Synthesis, Characterization, and Molecular Docking Studies of Zinc (II) Metal Complexes with Some New Biologically Active Schiff Base Ligands

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Abstract

Ten complexes of the type [$ZnX_2L_2^{1-5}$] (where X= Cl or Br and L = new Schiff base ligands derived by condensation of 2-carbaldehyde-8-hydroxyquinonile and 2-amino-6-methylpyridine or cyclopropylamine or 3-morpholine-4-ylpropylamine or 2-aminopyridine or homopiperonylamine) have been prepared and characterized by elemental analysis, molar conductivity, IR and XPS data i.e. X-ray photoelectron spectra. An octahedral geometry has been proposed for all these prepared[$ZnX_2L_2^{1-5}$] complexes. Using two protein receptors, the interaction between ligand and protein was investigated using molecular docking.

The proteins 7LDW and 6HV0 displayed binding energies of -6.5 and -7.8 kcal/mol respectively, suggesting that they may find use in medicine. Further, pharmacological actives based on 8-hydroxyquinoline-2-carbaldehyde and homopiperonylamine may benefit from this study.

Keywords: Schiff Base, Zinc metal complexes, Molecular Docking Studies, Molar conductivity, IR and XPS.

Introduction

Schiff bases are synthesized by the reaction of carbonyl (aldehyde or ketone) with a primary amine under specific conditions[6,47,54]. The general structure of Schiff base is R_1R_2C=NR (R=H); thus the main function in Schiff base is of azomethine [C=C-N] group i.e. imine. Schiff bases have shown various biological and pharmacological activities such as antifungal[7], antiviral, cytotoxic effect[11], antimalarial[68], antibacterial[25], anticonvulsant[48], antioxidant[39], antidepressant[57], chitosan- based Schiff bases used as antibacterial[12], corrosion inhibitors[70], analgesic activities[18], anti-inflammatory[1,53], anticancer activities[27,28,46,50], solvent extraction of metal ions[5], antiproliferative[40], a green catalyst[43],catalyst[73], antimicrobial[60], in DNA interaction studies[65], nanoparticles of Schiff bases as determination of heavy metal ions[4], nanomedicines[41],antischistomal activities[2], anti-Alzheimer's disease[24,51], cosmetic and in polymer industry[10,56], electroluminescence[49] and fluorescence properties[16], pigments and dye[42], oxidant activities[3], antidiabetic[69].

Few market drugs having heterocyclic Schiff base have been also reported e.g. Nifurtimox and Nitrofurantoin[19,20,21]. 4-((E-[(4-chloro-2-hydroxyphenyl) methyldene] amino)-N-(6-methoxypyridazin-3-yl) benzene-1-sulfonamide has shown potent inhibition of urease enzyme[17]. (E)-2-((4-hydroxybenzylidene amino)-9-((2-hydroxyethoxy) methyl-1, 9-dihydro-6H-purin-6-one has shown antibacterial activities[23]. (E)-2-(pyren-1-ylimine-3-ol) has shown antioxidant and antibacterial activities[15]. Complexes of different metals e.g. Mo[36], Cu[31,37,61], Zr[13,58,59], Pd[33], Cu[55], Ni[52], Ru[8,29,30], Mn[26], Zn[32,34] and W[35] with Schiff base have shown myriad activities[22,62] and catalytic activities[38]. Hydrazone derivatives and antipyrine-derived Schiff base have an interesting class of compounds mainly in antimicrobial drug research[44,45,67]. Moreover, Schiff base derivatives obtained from sulfa drugs have too much attention due to their biological properties[9,66].

This research study deals with the synthesis and characterization of new five Schiff bases derived from the condensation of 2-carbaldehyde-8-hydroxyquinoline and 2-amino-6-methylpyridine or cyclopropylamine or 3-morpholine-4-ylpropylamine or 2-aminopyridine or homopiperonylamine. These five Schiff bases are again treated with ZnX_2 (Where X = Cl or Br) to obtain their metal complexes and the product zinc metal complexes were characterized by elemental analysis, molar conductivity, IR, and XPS data.

Material and Methods

The chemicals 2- amino-6-methylpyridine, 2-carbaldehyde-8-hydroxyquinoline; cyclopropylamine,2-aminopyridine, 3-morpholine-4-ylpropylamine homopiperonylamine were used. All other solvents were distilled, purified and dried from appropriate drying agents prior to use[71]. The melting points of ligands and zinc metal complexes were measured on a capillary melting point apparatus. The C, H, and N analysis for ligands and metal complexes was carried out at CDRI, Lucknow. The Infra-red spectra were recorded on CsI/KBr pellets on a Perkin-Elmer 1000 FT-IR spectrophotometer. Molar conductance was done on 10^{-3} M solution of the compound in DMF at room temperature using Digisundigital conductivity meter model DL-909.

