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A SERIES OF MIXED LIGAND METAL COMPLEXES: SYNTHESIS, CHARACTERIZATION AND MOLECULAR DOCKING INVESTIGATIONS AGAINST CORONAVIRUS SPIKE PROTEIN

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ABSTRACT

A series of mixed ligand complexes with a Schiff base (HL1) (obtained from 2-hydrazinobenzimidazole and o-hydroxyacetophenone) acts as primary ligand and 1,10-phenanthroline (secondary ligand, L2) have been synthesized and investigated by various physico-analytical techniques. The spectral results suggested the tridentate nature of the Schiff base with NNO donor type. The prepared complexes exhibited distorted octahedral geometry. Moreover, molecular docking studies have been carried out against the SARS-CoV-2 spike receptor-binding domain (PDB ID: 6M0J) and SARS-CoV spike receptor-binding domain (PDB ID: 2AJF).

Keywords: Schiff Base, Ternary Complex, Spectral Characterization, Docking Studies, SARS Type.

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INTRODUCTION

Schiff base is providing a significant contribution in coordination chemistry due to ease in synthesis, stability and chelating behavior.[1–5] Moreover, these compounds exhibited a broad range of biological activities, including antioxidant, antimicrobial and anticancer properties. The effectiveness of such compounds increases when coordinated to several metal ions.[6-12] The C=N (azomethine) group nitrogen-bearing lone pair of electrons may be responsible for such biological activities. It was also reported that the ternary complexes of Schiff bases are useful in various analytical and biological chemistry.[13-15] Considering the versatile nature of such compounds, we have made an effort to report herewith the synthesis of such types of compounds with some transition metal ions.

Recently, the novel COVID-19 outbreak originated from animals (Bats, Pangolins, etc.) is causing a pandemic in the century and has affected most parts of the globe.[16,17] This outbreak also affected the stock market and consequently the global economy. As per reports, the 'S' (spike) protein of the virus may bind to ACE2 receptors present on various human cells including lung alveolar epithelial cells[18,19] and responsible for virus transmission. This pathogenic viral infection is mainly transmitted through respiratory droplets (coughs, sneezes and talks). No vaccine or effective drugs are yet available and we are struggling to find new compounds capable of contracting the virus. This encouraged us to perform the molecular docking studies against PDB ID: 6M0J and PDB ID: 2AJF.

EXPERIMENTAL

Material and Methods

The chemicals and reagents were obtained from Sigma Aldrich and used as such. The electronic and FTIR spectra of these compounds were recorded on Perkin-Elmer and Varian FTIR spectrophotometer, respectively. TGA was carried out by using the Netzch-429 thermo analyzer. CHN analysis was done by MLW-CHN microanalyzer. The molar conductance measurements in DMSO were done with a Toshniwal conductivity Bridge at room temperature. Also, ^{1}H-NMR spectral analysis in DMSO-d_6 was recorded on JEOL, GSX-400 model equipment.

Preparation of the Compounds

The Schiff base (HL1) was synthesized by condensing 2-hydrazinobenzimidazole and o-hydroxyacetophenone as reported.[10] The ethanolic solution of Schiff base (0.01 mol, 20 mL), 1,10-

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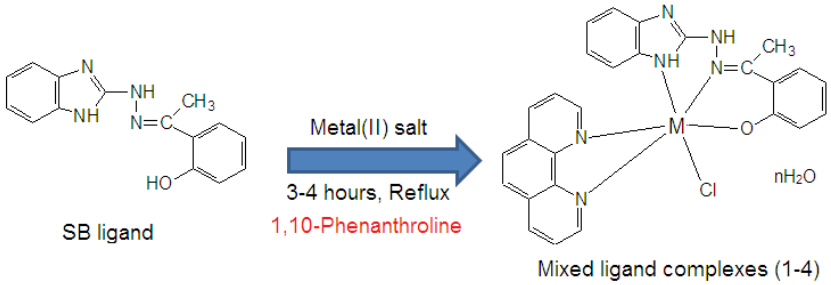
phenanthroline (0.01 mol, 20 mL) and metal salt (0.01 mol, 20 mL) in 1:1:1 molar ratio were refluxed for 3-4 hours at pH = 7-8. The resulting mixture was cooled, filtered, washed and dried. The preparation of these compounds was represented in Scheme-1. The optimized molecular structure of these reported metal complexes with atom numbering are shown in Fig.-1.



