, 0.726 g) was added dropwise. After stirring the solution for 10 min triethylamine (0.2mL) was added dropwise and mixture was stirred followed by refluxing for 3h (Gautam *et al.,* 2021). The colour of reaction mixture was changed from saffron brown to green-yellowish brown for H_2L^1 and from deep bright yellow to greenish-pale muddy for H_2L^2. The precipitate was filtered and washed with ethanol followed by diethyl ether. The precipitate was vacuum dried over anhydrous calcium chloride. The synthesis route of ligand and complex and their proposed structure is given in Fig. 1.

Antimicrobial properties

The *in vitro* antimicrobial screening of synthesized Schiff bases and their complexes was performed against bacteria and fungi by using agar well diffusion method (Chah *et al.,* 2006) in DMSO solvent. Erythromycin and Fluconazole were used as standard drugs for antibacterial and antifungal activity respectively. Antibacterial studies

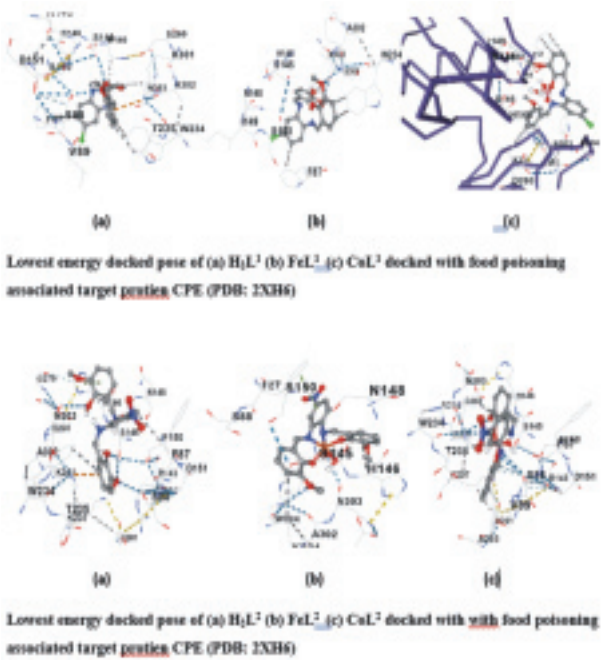

Fig. 3

were performed against the bacterial strains *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and fungal studies against strains *Candida albicans and Aspergillus niger.*

The assessment of activity was based on the measurement of diameter of inhibition zone (IZD) around the wells. The test was carried out at the MRD Life Sciences, Lucknow.

RESULTS AND DISCUSSION

The physical properties and elemental analyses data for the schiff base ligands $H_2L^1$and H_2L^2 and their complexes are provided in Table 1. The experimental percentage of C,H,N,O and halogens were in close accordence with the theoratical values, indicating that the desired compounds were formed. The melting points of complexes were greater than the ligands, likely due to increase in molecular masses and stronger dative covalent and ionic bonds.

Infrared spectroscopy

The significant infrared bands of the ligands and their metal complexes are provided in Table 2. The spectra, as given in Fig. 2, provide valuable information on the functional groups present in the ligand and their metal complexes. The spectra of free schiff bases show weak intensity stretching band at 3067, 3002 cm^{-1} for C-H stretching. The asymmetric and symmetric stretching modes for -CH_3 were found at 2947, 2831 cm^{-1} in H_2L^1 and at 2976, 2938 cm^{-1} in H_2L^2 (Venkatesh *et al.,* 2024). The spectra of free schiff bases H_2L^1 and H_2L^2 show high intensity band at 1611 and 1627 cm^{-1} respectively, attributed to ν(C=N) stretching (Ghani *et al.,* 2014). These bands were observed to be shifted towards lower frequencies in the complexes(1605-1625 cm^{-1}), due to coordination of imine nitrogen to metal center with the help of its loan pair in a dative manner. The lowering of stretching frequency indicates the weakening of the C=N bond on coordination to the metal center which decreases π electron density.

The phenolic oxygen of o-vanillin unit were involved in chelation in deprotonated form. It was indicated by the shifting of ν(C-O) phenolic peak towards lower frequencies. The medium intensity ν(C-O) phenolic band was observed at 1252 and 1255 cm^{-1} in free ligands H_2L^1 and H_2L^2 respectively, which were slightly shifted towards lower side at 1243 to 1248 cm^{-1}. There are two additional bands at 1488 and at 1544 cm^{-1}appeared in spectra of complexes which are not present in ligand spectra can be assigned to couppled ν(C=N) and ν(C=C) modes. Weak bands at 526-543 cm^{-1} and 456-462 cm^{-1} are attributed to ν(M-N) and ν(M-O) which supports involvement of imine N and phenolic O in the coordination with metal centers.

Table 6: Antimicrobial activity

PATHOGENS	INHIBITION ZONE DIAMETER (IZD in mm)						
	H_2L^1	H_2L^2	$[FeL^1(H_2O)_2]Cl$	$[CoL^1(H_2O)_2]Cl$	$[FeL^2(H_2O)_2]Cl$	$[CoL^2(H_2O)_2]Cl$	Positive control
E. coli	26.4	10.3	6.3	9.7	4.5	6.7	12.66 mm
P. aeruginosa	23.33	9.6	8.9	8.1	6.2	5.8	15.09 mm
S. aureus	26.4	12.4	10.6	8.9	5.9	7.6	17.68 mm
C. albicans	10.1	9.9	7.3	6.9	5.6	6.1	34.12 mm
A.niger	9.7	8.9	7.5	7.9	6.3	5.9	27.09 mm