The X-ray photoelectron i.e. XPS was recorded on a VG Scientific ESCA-3MK II electron spectrometer using MgKα (1253.6 eV) for photoexcitation. All the XPS peaks were fitted with Shirley background and a combination of Gaussian and Lorentzian line-shapes using ESCApesoftwere[63,64]. 2-carbaldehyde-8-hydroxyquinoline (2mmol) in methanol and amines (2mmol) i.e. 2- amino-6-methylpyridine or cyclopropylamine or 3-morpholine-4-

ylpropylamine or 2-aminopyridine or homopiperonylamine were refluxed for 2 hrs and later on a solution of ZnX_2 (where X= Cl or Br) in methanol (1mmol) were poured dropwise in this and refluxed again for 2 hrs. The resulting precipitate was filtered, dried, and recrystallized by ethanol: ether (9:1). The synthesized Schiff base and its metal complexes are shown in figures 1-6.

Results and Discussion

All these synthesized Schiff base ligands i.e. L^1 or L^2 or L^3 or L^4 or L^5 and their zinc metal complexes were solid. The elemental analysis calculated and found percentages for C, H, and N were found within ± 0.5%. The molar conductance of all these prepared zinc metal complexes was observed in the range of 24-35 ohm^{-1} cm^2 mol^{-1} in 10^{-3} M DMF solution at room temperature, suggesting that these complexes are nonelectrolyte[14]. In each ligand i.e. L^1 or L^2 or L^3 or L^4 or L^5, the IR band for the –CH=N– group appears at 1580cm^{-1}. But this –CH=N– IR band shifted to a lower wave-number in the range of 1540-1560 cm^{-1} which suggested the coordination of azomethinenitrogen to zinc metal ion[73]. Two new IR bands also appeared at 480-518 cm^{-1} and at 420-438 cm^{-1} in each $[ZnX_2L_2^{1-5}]$ complexes, corresponding to γ_{M-N} and γ_{M-X} respectively[72].

The Cl2p, N1s and Zn3p1/2 binding energies (eV) are listed in table 1 (Figures 7-11). It was observed that binding energies of Zn3p1/2 in the starting material i.e. $ZnCl_2$ or $ZnBr_2$ were higher than in $[ZnX_2L_2^{1-5}]$ complexes, suggesting the electron density in zinc metal ions is more in prepared complexes $[ZnX_2L_2^{1-5}]$, than ZnX_2 (where X= Cl or Br) due to coordination[70,71] (Table 1 and Figures 7-8). The N1s photoelectron peaks in these zinc metal complexes $[ZnX_2L_2]$ have shown one symmetrical peak towards higher binding energy side than their corresponding ligand, except in $[ZnX_2L_2^5]$ complexes in which two N1s photoelectron peaks appeared.

One on same position as in ligand and other towards higher binding energy in 1:2 intensity suggested that out of three nitrogen atoms, one nitrogen is uncoordinated and two nitrogen atoms are coordinated shown in figure 11.

Moreover, X2p (where X= Cl or Br) photoelectron peaks in these prepared metal complexes $[ZnX_2L_2^{1-5}]$ have shown higher binding energies than the starting zinc salts i.e. ZnX_2, suggesting that halide atoms are coordinated to the metal ion in the inner coordination sphere[63,64].