Scheme-1: Preparation of Mixed Ligand Complexes, M= Co(II), Cu(II), Ni(II) and Zn(II)

Ternary Complex 1, [CoL1L2Cl]H_2O
Yield 71%; Anal. Calc. (%): C, 58.11; H, 4.12; N, 15.06; M, 10.58, Found (%): C, 58.02; H, 3.97; N, 14.95; M, 10.52.

Ternary Complex 2, [NiL1L2Cl]H_2O
Yield 67%; Anal. Calc. (%): C, 58.17; H, 4.13; N, 15.08; M, 10.50, Found (%): C, 58.10; H, 4.02; N, 14.90; M, 10.38.

Ternary Complex 3, [CuL1L2Cl]2H_2O
Yield 68%; Anal. Calc. (%): C, 55.86; H, 4.31; N, 14.48; M, 10.94, Found (%): C, 55.75; H, 4.25; N, 14.40; M, 10.85.

Ternary Complex 4, [ZnL1L2Cl]H_2O
Yield 64%; Anal. Calc. (%): C, 57.49; H, 4.08; N, 14.90; M, 11.53, Found (%): C, 57.24; H, 3.96; N, 14.76; M, 11.42.

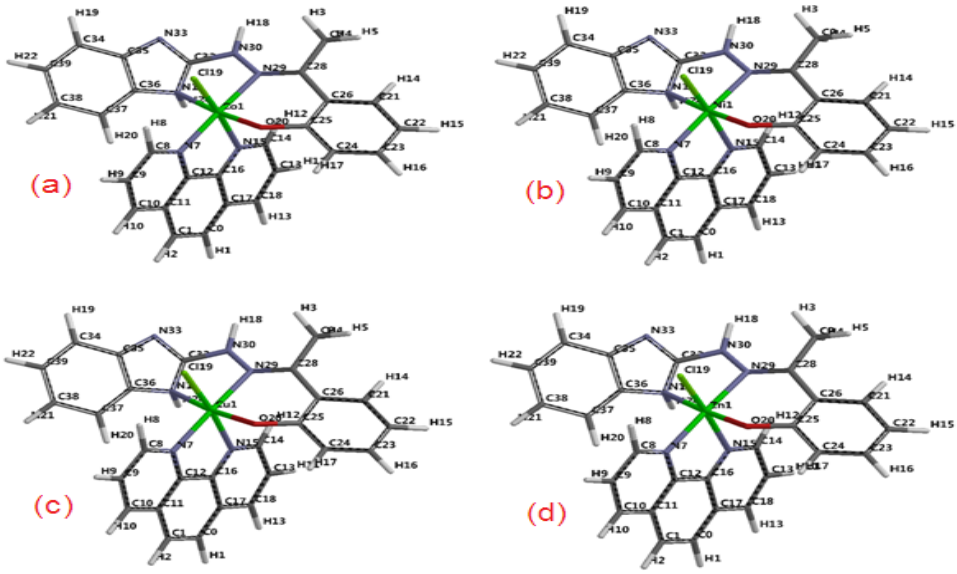


Fig.-1: The Optimized Molecular Structure with Atom Numbering, (a) Co-complex, (b) Ni-complex, (c) Cu-complex, (d) Zn-complex.

