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Synthesis, Characterization and Docking Studies of a Schiff Base Ligand and Some Metal Complexes

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ABSTRACT
Objective: To synthesize a Schiff base ligand and some metal complexes, perform characterization studies and elucidate the action mechanisms of the synthesized compounds with the Schrödinger Suite computer aided molecular modeling program.
Methods: A Schiff base ligand has been synthesized by the reaction of a salicylaldehyde derivate with an aminophenol. With using this ligand, metal complexes were prepared from Co(II), Ni(II), Cu(II) and Zn(II) acetate salts. The structures of the synthesized compounds were confirmed by different spectroscopic and microscopic techniques such as Elemental Analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis, XRD, SEM and TGA. In order to elucidate the mechanism of action of the synthesized compounds, some descriptive molecular properties were calculated using the Schrödinger Suite computer aided molecular modeling program.
Results: Within the scope of the study, a ligand and its complexes were synthesized. The structures of compounds were elucidated and molecular docking studies showed that Zn(II) complex had the highest scores obtained.
Conclusion: Structural characterization showed that ligand at the metal complexes act as bidentate chelates by binding to the metal ion from the imine nitrogen and phenolic oxygen. The mechanism of action of the synthesized compounds and the active site where the coupling will take place were determined, and the interactions of possible drug molecule candidates synthesized with the target receptor site were calculated.

Keywords: Ligand, Metal Complex, Molecular Docking, Schiff Base, Spectroscopic Characterization

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INTRODUCTION

The chemistry of coordination compounds is well known and widely studied because of many applications in different areas. This is due to the chelates they make with metal ions. An organic compound can be converted into inorganic compound as a complex with a transition metal. The applications of the metal complexes in qualitative and quantitative chemical analysis have also been the issue of many studies.[1, 2] Schiff bases are acknowledged condensation products in organic and inorganic chemistry.[3, 4]

These compounds are the class of ligands that are used frequently because of their useful chelates due to their easy synthesis, structural diversity, electronic control mechanisms, and ability to coordinate with transition metals. These compounds having several recourses in many fields such as organic chemistry, inorganic chemistry and also as pharmaceutical targets[5, 6] and they include a variety of therapeutically powerful applications in medicinal chemistry.[7] These ligands were synthesized from the condensation of an amino group with a carbonyl compound. Generally, nitrogen, oxygen and sulphur donor atoms are involved in the coordination of metals in the active sites of numerous metallo-biomolecules. In the literature, it has been reported that the binding of the drug to a metallo element increases its activity and in some case the complex has more curative properties than the parent drug.[8, 9] In addition to that, they used for purposes such as catalytic and enzymatic reactions, electronics, polymer industry, luminescence materials, magnetism, and molecular design.[10, 11]

In this study, the synthesis of a ligand and its complexes with Co(II), Ni(II), Cu(II) and Zn(II) acetate salts were performed and then the structures of the synthesized compounds characterized by elemental analysis, magnetic susceptibility, IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis, XRD, SEM, TGA methods. Molecular docking studies showed that the activity of the Zn (II) complex was higher.

METHODS

Experimental Materials and Instruments

o-Aminophenol (99%, Sigma-Aldrich), cobalt(II) acetate tetrahydrate (99%, Merck), 5-fluorosalicylaldehyde (97%, Sigma-Aldrich), nickel(II) acetate tetrahydrate (99.9%, Sigma-Aldrich), copper(II) acetate monohydrate (99%, Merck), zinc(II) acetate dihydrate (99.5%, Merck), *p*-toluenesulfonic acid (98%, Merck) and acetone, ethanol, methanol, diethyl ether, dimetilformamide, dimethyl sulfoxide were used as solvents at analytical reagent grade and provided from Merck Company.