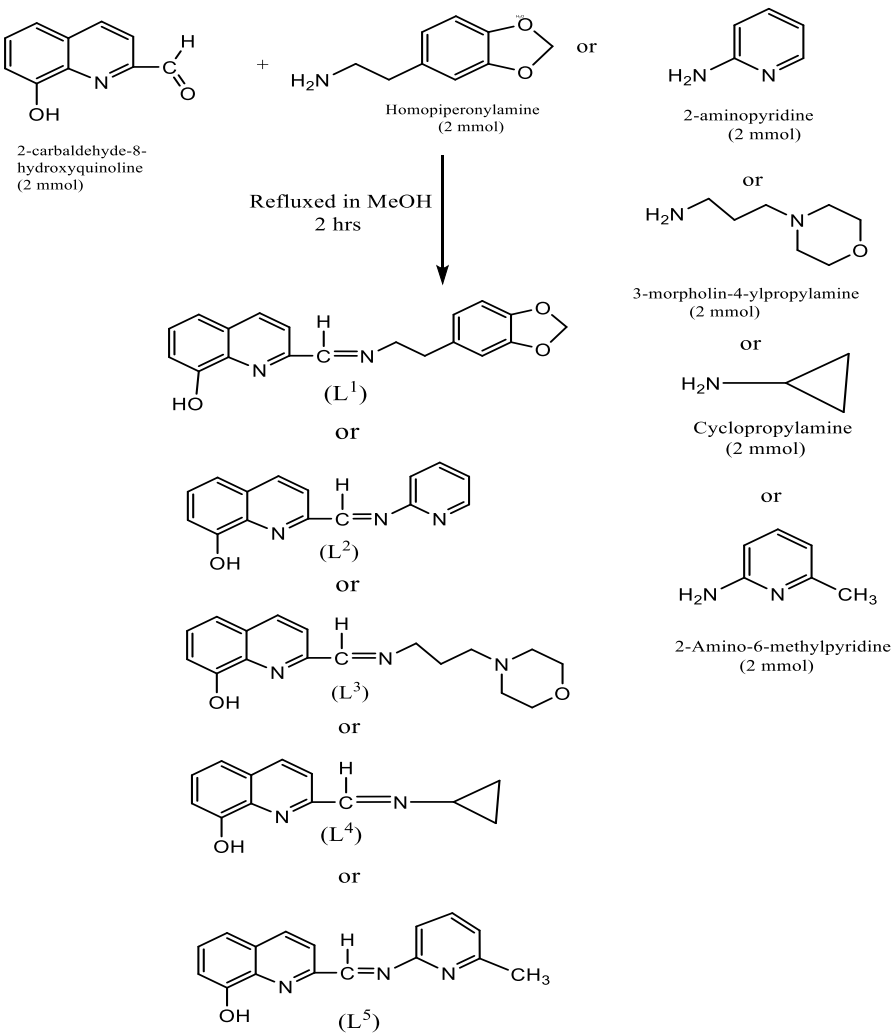

Figure 1: Synthesis of Schiff bases i.e. L^1 or L^2 or L^3 or L^4 or L^5

Table 1
Zn $3p_{1/2}$; XnP and N1s binding energies (eV) in ligands and $[ZnX_2L_2^{1-5}]$ complexes

S.N.	Ligand and Complex	$Zn3p_{1/2}$	Xnp		N1s	
			C12p	$Br3p_{1/2}$	Uncoordinated	Coordinated
1.	Ligand (L^1)				400.0	
2.	$[ZnCl_2L_2^1]$	87.2	202.2			402.2
3.	$[ZnBr_2L_2^1]$	87.0		190.6		402.2
4.	Ligand (L^2)				400.2	
5.	$[ZnCl_2L_2^2]$	87.2	202.2			402.2
6.	$[ZnBr_2L_2^2]$	87.0		190.6		402.2
7.	Ligand (L^3)				400.2	
8.	$[ZnCl_2L_2^3]$	87.2	202.2			402.2
9.	$[ZnBr_2L_2^3]$	87.0		190.6		402.2
10.	Ligand (L^4)				400.2	
11.	$[ZnCl_2L_2^4]$	87.2	202.2			402.2
12.	$[ZnBr_2L_2^4]$	87.0		190.6		402.2
13.	Ligand (L^5)				400.2	
14.	$[ZnCl_2L_2^5]$	87.2	202.2		400.2	402.2
15.	$[ZnBr_2L_2^5]$	87.0		190.6	400.2	402.2
16.	$ZnCl_2$	88.2	200.8			
17.	$ZnBr_2$	88.0		189.8		

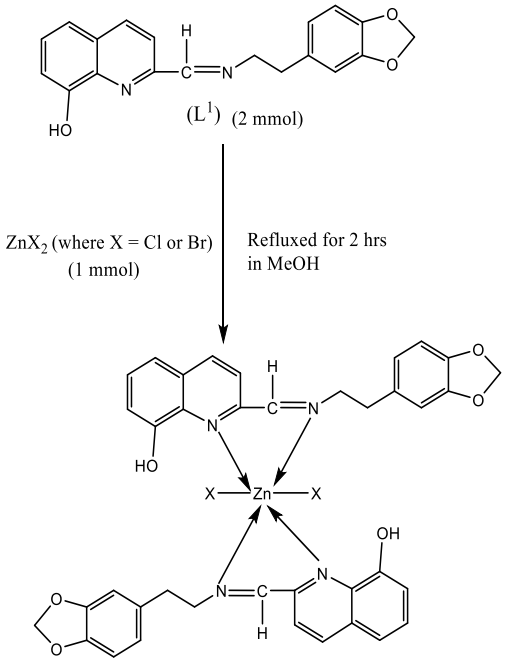

Figure 2: Synthesis of $[ZnX_2L_2^1]$ complexes (where X = Cl or Br)

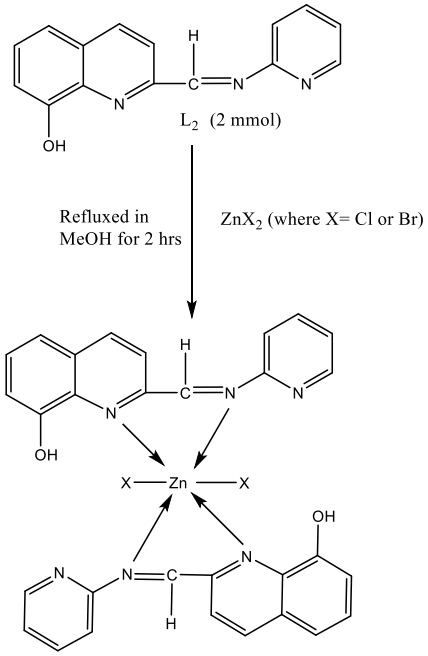

Figure 3: Synthesis of $[ZnX_2L_2^2]$ complexes (where X = Cl or Br)