RESULTS AND DISCUSSION

IR Spectra
The co-ordination through deprotonated phenolic oxygen atom was confirmed from the disappearance of phenolic -OH stretching band. Moreover, it is further substantiated by hypsochormic shift of ν_{C-O} mode (phenolic) in the spectra of these complexes, which may be due to the partial double bond character assumed by C-O on co-ordination. The band due to

ν_{N-H} (exocyclic) remains unchanged in these compounds indicating non-involvement of imino nitrogen in coordination. On the other hand, the involvement of benzimidazole -NH group in co-ordination was suggested as the position of this band (occurring at ~3150 cm^{-1} for free ligand) shifted to a lower frequency region. Besides the above, band due to $\nu_{C=N}$ (azomethine) vibrations was also shifted for metal complexes implying its participation in coordination.[10] Also, a sharp band at ~1110 cm^{-1-1} for ν(C=N) of 1,10-phenanthroline was also observed for the ternary complexes.[20]

Electronic Spectra

The Co(II) complex exhibited two main bands at ~10,475 cm^{-1} (broad) for $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1) and at ~22,245 cm^{-1} (strong) for $^4T_{1g}(F) \rightarrow {}^4T_{1g}$ (P) (ν_3) transitions. Here, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) transition was not observed as it involves a large amount of energy due to two-electron transition ($t^5_{2g}\ e^2_g \rightarrow t^3_{2g}\ e^4_g$).[21] The μ_{eff} value of Co(II) complex was found to be 4.84 BM. The Ni(II) complex displayed a split band at ~ 8,745 cm^{-1} and ~ 10,610 cm^{-1} followed by two main bands at ~ 15,135 cm^{-1} and ~ 23,950 cm^{-1}. The former split bands may be assigned to $^3B_{1g} \rightarrow {}^3E_g$ and $^3B_{1g} \rightarrow {}^3B_{2g}$ transitions. However, the last two bands are attributed to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ (ν_2) and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ (ν_3) transitions, respectively. Also, the observed magnetic moment value (2.86 BM) corresponds to six coordinated octahedral Ni(II) species. The copper complex showed two bands at ~14,445 cm^{-1} and ~16,850 cm^{-1}, assigned to $^2B_{1g} \rightarrow {}^2B_{2g}$ (ν_2) and $^2B_{1g} \rightarrow {}^2E_g$ (ν_3) transitions, suggesting distorted octahedral geometry. The μ_{eff} value was found to be 1.78 B.M. as expected for hexa coordinated geometry.

Thermal Analysis

All these reported compounds lose water molecule(s) below ~110 ℃ indicating them to have lattice water (Table-1). The anhydrous complexes followed two-stage decompositions between 220℃ – 345℃ and 370℃ – 600℃. Further, the degradation of organic constituents continues until the formation of end product as stable metal oxide. The decomposition temperature for the possible fragmentation process has been incorporated in Table-1.

Table-1: Thermal Data for the Reported Compounds

Reported Compounds	Range of Water Loss (℃)	Water Loss (%)		The Residue (%)		Composition of Residue
		Found	Calc.	Found	Calc.	
[CoL1L2Cl] H_2O	50-100	3.21	3.29	13.41	13.45	CoO
[NiL1L2Cl] H_2O	60-110	3.17	3.23	13.29	13.37	NiO
[CuL1L2Cl] $2H_2O$	50-100	6.15	6.20	13.62	13.70	CuO
[ZnL1L2Cl] H_2O	55-110	3.12	3.19	14.32	14.37	ZnO

^{1}H NMR Spectra

The ^{1}H NMR spectrum of Zn(II) complex (Fig.-2) displayed a multiplet at δ 7.4-7.9 ppm for phenyl group protons. In comparison, the signals at δ 7.0 ppm (downfield shift) and δ 9.0 ppm are due to ring NH and exocyclic NH protons, respectively[10] indicated the participation of ring NH in coordination. Moreover, a signal at δ 2.6 ppm was also noticed due to $–CH_3$ group protons. Furthermore, the disappearance of the signal due to phenolic -OH proton confirmed its participation in co-ordination through deprotonation.

