(E)-4-(5-(2- (4-Hydroxybenzy Lidene) Hydrazine)-1,3,4-Oxadiazol-2-Yi) Benzene-1,2,3-Triol and Its Complexes: Synthesis, Characterization, Quantum Chemical Calculations and Biological Activity

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Abstract
This manuscript reports the synthesis of (E)-4-(5-(2-(2,4-hydroxy benzylidene) hy brazenly)-1,3,4-oxadiazol-2-yl) benzene-1,2,3-triol and its complexes which are novel compounds. All prepared compounds were characterized by spectra of H1-NMR, Mass spectra, Fourier transform infrared (FTIR), as well as magnetic susceptibility. The magnetic studies suggest an tetrahedral and square planer geometry of the complexes, From results it was suggested square plainer geometry for Ni (II) complex and tetrahedral geometry for Fe (III) and Cr (III) complexes. HOMO-LUMO molecular orbitals analysis some quantum chemical parameters of the ligand derived from frontier molecular orbitals were studied. The ligand and its complexes have shown moderate to good activity as antibacterial against gram-negative bacteria Serratia and Pseudomonas

Keywords: oxadiazol, quantum chemical parameters, antibacterial, Frontier molecular orbitals.

1. Introduction

Bacterial resistance increasing of known antibiotics has been causing with concern in the population, since their therapeutic possibilities have been diminishing. The main cause for the development of bacterial resistance due to the indiscriminate use of antibiotics. The growth of bacterial resistance has caused the mortality of an expressive number of people worldwide.Even the main commercial antimicrobial compounds (e.g., ampicillin, posaconazole, ciprofloxacin) may have limited action, nowadays, against strains of resistant microorganisms [1-4]. . This has led to intensified research involving the synthesis and evaluation of heterocyclic derivatives with antimicrobial properties, such as 1,3,4-oxadiazoles. Among them the derivatives of oxadiazoles have been playing an important role in the medicinal chemistry [2]. The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial [3, 4], anti HIV (Human Immunodeficiency Virus) [5], antitubercular [6], antimalarial [7], anti-inflammatory [8, 9], anticonvulsant [10], and antitumor [11]. The choice of 1,3,4-oxadiazole is due to its multiapplicability in the field of medicine [12]. In the present study, new 1,3,4-oxadiazoles derivative have been synthesized and characterized by different spectral studies and quantum chemical calculations. All the new compounds were screened for their antibacterial studies.

2. 2.Materials and Methods

All the chemicals and solvents used were of chemically pure grade, and commercially available. All metal salts were used as chloride.

2.1. Physical measurement

The melting point or the decomposition temperature of all the prepared ligand and metal complexes were observed in an electro thermal melting point apparatus model (Melting SMP31). The FTIR spectra in the rang (250-4000) cm^{-1} were recorded as KBr disc using a Shimadzu FTIR spectrophotometer (Model: IR- affinity, Shimadzu). Nuclear Magnetic Resonance Spectra were obtained using Burker DXR System AL500(500 MHz). Mass Spectra were obtained using (Network Mass Selective Detector5973). purity of the ligand and metal complexes was tested by Thin Layer Chromatography (TLC).

2.2. Steps preparation of the Ligand

New (E)-4-(5-(2-(2,4-hydroxy benzylidene) hy brazenly)-1,3,4-oxadiazol-2-yl) benzene-1,2, 3-triol (Scheme 1) was prepared as follows [13]:

2.2.1. Preparation of 2,3,4-trihydroxybenzohydrazide (A)

A mixture of methyl 3,4,5-trihydroxybenzoate (18.4ml, 0.1mol) and hydrazine hydrate (10ml,

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0.2mol) was dissolved in (100 ml) ethanol were refluxed for 8 hours. The mixture (A) was evaporated to half, cooled, filtered and re-crystallized in methanol [7], the solid (A) was white, melting point 156 ˚C, yield 87%.