Table 2
Hydrogen bonding and molecular docking with 8-Hydroxyquinoline-2-Carbaldehyde

S.N.	Protein (PDB ID)	NO. of Residues (A)	Bond Distance (Å)	Inhibition constant (micromolar)	Binding energy (Kcal/Mol)	Reference RMSD
1	6HV0	3	2.296	1.88891	-7.8	5.734
2	4U6R	3	1.989	14.3481	-6.6	6.489
3	4PL5	3	2.031 2.343	23.8199	-6.3	5.007
4	4YZC	3	2.042 2.384	28.2047	-6.2	5.384

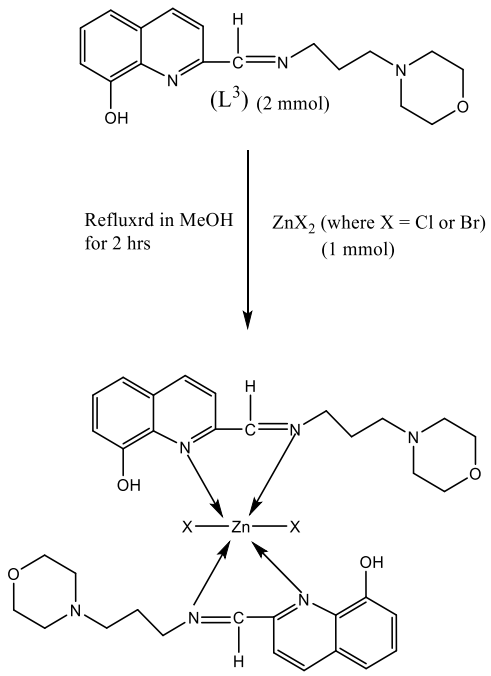

Figure 4: Synthesis of $[ZnX_2L_2^3]$ complexes (where X = Cl or Br)

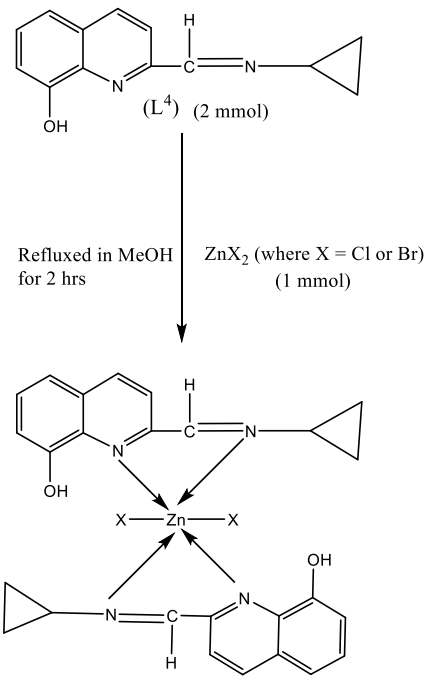

Figure 5: Synthesis of $[ZnX_2L_2^4]$ complexes (where X = Cl or Br)

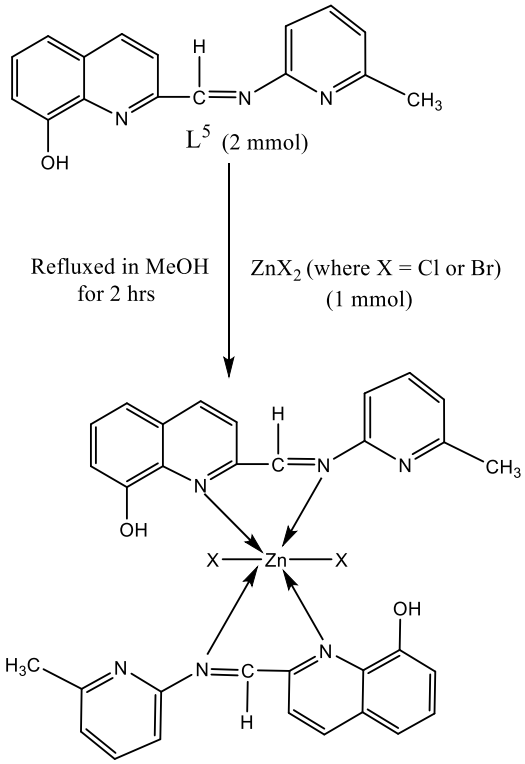

Figure 6: Synthesis of $[ZnX_2L_2^5]$ complexes (where X = Cl or Br)