Molecular Docking Study

The molecular docking study[22] has been realized on four metal-complexes (called ligand) to evaluate and predict the biological activity as reported earlier[14]. The protein/enzyme receptors have been imported from the protein data bank (http://www.rcsb.org/:PDB): PDB ID: 6M0J[23] and PDB ID: 2AJF[24]. In docking simulation, CLC Drug Discovery Workbench utilizes MMFF94 (MMFF) force field when generating 3D structure on import. The different conformations were generated and protein-ligand interactions were scored.

Docking Evaluation against PDB ID: 6M0J

All these compounds were docked against the SARS-CoV-2 spike receptor-binding domain (PDB ID: 6M0J). The docking pose of the co-crystallized NAG interacting with the active site of amino acid residues is shown in Fig.-3a.

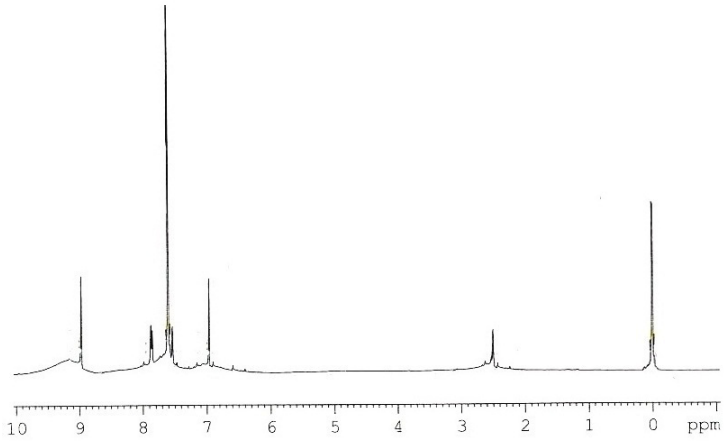


Fig.-2. ^{1}H NMR Spectrum of Zn(II) Complex

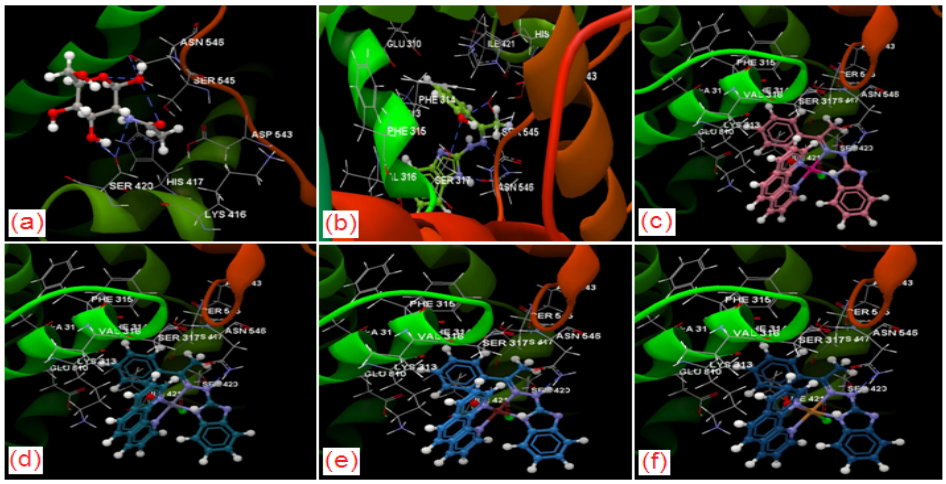


Fig.-3: Docking Pose of (a) NAG, (b) Ligand, (c) Co-complex, (d) Zn-complex, (e) Ni-complex, (f) Cu-complex

