Synthesis, Characterization, Theoretical Studies, and Biological Activity of (E)-4-(5-(2-(2, 4-Dihydroxy Benzy Lidene) Hy Draziny L) - 1, 3, 4-Oxadiazol-2-Y L) Benzene- 1, 2, 3-Triol and Its Complexes

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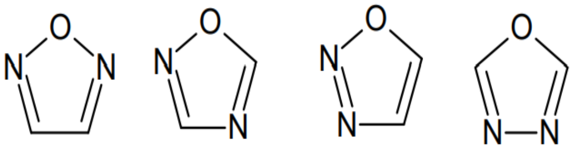
Abstract

In the present study we prepared (E)-4-(5-(2-(2,4-dihydroxy benzylidene) hy draziny l)- 1,3,4-oxadiazol-2-y l) benzene- 1,2, 3-triol and its complexes. All prepared compounds were characterized by spectra of H1-NMR, mass, 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 has shown moderate to good activity gram-positive bacteria against (Staphylococcus aureus), gram-negative bacteria (pseudomonas).

Keywords: 1, 3, 4-oxadiazol, magnetic susceptibility, IR spectra, mass spectra, Quantum chemical calculations.

1. Introduction

oxadiazole simple five membered heterocycles possessing one oxygen atom and two nitrogen atoms are considered as 1, 3, 4- oxadiazole and its derivatives. 1,3,4-oxadiazole can exist in different isomeric forms, they are 1,2,5-oxadiazole, 1,2,4-oxadiazole, 1,2,3-oxadiazole and 1,3,4-oxadiazole. Oxygen and nitrogen containing five-member heterocyclic nucleus is assessed against various diseases. So, they are given importance in medicinal chemistry because of their diverse medicinal potential. Substituted 1, 3, 4-oxadiazole is have broad spectrum of biological activities in pharmaceutical and agrochemical field [1].



1, 3, 4-oxadiazole shows wide variety of activities such as virucidal, CNS depressant, genotoxic, anticonvulsant, insecticidal, anti-tubercular, Anti-HIV, herbicidal, anti-inflammatory. It is also known to exhibit anti-malarial, Muscle relaxants, anti tumour, lipid peroxidation inhibitor, antimicrobial, and remarkable analgesic, anticonvulsant, diuretic, hypnotic and sedative properties. There for 1, 3, 4-oxadiazole is commonly used in the area of new drug development. [2-5] For the synthesis of 1,3,4-oxadiazole the conventional method used involve the intermolecular condensation of acid hydrazide with carboxylic acid in presence of cyclising agents such as phosphorous oxy chloride, polyphosohoric acid, acetic anhydride. Another reaction involves the condensation with carbon disulfide, potassium hydroxide and ethanol. In this reaction thiol substituted 1, 3, 4-oxadiazole is formed. [6, 7]. The aim of this study is to synthesize a new oxadiazole derivative and its complexes and study Biological activity and quantum chemical calculation of new the derivative

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.

2.1Physical 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) (Table.1). The FTIR spectrain 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. Preparation of the Ligand

A mixture of methyl 3,4,5-trihydroxybenzoate (18.4ml, 0.1mol) and hydrazine hydrate (10ml, 0.2mol) was dissolved in (100 ml) ethanol were

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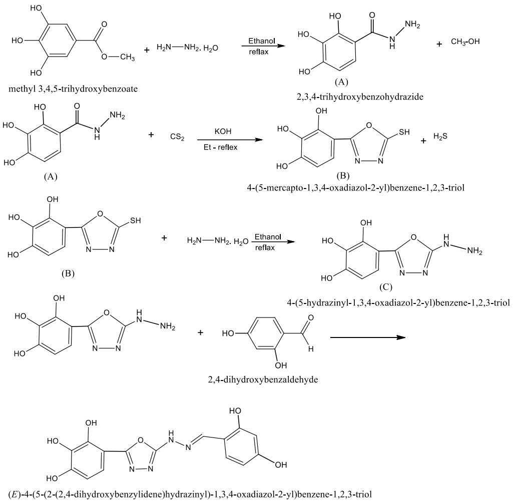
refluxed for 8 hours. The mixture (A) was evaporated to half,cooled, filtered and re-crystallized in methanol, the solid (A) was white, melting point 156 °C, yield 87%.

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.The solid (B) was white, melting point 227 °C, yield 84%.

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 [8]. white precipitate (C) was filtered and recrystallized from ethanol. Melting point 226 °C, yield 66.5%.

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%.



Scheme 1. Synthesis of ligand

2.3 Preparation of Complexes

The complexes were synthesized by mix (0.001mol) from ligand with salts (0.001mol) from salts [CrCl3.6H2O and FeCl3.6H2O] both alone in (50ml) ethanol and refluxed for 3 hours (monitored by TLC).then the precipitate was filtered and wash with ethanol or aqueous ethanol to removed unreacted salts or ligand,then precipitated complexes was dried [9-11].

Table 1. Physical properties of the ligands and their complexes

Yield	M.P. (°C)	Color	M.Wt. g\mol	Chemical Formula
58%	269	Brown	344	$C_{16}H_{14}N_4O_6$ (L)
73%	357	Light green	505	[Fe(L)Cl3]
70%	338	Black, blue	503	[Cr(L) Cl3]
68%	326	light brown	474	[Ni(L)Cl2]

3. Result and Discussion

3.1. Nuclear Magnetic Resonance

The 1H-NMR spectra of ligand was recorded in DMSO as solvent in Figure.1.The chemical shift at 7.63-7.81ppm(5H,s,OH), 7ppm (H, s, NH), 7.79(H,M,CH), 7-7.5ppm(5H,m,armatic protons) 2.5(s,DMSO).1H-NMR(DMSO-d6) spectral information was given extra support for the proposition of the structure [12].