2.2.2. Preparation of 4-(5-mercpto-1,3,4-oxadiazole-2yl) benzene-1,2,3-triol (B)

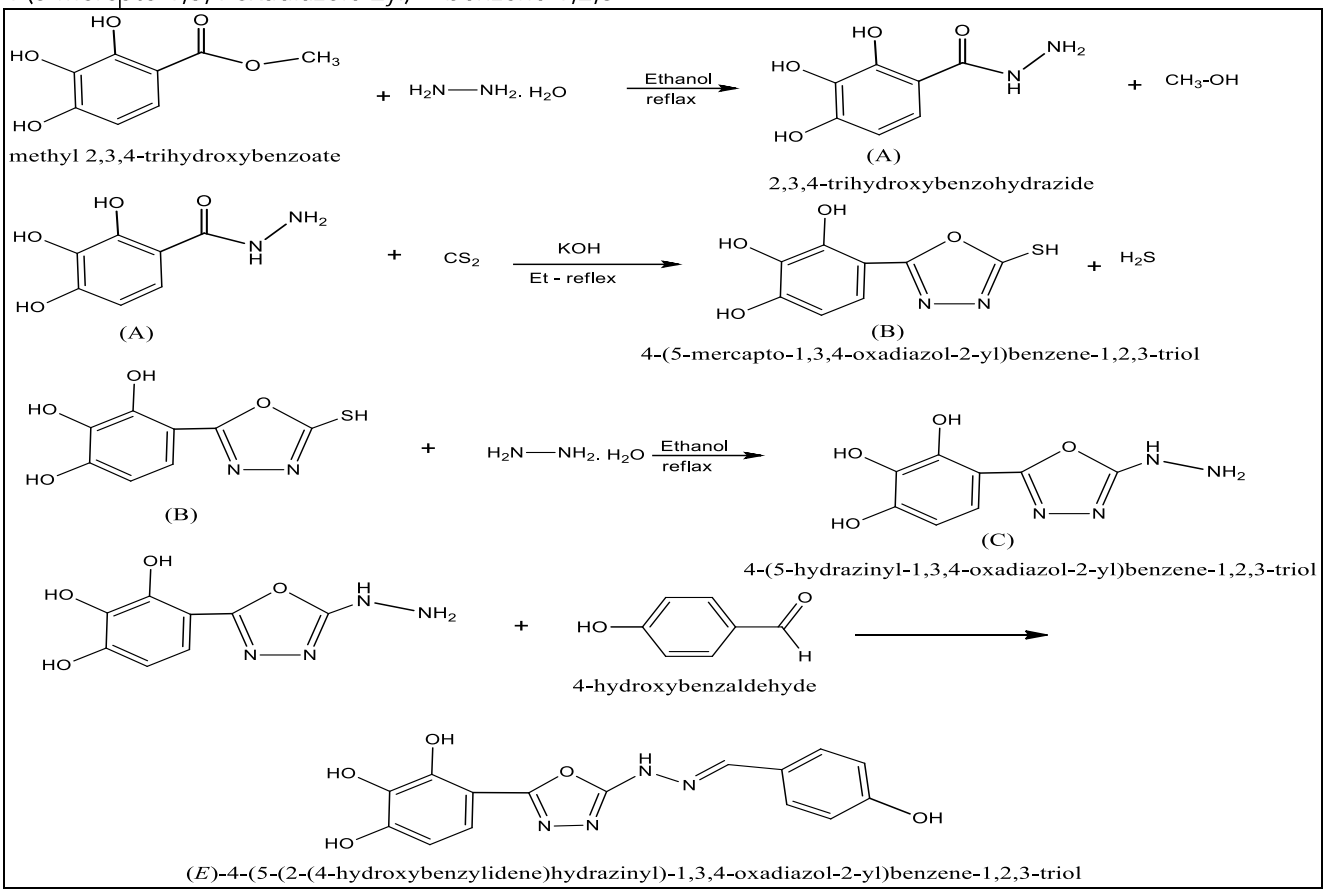
2,3,4-trihydroxybenzohydrazide (A) (18.4gm, 0.1mol), potassium hydroxide (5.6gm, 0.1mol) and carbon disulfide (6ml 0.1mol) were refluxed in (100 ml) ethanol. The solvent was evaporated and acidified with HCl (25%) then the precipitated was filtered and the result solid was recrystallized from ethanol absolute [8]. The solid (B) was white, melting point 227 ˚C, yield 84%.