The co-crystallized NAG (N-acetyl-D-glucosamine) showed the occurrence of five hydrogen bonds, two with SER 420 (2.764 Å and 2.880 Å), and three with ASN 546 (3.338 Å, 2.348 Å and 2.262 Å). The co-crystallized NAG was taken to compare the results of these reported compounds. The docking score of the metal-complexes is greater than the ligand (docking score: -38.78; RMSD: 2.80Å) and the co-crystallized NAG (docking score: -32.39; RMSD: 0.20Å) (Table-2). The ligand showed the occurrence of four hydrogen bonds: one with SER 545 (2.906 Å), one with SER 317 (3.008 Å) and two with ASN 546 (2.762 Å and 3.135 Å). The Co-complex is the metal-complex with the best docking score (-42.82; RMSD: 0.01 Å) and displayed the occurrence of one hydrogen bond with ASN 546 (2.863 Å). With ASN546 amino acid, one hydrogen bond was realized by Zn-complex (2.828 Å), Ni-complex (2.814 Å) and Cu-complex (2.729 Å). Depending on the nature of the metal atom in the complexes, the docking score decreased in the order: Co-complex (-42.82) > Zn-complex (-42,65)> Ni-complex (-42.41) > Cu-complex (-42.31). The docking pose of these studied compounds interacting with the amino acid residues of the binding site of 6M0J is presented in Figure 3b-f. Moreover, it was also observed that all these investigated compounds were placed in the same binding site as the cocrystallized one and also have the same orientation (Fig.-4).

Table-2: The interactions between the Investigated Compounds Docked with 6M0J

Ligand	Score*	RMSD Å	Interactions	Hydrogen bond**	Bond length Å
Co-crystallized	-32.39	0.20	ASP 543, SER 545, ASN 546, HIS 417, LYS 416, SER 420	N sp^2 (N2) – O sp^3-SER 420 O sp^3 (O3) – O sp^3 -SER 420 O sp^2(O7) – N sp^2 -ASN 546 O sp^3 (O5) – N sp^2 - ASN 546 O sp^3 (O1) – O sp^3 - ASN 546	2.880 2.764 3.338 2.348 2.262

Ligand	-38.78	2.80	ASP 543, SER 545, ASN 546, HIS 417, SER 317, VAL 316, PHE 314, PHE 315, LYS 313, GLU 310, ILE 421, SER 420	O sp^3(O0) – O sp^3–SER 545 O sp^3 (O0) – O sp^3 – SER 317 N sp^2(N11) – O sp^2-ASN 546 N sp^2 (N9) – N sp^2 -ASN 546	2.906 3.008 2.762 3.135
Co-Complex	-42.82	0.01	ASP 543, SER 545, ASN 546, HIS 417, SER 317, VAL 316, PHE 314, PHE 315, ALA 311, LYS 313, GLU 310, ILE 421, SER 420	N sp^3 (N30) – N sp^2 -ASN 546	2.863
Zn-Complex	-42.65	0.01	ASP 543, SER 545, ASN 546, HIS 417, SER 317, VAL 316, PHE 314, PHE 315, ALA 311, LYS 313, GLU 310, ILE 421, SER 420	N sp^3 (N30) – N sp^2 -ASN 546	2.828
Ni-Complex	-42.41	0.01	ASP 543, SER 545, ASN 546, HIS 417, SER 317, VAL 316, PHE 314, PHE 315, ALA 311, LYS 313, GLU 310, ILE 421, SER 420	N sp^3 (N30) – N sp^2 -ASN 546	2.814
Cu-Complex	-42.31	0.37	ASP 543, SER 545, ASN 546, HIS 417, SER 317, VAL 316, PHE 314, PHE 315, ALA 311, LYS 313, GLU 310, ILE 421, SER 420	N sp^3 (N30) – N sp^2 -ASN 546	2.729

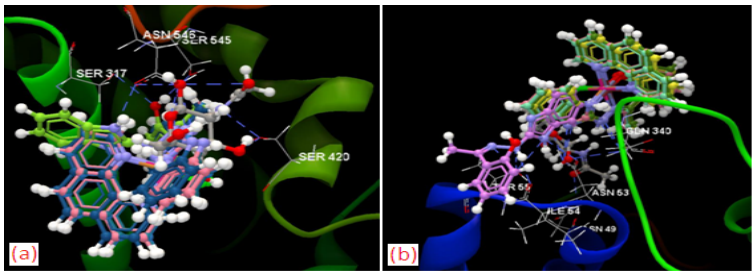


Fig.-4: The Docking Pose of these Investigated Compounds in the Binding Site of (a) 6M0J, (b) 2AJF.