Infrared spectra was recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrophotometer. The NMR spectra of compounds were recorded at room temperature using a Bruker DPX-400 spectrophotometer. Melting points were determined with a Buchi B-540 digital apparatus. The UV–Vis spectra of the compounds were taken a Shimadzu 1240 model UV-Vis spectrophotometer. The elemental analyses for C, H and N were obtained from the LECO-932 CHNSO model elemental analyzer. The X-ray diffraction data of ligand was recorded using a Panalytical Empyrean diffractometer with a scan rate of 2 min^{-1} in the 2θ range of 10–80˚. Morphological study of ligand (SEM with EDAX) was carried out using the Scanning Electron Microscope Fei Quanta FEG 450 instrument. Schrödinger Suite computer-aided molecular modeling program was used to elucidate the action mechanisms of the synthesized compounds.

Synthesis of LH Ligand

o-Aminophenol (1.09 g, 10 mmol) and (0.01 g) *p*-toluene sulphonic acid were dissolved in 20 mL absolute ethyl alcohol and slowly dropped onto the solution of 5-fluorosalicylaldehyde (1.40 g, 10 mmol) in 20 mL absolute ethyl alcohol. This solution was reflux at 60 °C for 3 hours. The pomegranate flower color product obtained as a result of the reaction was filtered off, washed several times with hot distilled water and diethyl ether, recrystallized from ethanol and dried at room temperature.[12, 13] The synthesis of Schiff base ligand is shown in Figure 1.

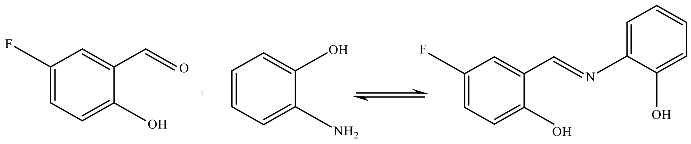

Figure 1. Synthesis of (E)-2-(((2-hydroxyphenyl)imino)methyl)-4-fluorophenol

Synthesis of Metal Complexes

The synthesized ligand (0.46 g, 1.00 mmol) was dissolved in 10 mL absolute ethyl alcohol and released into a 100 mL flask in the parallel synthesis device, and metal acetates [cobalt(II) acetatetrahydrate (0.125 g, 0.50 mmol), nickel(II) acetatetrahydrate (0.124 g, 0.50 mmol), copper(II) acetate monohydrate (0.10 g, 0.50 mmol), zinc(II) acetate dihydrate (0.110 g, 0.50 mmol)] were mixed dropwise with a dropping funnel. The reaction mixture was refluxed for 2-4 hours. After the synthesized products were rested, they were washed with hot pure water, ethyl alcohol and diethyl ether and dried under vacuum. [12, 13] The synthesis of Schiff base complexes is shown in Figure 2.

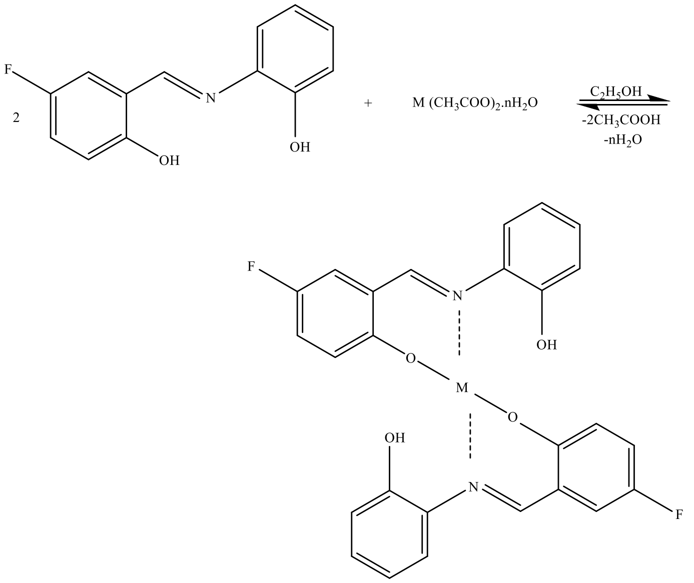

Figure 2. Synthesis of metal complexes of LH Ligand. [M: Co(II), Ni(II), Cu(II), Zn(II)]

RESULTS AND DISCUSSION

Structural Characterization

The stoichiometric ratio of ligand with Co^{+2}, Ni^{+2}, Cu^{+2}, Zn^{+2} structural characterization were investigated by various instrumental analysis methods. As can be seen in Table 1, the metal: ligand ratio is 1:2 in the elemental analysis of the complexes of ligand. [14, 15] Some analytical and physical data of the synthesized compounds were given in Table 1.