2.2.3. Preparation of 4-(5- hydrazine -1,3,4-oxadiazol-2-yl) benzene-1,2,3-triol (C)

4-(5-mercpto-1,3,4-oxadiazole-2yl) benzene-1,2,3-triol (B) (4gm) (6.33gm ,0.028 mol) and hydrazine hydrate (1.8ml ,0.057 mol) in ethanol as solvent (50 ml) were refluxed for 20 hours. The mixture was concentration and then cooled [9]. white precipitate (C) was filtered and recrystallized from ethanol. Melting point 226 °C, yield 66.5%.

2.2.4. Preparation of (E)-4-(5-(2-(2,4-hydroxy benzylidene) hy drazinyl)-1,3,4-oxadiazol-2-yl) benzene-1,2, 3-triol (ligand)

The ligand was synthesized by condensation of 4-(5-hydrazinyl -1,3,4-oxadiazol-2-yl) benzene-1,2,3-triol (C) and 2,4-dihydroxybenzaldehyde (2.52gm ,0.01mol) (1.52ml, 0.01mol) in ethanol (30 ml). Then the mixture refluxed for 4 hours. The ligand was precipitated, filtered and recrystallized from ethanol to get yellow ligand, melting point 289 °C, yield 57%.



Scheme1. Steps preparation of the Ligand

2.3 Preparation of complexes

The metal complexes were obtained by reflex (1 mmol) of transition metal chloride (1mmol) Cr (III), Fe(III)and Ni(II) in 50 ml ethanol with the ligand (1mmol, 0.2 gm) for 2 hrs. The resultant solids which separated were filtered, washed with ethanol and dried in air.

3. Result and Discussion

3.1. FT-IR spectra

FT-IR spectroscopy is one of the most commonly used tools for the detection of functional groups in pure compounds and mixtures. FT-IR of the synthesized ligand and its complexes were carried out KBr disc to ligand and CsI for complexes. The free ligand exhibited six major bands at (3346) cm^{-1}, (3132) cm^{-1} (1613) cm^{-1},(1573) cm^{-1},(1380-1124) cm^{-1},[1]which are attributable to(υ oH), (υ NH), (υ C=N) imine, (υ C=N) oxa,(υ C-S-C) , (υ C-O-C) sym, (υ C-O-C) asy and structure movement bands respectively, as shown below (table1). New bands were formed attributed to the coordinated (M-N), (M-O) and (M-Cl) bonds and appeared at the region (507) cm^{-1}, (437) cm^{-1} and (304) cm^{-1} respectively. This indicates that the coordinate occurred through the (N), (O) and (Cl) atoms [14-17] (Figure.1) .