Docking Evaluation against PDB ID: 2AJF

All the compounds were again docked on the crystal structure of the SARS-CoV spike receptor-binding domain (PDB ID: 2AJF). The co-crystallized NAG created hydrogen bonds with GLN 340 (3.375 Å), ASN 53 (2.383 Å) and ASN 49 (3.051Å). The docking score of the metal-complexes are greater than the co-crystallized (docking score: -24.97; RMSD: 2.20Å) and the ligand (docking score: -31.69; RMSD: 1.26Å) (Table-3). The ligand displayed the occurrence of five hydrogen bonds: one with ASN 53 (2.911Å), one with ILE 54 (2.854Å) and three with THR 55 (3.152 Å, 2.957 Å and 3.305 Å). The Ni-complex has the best docking score (-38.18; RMSD: 0.01) and showed the occurrence of two hydrogen bonds with GLN340 (2.893 Å) and ASN 53 (3.151 Å). With the same amino acids, GLN 340 and ASN 53, two hydrogen bonds realized by Co-complex (2.877 Å and 3.159 Å), Zn-complex (2.822 Å and 3.268 Å) and Cu-complex (2.862Å and 3.175 Å). The docking pose of these investigated compounds interacting with amino acid residues was shown in Figure 5a-f. Depending on the nature of the metal atom in the complexes, the docking score decreased in the order: Ni-complex (-38.18) > Co-complex (-38.11) > Zn-complex (-38.08) > Cu-complex (-37.91).

As per Lipinski's rule of five, the calculated parameters (Table-4) may predict whether a molecule possesses properties that might turn it into an active drug[26]. Moreover, several Lipinski violations allow evaluating the drug-likeness of a molecule. It was also observed that all these investigated compounds have two violations of all the parameters involved.

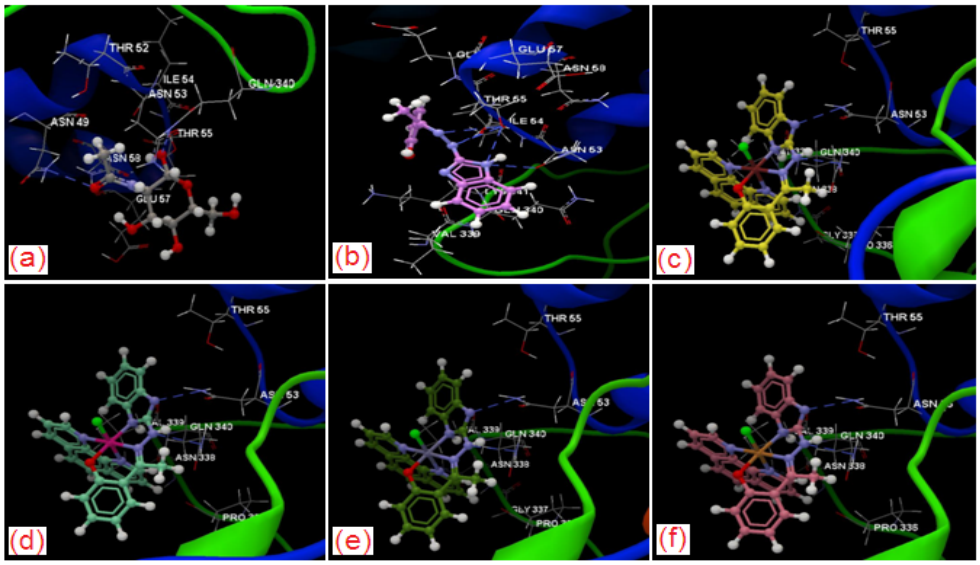


Fig.-5: Docking Pose of (a) Co-crystallized NAG, (b) Ligand, (c) Ni-complex, (d) Co-complex, (e) Zn-complex, (f) Cu-complex.