Table 1. Analytical and Physical Data of Ligand and Metal Complexes

Formula	W (g/mol)	Colour	m.p (°C)	μ_{eff}	Yield (%)	Elemental Analysis, % Calculated (Found)		
						C	H	N
$C_{13}H_{10}NO_2F$	231.226	Pomegranate Flower	118-120	-	89.00	67.53 (67.29)	4.36 (4.29)	6.06 (6.06)
$CoC_{26}H_{18}N_2O_4F_2$	519.369	Dark Brown	> 300	4.19	56.00	60.13 (60.02)	3.49 (3.36)	5.39 (5.21)
$NiC_{26}H_{18}N_2O_4F_2$	519.129	Light Green	> 300	2.62	48.00	60.16 (60.07)	3.50 (3.27)	5.40 (5.36)
$CuC_{26}H_{18}N_2O_4F_2$	523.982	Dark Green	> 300	1.86	62.00	59.60 (59.86)	3.46 (3.48)	5.35 (5.19)
$ZnC_{26}H_{18}N_2O_4F_2$	525.826	Light Yellow	> 300	Dia.	66.00	59.39 (59.27)	3.45 (3.37)	5.33 (5.28)

IR spectra of the LH ligand and Co(II), Ni(II), Cu(II), Zn(II) complexes taken in KBr were examined. The stretching vibration of the phenolic O-H group was seen as a flat peak at 3442 cm^{-1} at LH ligand IR spectrum (Figure 3). A sharp peak was observed at 1632 cm^{-1}, which indicates the presence of imine group in the structure. The aromatic C-H weak peak was at 3045 cm^{-1}, the aliphatic C-H stretching vibration was at 2965-2920 cm^{-1}, the C=C stretching vibration was at 1500 cm^{-1}-1440 cm^{-1} and the phenolic C-O stretching vibration was at 1282 cm^{-1} at the spectrum. In addition, the disappearance of the peak at 1656 cm^{-1} belonging to –C=O stretching vibration of 5-fluorosalicylaldehyde, which was the starting material and the formation of a peak belonging to –C=N stretching vibration instead of this peak, also was supported the completion of the reaction.[16, 17]

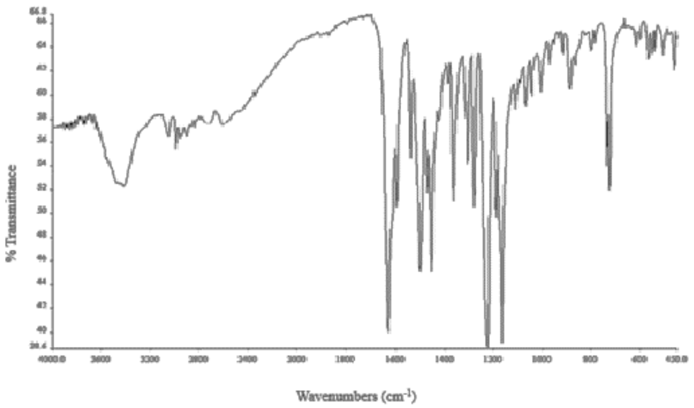

Figure 3. IR Spectrum of LH Ligand

Some changes were observed in the stress vibration of the –C=N group and the bending vibration of the phenolic O-H group at IR spectra metal complexes. The characteristic -C=N stretch vibration, which shows the presence of imine in the ligand and observed at 1632 cm^{-1}, shifted to the low frequency region of 1608-1617 cm^{-1}. This shift can be explained by the coordination of the nitrogen atom in the azomethine group with the metal during the complex formation. In other words, the nitrogen atom is in coordination by giving its unshared electrons to the metal ion.