Molecular Docking: Molecular docking is a significant approach in computer-aided drug design and structural molecular biology. Predicting the predominant binding mode of a ligand with a protein that has a known three-dimensional structure is the aim of ligand-protein docking. Because molecular docking is so frequently utilized in drug development, the pharmaceutical industry places a high value on it. The SWISS ADME-Target prediction, an online drug predictor, selects a suitable protein and downloads it from the protein data bank (PDB). Proteins are docked with the titlized molecule using Chimera 1.14 and auto dock-vina. The molecule's bioactivity is demonstrated by the binding energy value. The titlized molecules, 8 – Hydroxyquinoline -2- Carbaldehyde is docked with the distinct protein i.e. 6HVO(A), 4U6R(B), 4PLS(C) and 4Y2C(D) shown in figure 12 and the values are illustrated in table 2.

The finest binding energies are -7.8 and -6.6 kcal/mol with Inhibition constant value (ki) of 1.88 and 14.3 µM respectively. The titlized molecule homopiperonylamine is docked with distinct proteins i.e. 7LDW(A), 6W2B(B), 6VRL(C), 6DZV(D) shown in figure 13 and the values are illustrated in table 3. The finest energies are – 6.5 and -6.2 Kcal/mol with inhibition constant value (ki) of 16.98 and 28.20 µM respectively.

The receptor protein, 6 HVO has one bond with binding energy of -7.8 kcal/mol and bond distance of 2.296 Å. The 4U6R protein has one bond with binding energy of -6.6 kcal/mol and bond distance of 1.989 Å. The 4PL5 protein has one bond with binding energy of -6.3 kcal/mol and bond distance of 2.031 Å.

The 4Y2C protein has one bond with binding energies of -6.2 Kcal/mol and band distance of 2.042 Å. The receptor protein, 7LDW has four bond with bond energy of -6.5 kcal/mol and bond distances of 2.505, 2.178, 2.091, 2.177 Å. The 6W2B protein has three bond with binding energy of -6.2 kcal/mol and bond distance of 2.143, 2.337, 1.996 Å. The 6VRL protein has three bond with binding energy of -6.1 kcal/mol and bond distance of 1.239, 2.163, 2.251 Å. The 6DZV has three bond with binding energy of -5.8 kcal/mal and bond distance of 2.019, 2.395, 2.352 Å.

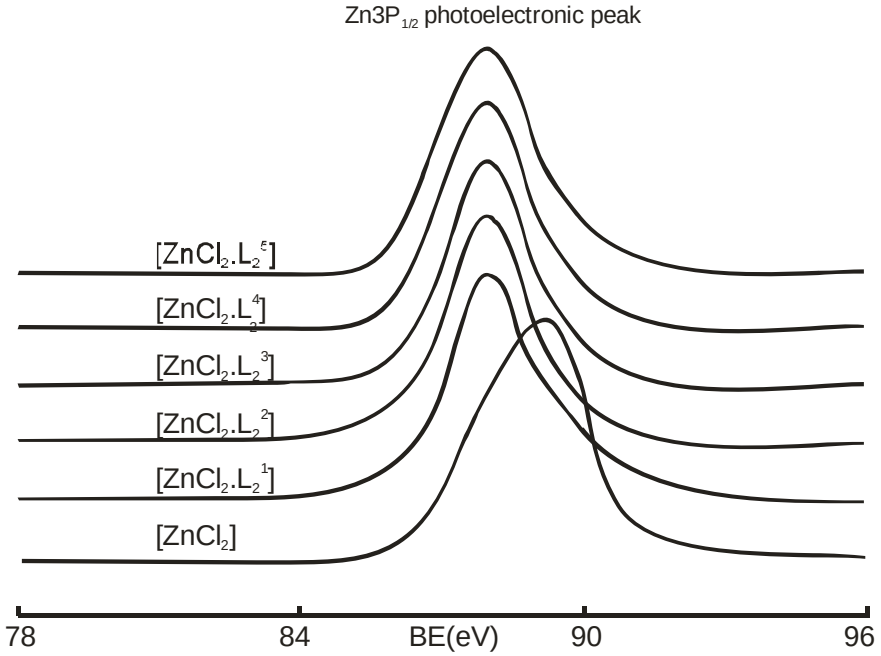

Figure 7: $Zn3p_{1/2}$ binding energies (eV) in $ZnCl_2$ and $[ZnCl_2.L_2^{1-5}]$ complexes