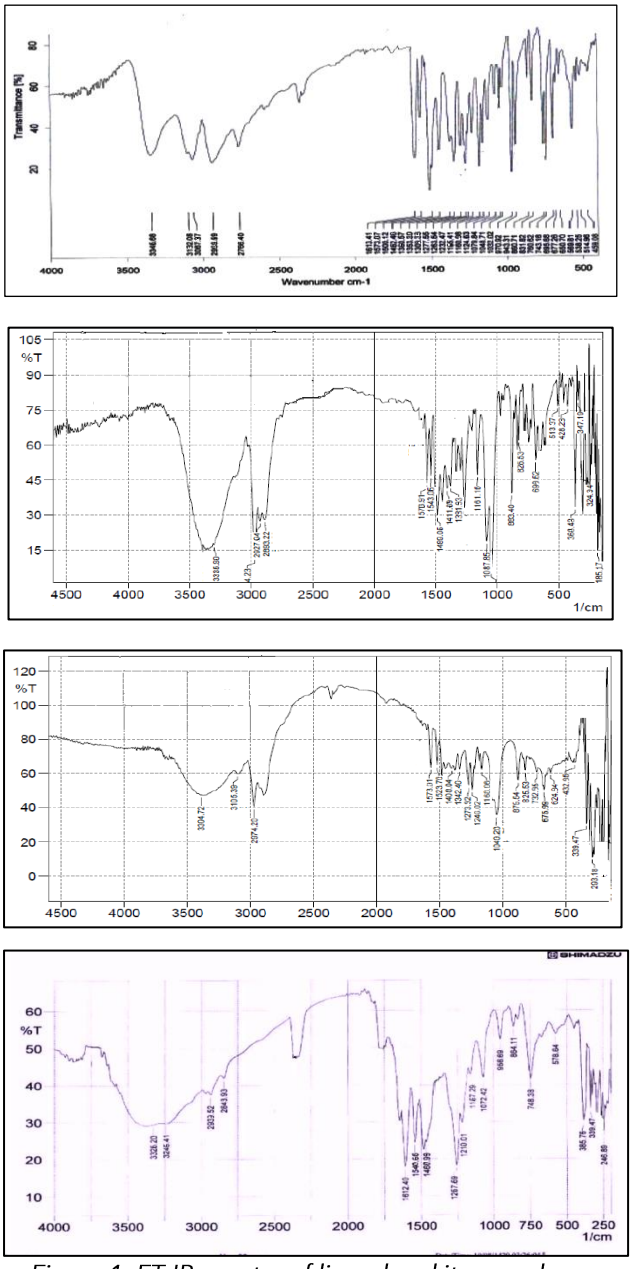


Figure 1. FT-IR spectra of ligand and its complexes

3.2. Nuclear Magnetic Resonance

The ^{1}H-NMR spectra of ligand exhibit a 9.59 ppm (3H,S, OH protons), 7.57-7.88 PPM (6H,m,armatic protons) ,6.79 PPM(1H,m, NH protons), 8.08 PPM(1H,m, =CH protons), 2.5(s, DMSO). The proton NMR of the ligand shown in figure (1). (^{1}H-NMR(DMSO-d^{6}) spectral information was given extra support for the proposition of the structure .

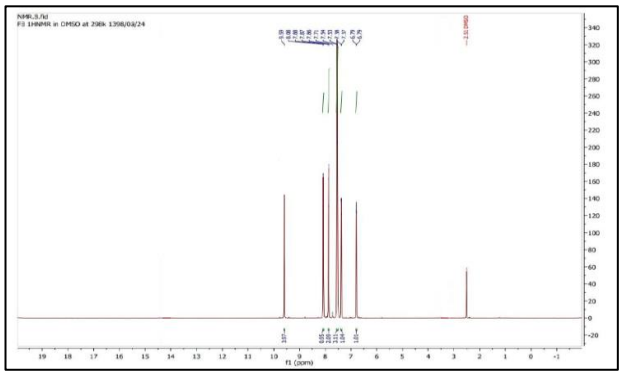


Figure 2. 1H-NMR spectra of the ligand

3.3. Mass spectra

The mass spectrum of the ligand exhibits a molecular ion peak [M]+.at 328 m/z, the ligand spectra shows fragments at (43 ,57, 83, 97, 109, 125, 152, 236,264) m/z as shown in figure (3).

The mass spectrum of the complex [Ni(L)Cl2] shows a molecular ion peak [M]+. (458) m/z which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at (423,388) due to [Ni(L)Cl] + and [Ni(L)] + respectively(Figure (4).).

The mass spectrum of the complex [Cr(L)Cl3] shows a molecular ion peak [M]+. (487) m/z which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at (452,417,382) due to [Cr(L)Cl2] + [Cr(L)Cl]+, and [Cr(L)]+ respectively. The mass spectrum of the complex [Fe(L)Cl3] shows a molecular ion peak [M]+. (489) m/z which is equivalent to molecular mass of the complex. This complex shows another a fragment ion peak with loss of chlorine atom at (454,419,384) due to [Fe(L)Cl2] + [Fe (L)Cl]+, and [Fe (L)]+ respectively The mass spectra of the complexes shown in figures (5) , (6).