It also shows that in the shift in the O-H peak in the ligand, the phenolic O-H is in coordination with the metal ion by throwing its proton. In addition, complex structures, which are observed at 1282 cm^{-1} and are characteristic band for phenolic C-O stress vibration, showed slippage. This shift supports that the protonated phenolic oxygen enters into coordination with metal ions during complex formation. Like in the ligand, the O-H stretch vibration in the complexes is in the form of a flat peak in the region of 3400-3450 cm^{-1}.[16, 17]

A proton singlet at 14.25 ppm was observed in the ^{1}H-NMR spectrum of LH ligand and belongs to the proton of the phenolic OH group. The chemical shift observed as a single proton singlet at 9.04 ppm in the spectrum of H proton of the –CH=N group in the structure. Protons belongs to the aromatic ring were observed as multiplets in the range of 6.89-7.48 ppm. Considering the integral ratios, the proton numbers were in harmony with the predicted structure. In addition, the chemical shift of the OH group proton was observed at 9.98 ppm.[18, 19]

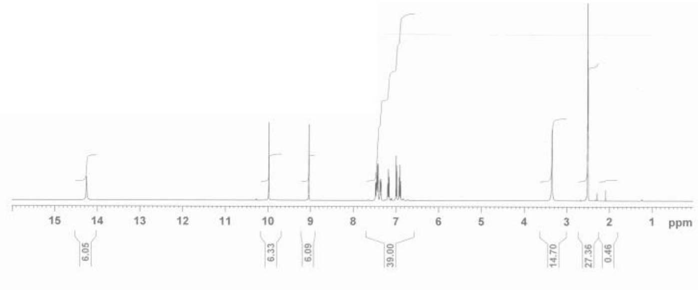

Figure 4. ^{1}H-NMR Spectrum of LH Ligand

The ^{13}C-NMR spectrum of LH ligand (Figure 5) taken in the mixture of $CDCl_3$ and DMSO-d_6 was examined the signal of the carbon atom in the imine bond was resonated at 162.03 ppm and chemical shift of the C-OH carbon was observed at 159.80 ppm. Chemical shift of C-N group carbon was observed at 134.85 ppm and the peaks for the aromatic ring carbons were observed in the range of 119.59-132.95 ppm.[18, 20]

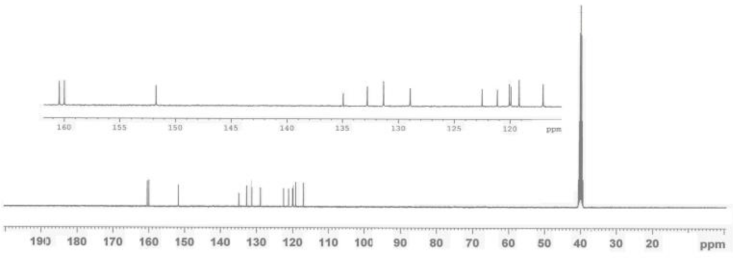

Figure 5. ^{13}C-NMR Spectrum of LH Ligand

The geometries of metal complexes were determined from the magnetic susceptibility measurements of the LH ligand of Co^{+2}, Ni^{+2}, Cu^{+2} and Zn^{+2} complexes. The measured magnetic susceptibility values show that the Co^{+2}, Ni^{+2} and Cu^{+2} complexes were paramagnetic and the Zn^{+2} complex was diamagnetic.[21, 22] The measured μ_{eff} value for the Co^{+2} complex was 4.09 B.M. and corresponds to 3 electrons. This value shows us that the Co (II) complex with the d^7 configuration was in tetrahedral geometry. The μ_{eff} value measured for the Ni^{+2} complex was 2.71 B.M. and corresponds to 2 electrons. This value shows us that the Ni (II) complex was also in tetrahedral geometry. For the Cu^{+2} complex, the μ_{eff} value corresponds to 1.70 B.M. and corresponds to 1 electron. However, it is not possible to determine whether the Cu (II) complex was tetrahedral or square. The diamagnetic Zn (II) complex prefers the tetrahedral structure because it has d^{10} configuration.