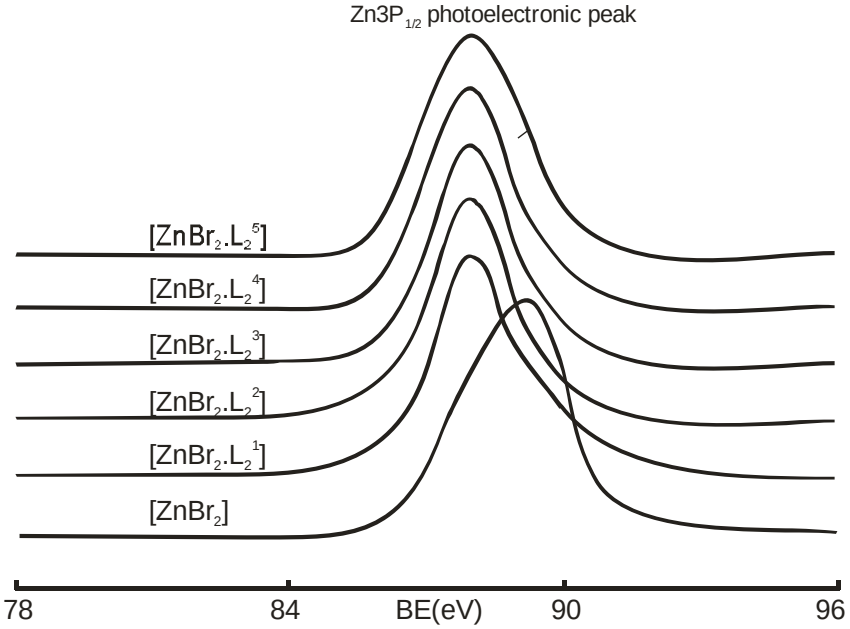

Figure 8: $Zn3p_{1/2}$ binding energies (eV) in $ZnBr_2$ and $[ZnBr_2.L_2^{1-5}]$ complexes

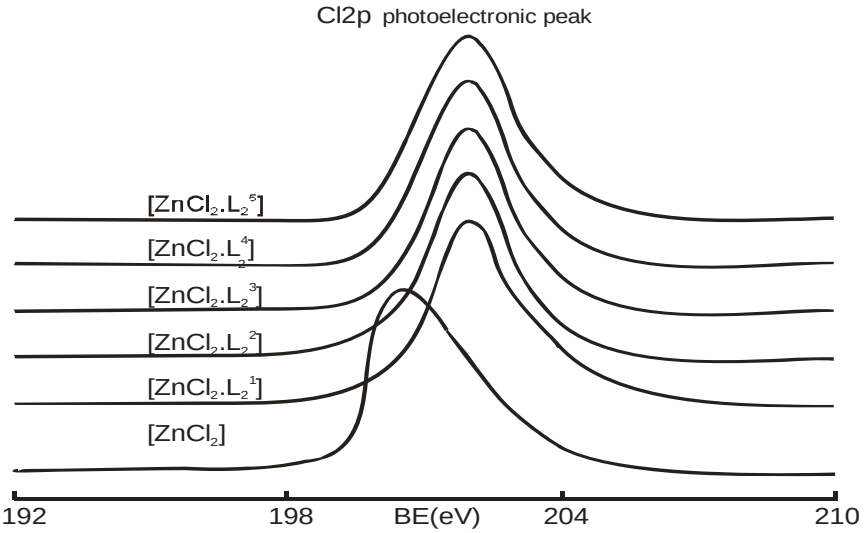

Figure 9: Cl2p binding energies (eV) in $ZnCl_2$ and $[ZnCl_2.L_2^{1-5}]$ complexes

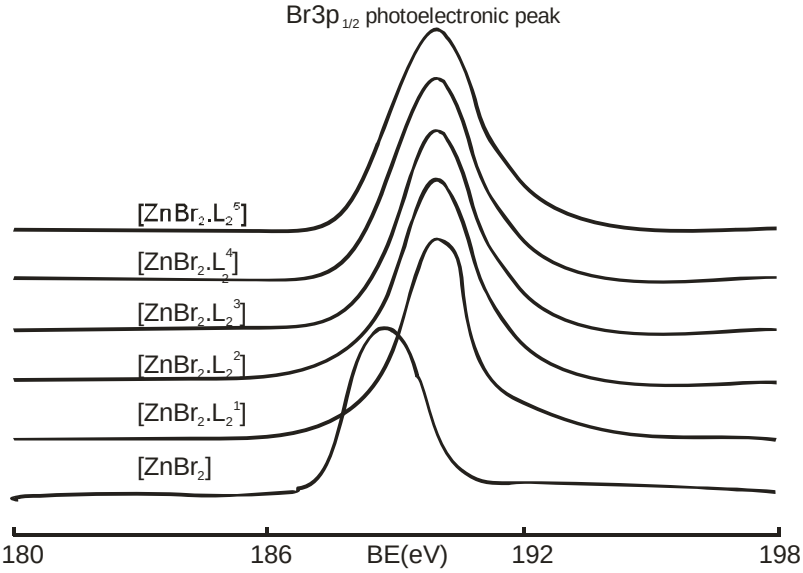

Figure 10: $Br3p_{1/2}$ binding energies (eV) in $ZnBr_2$ and $[ZnBr_2.L_2^{1-5}]$ complexes