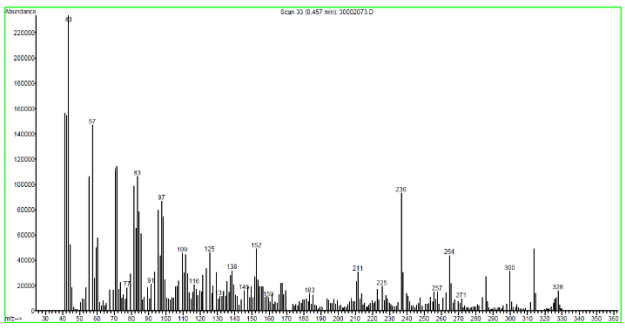


Figure 3. Mass spectra of The ligand

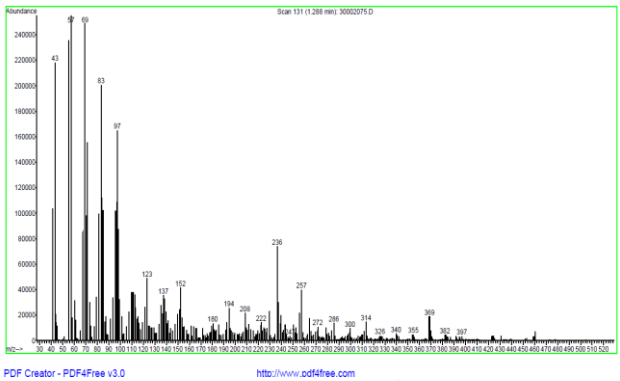


Figure 4. Mass spectra of [Ni(L)Cl$_2$]

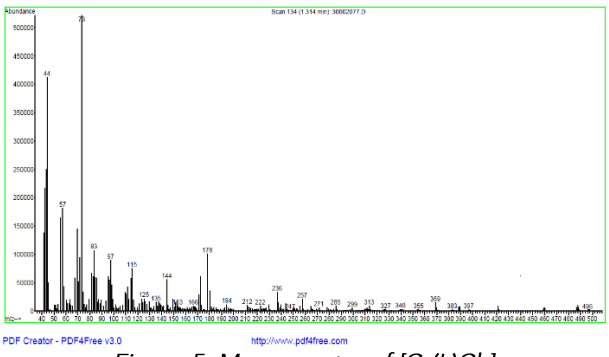


Figure 5. Mass spectra of [Cr(L)Cl$_3$]

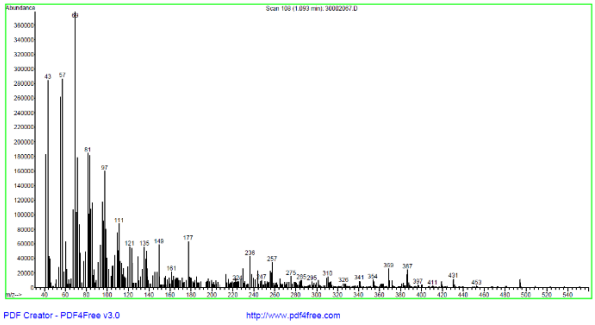


Figure 6. Mass spectra of [Fe(L)Cl₃]

3.4 Magnetic susceptibility

The magnetic susceptibility data (μeff B.M) for metal complexes is gives an information about the electronic state of central ion (transition metal ion) of the complexes. The (μeff B.M) value of Cr (III)complex 3.75BM. The (μeff B.M) value of Fe (III)complex 2.07BM This value is likely to be octahedral geometry. The (μeff B.M) value of Ni (II)complex 0.12BM This value is likely to be square planar geometry.

3.5. Quantum chemical calculations

Quantum chemical methods and molecular modeling techniques enable the definition of a large number of molecular quantities characterizing the reactivity, shape, and binding properties of a complete molecule as well as of molecular fragments and substituents The use of theoretical parameters presents two main advantages: firstly, the compounds and their various fragments and substituents can be directly characterized on the basis of their molecular structure only; and secondly, the proposed mechanism of action can be directly accounted for in terms of the chemical reactivity of the compounds under study . The calculated quantum chemical parameters, As illustrated in table (1)