In the UV-Vis spectrum of the LH ligand (Figure 6), a band is observed at 290 nm due to the $\pi \rightarrow \pi^*$ electronic transition, while the $n \rightarrow \pi^*$ transition is observed as a broad peak at 360 nm. In the complexes, this band, which was observed at 290 nm and belongs to the $\pi \rightarrow \pi^*$ electronic transition, observed at approximately the same location. The band originating from the $n \rightarrow \pi^*$ transition of the unpaired electrons of the nitrogen atoms of the imine group has shifted to the wavelength of 380-420 nm in the complexes. This supports the coordination between the imine group and the metal ions.[23]

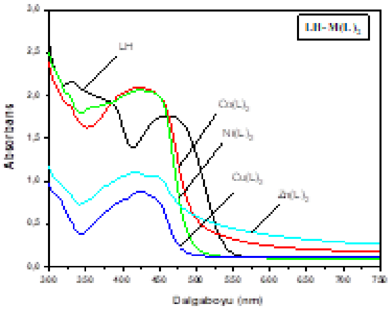

Figure 6. UV-Vis. Spectrum of LH Ligand

XRD patterns of the Schiff base ligand was obtained at room temperature with using CuKα1 λ=1.5405 Å in the range 2θ=10–100°, operated at 45kV and 40 mA. As seen in Figure 7, Schiff base ligand exhibited sharp crystalline peaks. The obtained diffractogram was put out the ligand was acknowledged by two important characteristic peaks appearing at 2θ=19.28˚and 22.54˚, due to imine group. The XRD pattern of ligand was showed a semicrystalline nature.[24, 25]

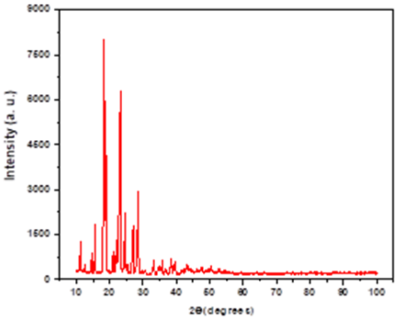

Figure 7. XRD Pattern of LH Ligand

The surface morphology of the ligand was investigated using SEM analysis and the ligand had a compact and dense surface morphology (Figure 8). Also, ligand had nanorod structure and localized clusters on the surface morphology.[25 ,26]

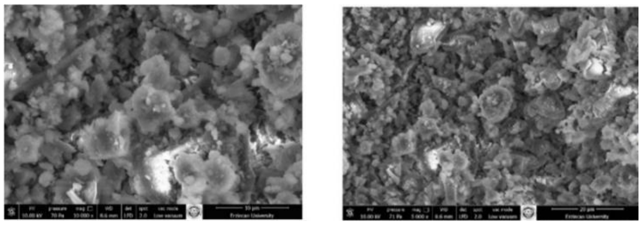

Figure 8. SEM of LH Ligand

Schrödinger Suite computer-aided molecular modeling program was used to elucidate the mechanism of action of the synthesized compounds. The active site where the docking will occur was determined and the interactions of possible drug molecule candidates synthesized by the Structure Based Drug Design method with the target receptor site were calculated using the Glide module in the Schrödinger program package. The ZnL_2-CA I (PDB ID: 6F3B) interaction diagram and ZnL_2-CA II (PDB ID: 6H34) interaction diagram obtained as a result of molecular docking were given at Figure 9 and Figure 10.[27]