NMR Spectroscopy

The PMR data of ligands is listed in Table 3. In the ^{1}HNMR spectra of H_2L^1, the peaks at δ 12.8 ppm(1H) and δ 12.7 ppm(1H) represent the signal for phenolic proton, at δ 8.97 ppm (1H)and δ 8.93 ppm(1H) for azomethine protons, at δ 6.8-7.7 ppm(9H) for aromatic protons and peak at δ 3.9 ppm(6H) for -OCH_3 protons. It shows both the phenolic protons and azomethyne protons flip at different fields due to asymmetric diamine ring. In the ^{1}HNMR spectra of H_2L^2, the peaks at δ 12.8 ppm (1H) and δ 12.7 ppm(1H) represent the signal for phenolic proton, at δ 8.97 ppm(1H) and δ 8.93 ppm(1H) for azomethyne protons, at δ 6.8-7.7 ppm(9H) for aromatic protons and peak at δ 3.9 ppm(6H) for -OCH_3 protons. It shows both the phenolic protons and azomethyne protons flip at different fields due to asymmetric diamine ring.

UV-Visible spectra and magnetic moment

The UV-Visible spectroscopic analysis serves to investigate charge transfer phenominon within the molecular structure. The UV-Visible spectra of ligands and complexes are recorded in DMF solvent in the range between 200-800 nm. The UV-Visible bands are listed in Table 4. Generally, ligand-induced transitions were observed in the ultraviolet region, where as d-d transitions were observed in visible region.The bands caused by -CH=N are visible due to transfer of charge during interaction between metal and ligand (Venkatesh *et al.,* 2024). The free ligands and their complexes exhibited a high intensity band in the region 250-298 nm, assigned for π→π* (C=C) of aromatic benzene 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 Fe(III) and Cr(III) complexes, while hypsochromic shift in Co(III) complexes. All the complexes have weak band between 390-440 nm which are attributed to LMCT from HOMO of ligand to the hybrid orbitals of the metal atom.

The magnetic moment values of Cr(III) complexes lies between 3.78-3.96 BM, which indicates that Cr(III) complexes are of high spin having 3 unpaired electrons. The magnetic moment values of Fe(III) complexes lies between 5.75-5.91 BM, which indicates that Fe(III) complexes are of high spin having 5 unpaired electrons. Complexes of Co(III) are diamagnetic. The possible geometry for M(III)is octahedral which is supported by magnetic moment values.

Molecular docking analysis

Molecular docking is employed to predict the atomic interaction between ligand molecule and a known target protein. It provides molecule interaction behaviour at target protein binding sites and also elucidates key biochemical processes (Kanagavalli *et al.,* 2023, Prihantono & Irfandi *et al.,* 2020). In recent years H_2L^1, H_2L^1 based complexes have been found to have significant anticancer activity against various cancers, and also exhibit biological activity against various bacteria. In this case H_2L^1, H_2L^2 and their Fe (III) and Co(III) complexes were docked with food poisoning target protein CPE (PDB: 2XH6). Fig. 3. depicts lowest energy docking pose of H_2L^1, H_2L^2 and their Fe (III) and Co(III) complexes with CPE.

The aminoacid in the target protein molecule that participates in H bond formation and length of H bonds is also depicted in Fig. 3. The computed molecular docking parameter (binding energies/vina score) are documented in Table 5. These results indicates that Fe(III) complex of H_2L^1 has lowest binding energy(-7.8 Kcal/mol) in comparision with ligand (-7.4 Kcal/mol) and Co(III) complex (-7.4 Kcal/mol). This indicates that H_2L^1dopped with Fe(III) shows high biological activity than free ligand. In case of H_2L^2, its Co(III) complex has max. vina score (-9.0 Kcal/mol) than its Fe(III) complex (-7.4 Kcal/mol) and free ligand(-6.9 Kcal/mol). So it is clear that both complexes of H_2L^2 show high efficiency than free ligand.

Antimicrobial Screening

Table 6 shows the results of antimicrobial activity of ligands and their compounds. The ligands show good control against tested bacteria but are inactive towards tested fungal cultures, where as their complexes exhibit less/no activity towards bacteria and fungi. Ligand H_2L^1 was found to be very active towards bacteria *E. coli* (IZD=26.4mm), *P. aeruginosa*(IZD=23.33mm) and *S. aureus*(IZD=26.4mm) than the ligand H_2L^2(IZD values are 10.3mm, 9.6mm, 12.4mm respectively).These values for H_2L^1 are much greater than the used standard drug Erythromycin. These results showed that ligand H_2L^1 has good antibacterial property.

The activity against fungus *C. albicans* and *A. flavus* were tested and it was found that the ligand H_2L^1 show good control than H_2L^2, but both are less active than standard drug fluconazole. The complexes had less activity than free ligands.

CONCLUSION

Schiff base ligands H_2L^1, H_2L^2 acts as tetradentateligand and coordinated to metal centers through their phenolic O and azomethyne N donar atoms. Dissapearance of phenolic O-H peak in ^{1}H NMR spectra of complexes shows that deprotonated phenolic O coordinates with metal. Absorption bands between 3288-3390cm^{-1} in IR spectra of complexes shows evidance of coordinated water molecules, So the geometry of the

complexes will be octahedral on the basis of above spectral analysis. The magnetic moment studies reveals that the complexes of Fe(III) and Cr(III) are high spin and of Co(III) are diamagnetic.

The docking process involved H_2L^1, H_2L^2 and their Fe(III) and Co(III) complexes interacting with the target protien CPE (PDB: 2HX6) which is linked to food poisoning.The findings support the FeL^1 and CoL^2 complex has best inhibition property towards CPE. The in vitro antimicrobial screening reveals that H_2L^1 is most active towards bacteria.

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