Table 3
Hydrogen bonding and molecular docking with Homopiperonylamine

S.N.	Protein (PDB ID)	No. of Residues (A)	Bond Distance (Å)	Inhibition constant (micromolar)	Binding energy (Kcal/Mol)	Reference RMSD
1	7LDW	3	2.505 2.178 2.091 2.177	16.9893	-6.5	5.663
2	6W2B	3	2.143 2.337 1.996	28.2047	-6.2	5.663
3	6VRL	3	1.239 2.163 2.251	33.3967	-6.1	5.062
4	6DZV	3	2.019 2.395 2.352	55.4434	-5.8	6.612

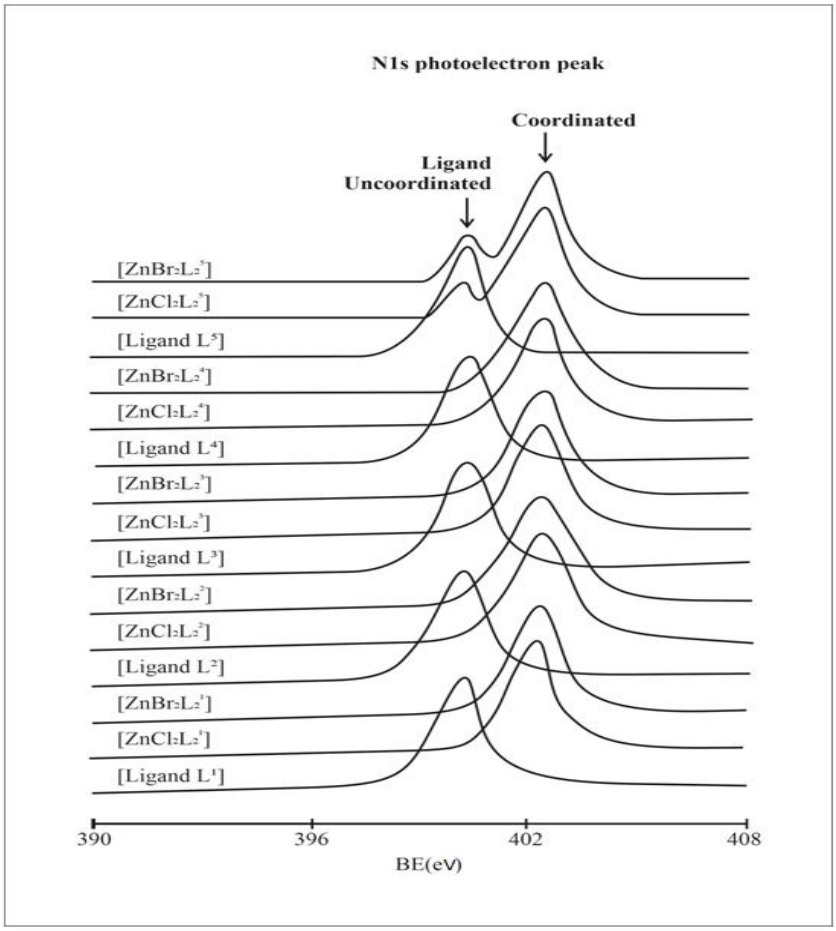

Figure 11: N1s binding energies (eV) in Ligands (L^{1-5}) and [$ZnX_2L_2^{1-5}$] Complexes.