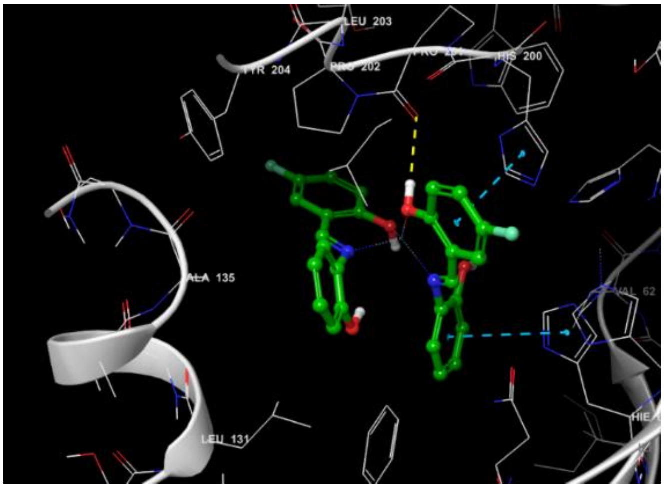

Figure 9. Interaction Diagram of ZnL_2-CA I (PDB ID: 6F3B)
(Obtained as a Result of Molecular Docking of Schiff Base Ligand with Metal Complexes)

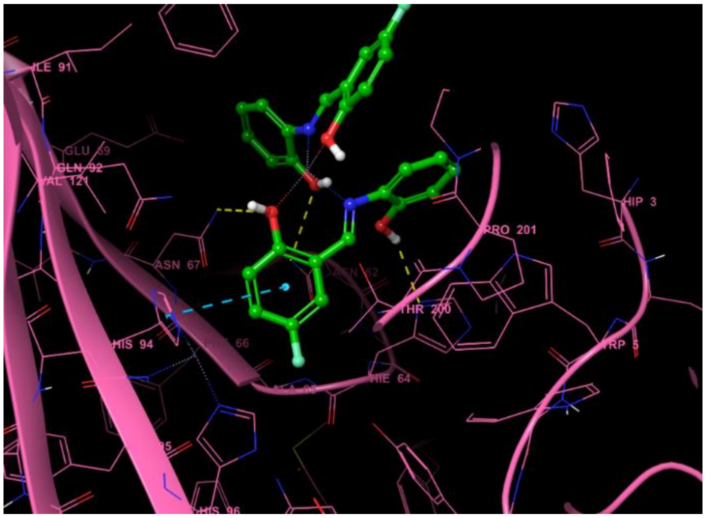

Figure 10. Interaction Diagram of ZnL_2-CA II (PDB ID: 6H34)
(Obtained as a Result of Molecular Docking of Schiff Base Ligand with Metal Complexes)

CONCLUSION

In conclusion, Schiff base ligand, (E)-2-(((2-hydroxyphenyl)imino)methyl)4-fluorophenol, was synthesized from the reaction of 5-fluorosalicylaldehyde and *o*-aminophenol. The metal complexes were prepared from the reaction with metal acetates. The structures of Schiff base ligand and metal complexes obtained were elucidated by using elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR, UV-Vis, XRD, SEM, magnetic susceptibility and thermogravimetric analysis techniques. It was determined that the metal/ligand ratio was 1:2 in all complexes and that Schiff base ligand was bonded to the metal atom with the nitrogen atom in the imine and the phenolic oxygen atom. As a result of molecular docking of CA I and CA II enzymes with the synthesized Schiff base ligands and complexes, it was determined that the Zn (II) complex had the highest scores obtained.

Ethics Committee Approval: Ethical approval and informed consent are not required in our study as no research was conducted on human or animal specimens.
Peer-review: Externally peer-reviewed.
Author Contributions: F.O. and S.T.Y. contributed equally. Concept, Design, Supervision, Resources, Data Collection, Literature Search, Synthesis, Characterization, Writing Manuscript was carried out by both authors. All authors have read and agree to the published version of the manuscript.
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