Table 1. Quantum chemical Parameter of ligand		
Quantum Parameter	Equation	Values with (ev)
ELUMO	-	-5.903
EHOMO	-	-1.299
Energy bandgap	EHOMO - ELUMO	4.604
Ionization potential	I = –EHOMO	-5.903
Electron affinity	A = –ELUMO	-1.299
Electronegativity	$\chi = \left(\frac{1+A}{2}\right) = -\left(\frac{\mathbf{EHOMO} + \mathbf{ELUMO}}{2}\right)$	-3.601
Chemical hardness	$\eta = \left(\frac{1-A}{2}\right)$	-2.302
Chemical potential	$\mu = -\left(\frac{1+A}{2}\right)$	3.601
Electrophilicity index	$\omega = \frac{\mu^2}{2\eta}$	-2.817
Chemical softness	$\sigma = \frac{1}{\eta} = \frac{1}{(\mathbf{EHOMO} - \mathbf{ELUMO})}$	-0.217
Electronic Energy	-	-1248.981
Dipole Moment (Debye)	-	5.066

The energy gap between HOMO and LUMO (ΔE) was calculated and was found to be 4.604 eV (Table 1). This large gap between HOMO and LUMO infers good stability, high excitation energies, and large chemical hardness of this molecule. Two energetic parameters correlated with the frontier orbitals were calculated, Ionization potential (I), and electron affinity (A). The high ionization potential of the ligand indicates that it is a good electron donor, and the relatively low electron affinity shows it is not highly reactive. The dipole moment (μ in Debye) is another important electronic parameter used to describe the polarity of the molecule [39]. Molecules that have high dipole moment have a tendency to interact with other molecule through electrostatic interactions The electronic chemical potential (**μ**), the absolute electronegativity (χ), the global hardness (η), the Chemical softness (σ), and the global electrophilicity index (ω). The results show that this compound has good stability, high excitation energy, and high electrophilicity [18], comparison with another compounds, As illustrated in table 1,2 and Figures

Table 2. Comparision of Energy bandgap of prepared ligand with some other compound		
Compound	Energy bandgap(ev)	Reference
1,4-BENZOTHIAZINE DERIVATIVES	6.618-6.658	19
sulfamethoxazole	5.091	20
Olmesartan	7.026	21
2-thiophene carboxylic acid	7.0073	22
2-thiophene carboxylic acid hydrazide	6.9464	22
Prepared ligand	4.6o4	In this study