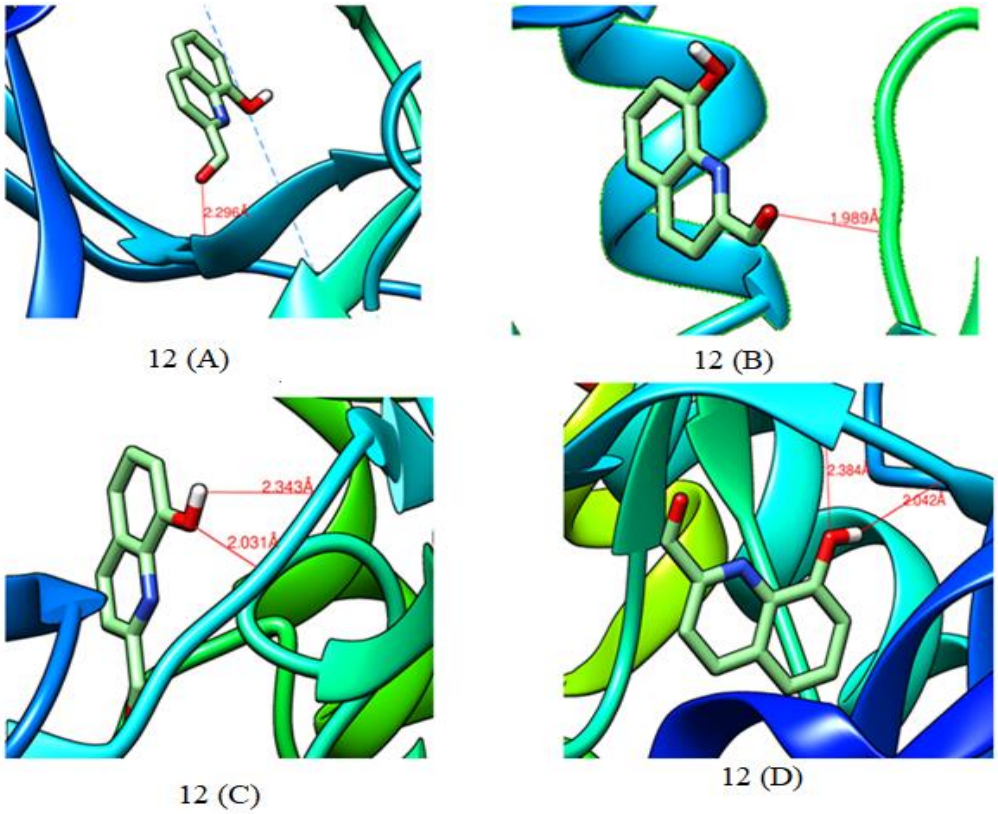

Figure 12: Ligand 8-Hydroxyquinoline-2-Carbaldehyde embedded in the active site of (A) 6HV0, (B) 4U6R, (C) 4PL5, (D) 4YZC proteins.

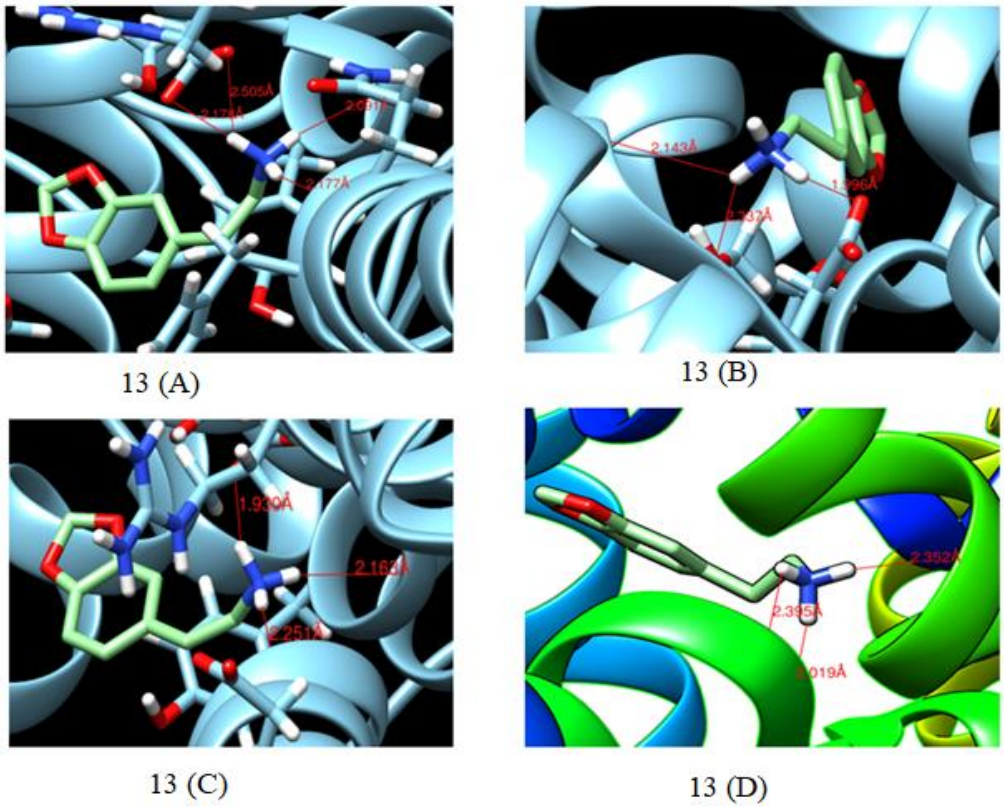

Figure 13: LigandHomopiperonylamine embedded in the active site of (A) 7LDW, (B) 6W2B, (C) 6VRL, (D) 6DZV (D) proteins.

Conclusion

On the basis of the above physicochemical data of $[ZnX_2L_2^{1-5}]$ complexes i.e. elemental analysis, molar conductance, Infra-red, and X-ray photoelectron spectra, the structure of $[ZnX_2L^{1-5}]$ complexes as shown in figures 2-6 and octahedral geometry may be established.The molecule was shown to be harmless by molecular docking with the 6HV0 and 7LDW proteins, which revealed binding energies of -7.8 and 6.5 kcal/mol.

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