Table-3: The Interactions between the Investigated Compounds Docked with 2AJF

Ligand	Score*	RMSD Å	Interactions	Hydrogen Bond**	Bond Length Å
Co-crystallized	-24.97	2.20	GLU 57, ASN 58, ASN 49, THR 55, GLN 340, ASN 53, ILE 54, THR 52	O sp^3(O3) – N sp^2 -GLN340 O sp^2 (O5) – N sp^2 -ASN 53 O sp^2 (O7) – N sp^2 -ASN 49	3.375 2.383 3.051
Ligand	-31.60	1.26	GLU 56, GLU 57, ASN 58, THR 55, ASN 53, ILE 54, VAL 339, GLN 340, LYS 341	N sp^2 (N11) – O sp^2 – ASN 53 N sp^2 (N11) – O sp^3 – THR 55 N sp^3 (N10) – O sp^3 – THR 55 N sp^2 (N10) – O sp^2 – ILE 54 N sp^2 (N9) – O sp^3 – THR 55	2.911 3.152 2.957 2.854 3.305
Ni-Complex	-38.18	0.01	THR 55, VAL 339, ASN 338, GLN 340, GLY 337, ASN 53, PRO 336	N sp^3 (N30) – N sp^2 -GLN 340 N sp^3 (N1) – N sp^2- ASN 53	2.893 3.151
Co-Complex	-38.11	0.02	THR 55, VAL 339, ASN 338, GLN 340, ASN 53, PRO 336	N sp^3 (N30) – N sp^2 -GLN 340 N sp^3 (N1) – N sp^2- ASN 53	2.877 3.175
Zn-Complex	-38.08	0.03	THR 55, VAL 339, ASN 338, GLN 340, GLY 337, ASN 53, PRO 336	N sp^3 (N30) – N sp^2 -GLN 340 N sp^3 (N1) – N sp^2- ASN 53	2.882 3.243
Cu-Complex	-37.91	0.01	THR 55, VAL 339, ASN 338, GLN 340, ASN 53, PRO 336	N sp^3 (N30) – N sp^2 -GLN 340 N sp^3 (N1) – N sp^2- ASN 53	2.862 3.175

*The docking score (PLANTS$_{PLP}$ score) is a function as described by Korb *et al.*[25]

Table-4: Calculated Parameters of the Compounds

Compounds	Atoms	Weight [Daltons]	Flexible bonds	Lipinski violations	Hydrogen donors	Hydrogen acceptors	Log P
Co-crystallized*	30	221.21	2	0	5	7	-2.54
Co-crystallized**	30	221.21	2	0	5	7	-2.54
Ligand	34	266.30	3	0	3	5	3.20
Co-Complex	57	539.88	0	2	2	7	7.26
Ni-Complex	57	539.64	0	2	2	7	7.26

Zn-Complex	57	546.36	0	2	2	7	7.26
Cu-Complex	57	544.49	0	2	2	7	7.26

* PDB ID: 6M0J; ** PDB ID: 2AJF

CONCLUSION

A series of ternary metal complexes were synthesized and investigated. As per the study, all the synthesized metal complexes are neutral and contain lattice water molecules. The spectral study revealed octahedral geometry for these metal complexes in which the primary ligand behaves as tridentate chelating with the central metal ion. Moreover, molecular docking studies have been performed against PDB ID: 6M0J and PDB ID: 2AJF. It was observed that all these investigated compounds have two violations of all the parameters involved in Lipinski's rule of five. The study will be helpful for the researchers working in this field.

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