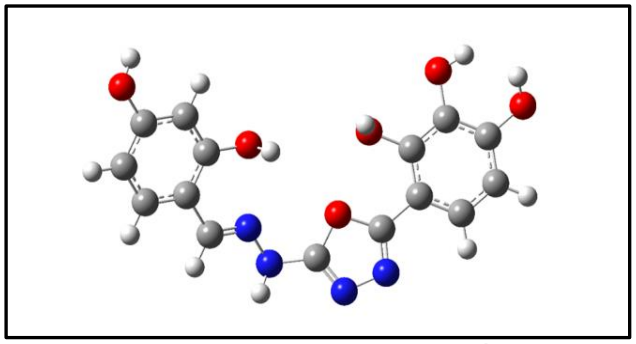


Figure 7. Optimized Structure of L

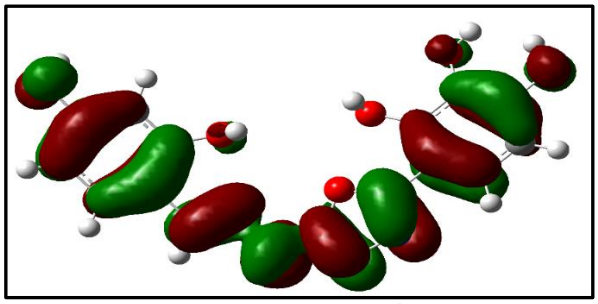


Figure 8. HOMO of L

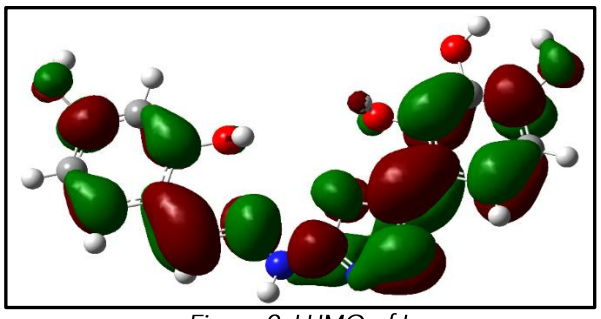


Figure 9. LUMO of L

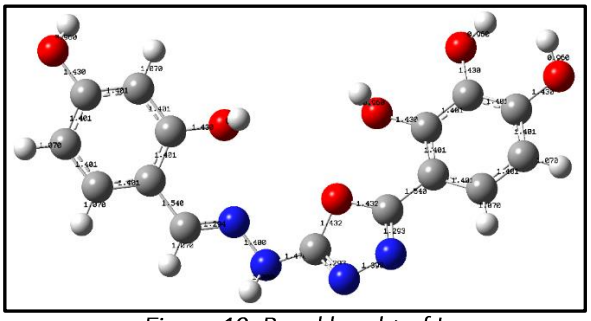


Figure 10. Bond lenght of L

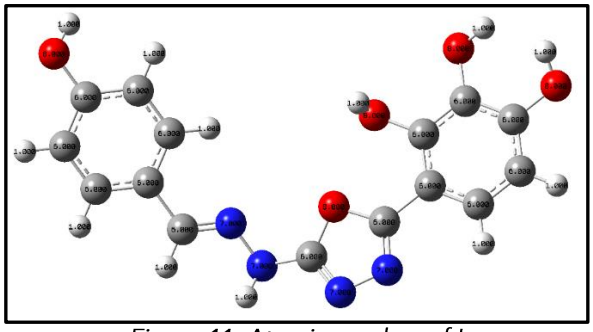


Figure 11. Atomic number of L

3.6 Biological activity

The ligand and its transition metal ions complexes were evaluated for antimicrobial activity against gram negative bacteria such as Serratia and Pseudomonas, by using agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standard, dimethyl sulphoxide (DMSO) were used to prepared all the test solutions. The area of inhibition was measured in millimeter. nutrient agar used as culture medium. The observe result showed transition metal complexes enhanced antimicrobial activity than that of free ligand. This result can be due to the greater lipophilic nature of the complexes and favors its permeation through the lipoid layers of the bacterial membranes. The activity of transition metal complexes can be expound on the basis of Overton's concept and Chelation theory [15] (Table3 and Figures 12, 13).

Table 3: Anti-bacterial data of ligand and its complexes

Compound	Pseudomonas Inhibition zone(mm)	Serratia Inhibition zone(mm)
L	5	10
[Cr(L) Cl3]	16	20
[Ni(L)Cl2]	12	14
[Fe(L)Cl3]	13	15

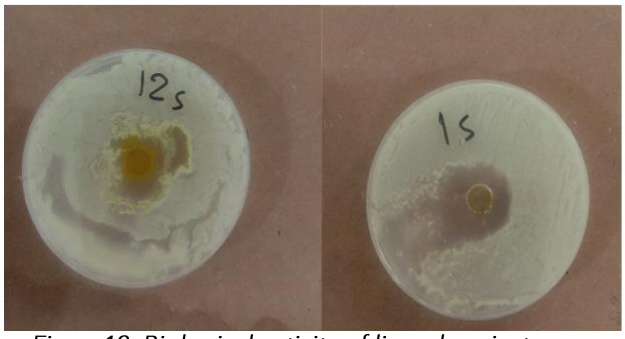


Figure12. Biological activity of ligand against gram negative bacteria Serratia and Pseudomonas

Figure13. Biological activity of the complexes against gram negative bacteria Serratia and Pseudomonas

4. Conclusion

The ligand ((E)-4-(5-(2-(2,4-hydroxy benzylidene) hy drazinyl)-1,3,4-oxadiazol-2-yl) benzene-1,2,3-triol) was successfully synthesized. The ligand was treated to different transition metal salt to afford the corresponding complexes such as Cr (III),Fe(III),Ni(||).The ligand and its complexes are characterized using infrared spectra, NMR spectra and mass spectrometry.Magnetic susceptibility data suggests the octahedral geometry for the Fe(III) Cr(III) and square planar geometry was proposed for Ni(II) . The ligand and its complexes has shown moderate to good activity as antibacterial against gram-negative bacteria Serratia and Pseudomonas.

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