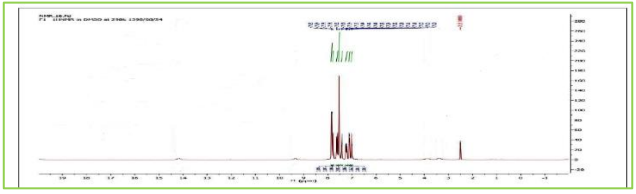


Figure1. 1H-NMR spectrum of ligand

3.2. Mass spectra

Characterize mass spectra of the ligand appearance of molecular ion peak [M]+.at 57 m/z and the ligand spectrum showed series fragments at (344,327,312,264,236,111,97,83,68,43) m/z in figure (2). The mass spectrum of the complex [Cr (L) Cl3] shows a molecular ion peak [M] +. (503) 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 (468,433,398) 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] +. (505) 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 (470,435,400) due to [Fe(L)Cl2]+ [Fe(L)Cl]+, and [Fe(L)]+ respectively. The mass spectrum of the complex [Ni (L) Cl2] shows a molecular ion peak [M] +. (474) 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 (439,404) due to [Ni (L) Cl] + and [Ni (L)] + respectively. The mass spectra of the complexes shown in figure 2.

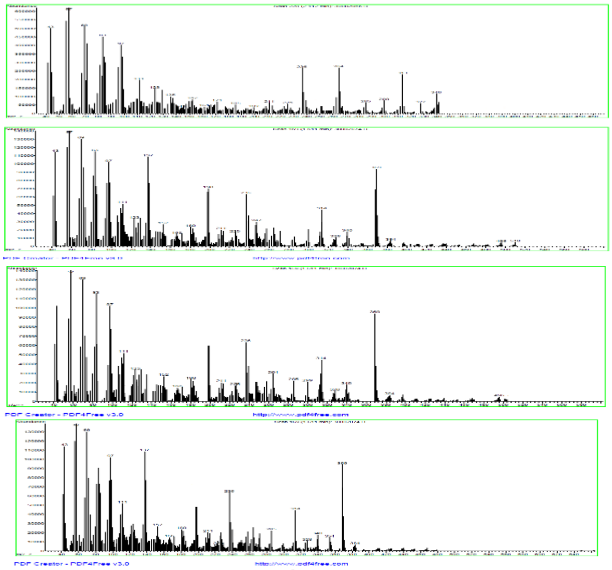


Figure 2. Mass spectra of (a) ligand, (b) [Cr (L) Cl3] (c) [Fe(L) Cl3] (d) [Ni(L)Cl2]

3.3. 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 3.63BM. The (μeff B.M) value of Fe (III) complex 2.05BM This value is likely to be octahedral geometry. The (μeff B.M) value of Ni (II) complex 0.15BM This value is likely to be square planar geometry

3.4. Quantum chemical calculations

Quantum chemical methods are useful in determining the molecular structure as well as elucidating the electronic structure and reactivity [9]. The highest occupied molecular orbitals (HOMO) populations and lowest unoccupied molecular orbitals (LUMO) for the prepared ligand is shown in Figs (3-7).The tendency of the molecule to donate and accept electrons is related to the energy levels of HOMO and LUMO respectively, the higher HOMO energy level (EHOMO) is higher in donation ability and the lower LUMO energy level (ELUMO) is higher in acceptance ability, so, the lower energy band gap (ΔE = ELUMO – EHOMO) leads to stronger interactions through the donation and acceptance of electrons.The calculated quantum chemical parameters, that is, the highest occupied molecular orbital energy (EHOMO), lowest unoccupied molecular orbital energy (ELUMO), the energy gap (ΔEgap = ELUMO – EHOMO), the electronic chemical potential (μ), the absolute electronegativity (χ), the global hardness (η), the global softness (σ), Electronic Energy, Dipole Moment (Debye), and the global electrophilicity index (ω). The results show that this compound has good stability, high excitation energy, and high electrophilicity [4, 10] are given in Table 2.

Table 2. Quantum chemical Parameter of ligand

Quantum Parameter	Values with (ev)
ELUMO	-5.903
EHOMO	-1.299
Energy bandgap (ΔE)	4.604
Ionization potential(I)	-5.903
Electron affinity(A)	-1.299
Electronegativity (**χ**)	-3.601
Chemical hardness (η)	-2.302
Chemical potential (**μ**)	3.601
Electrophilicity index (**ω**)	-2.817
Chemical softness (**σ**)	-0.217
Electronic Energy	-1248.981
Dipole Moment (Debye)	5.066

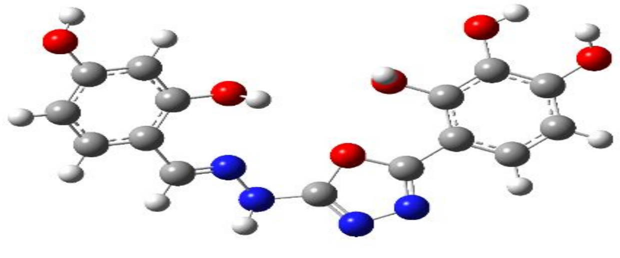


Figure 3. Optimized Structure of L

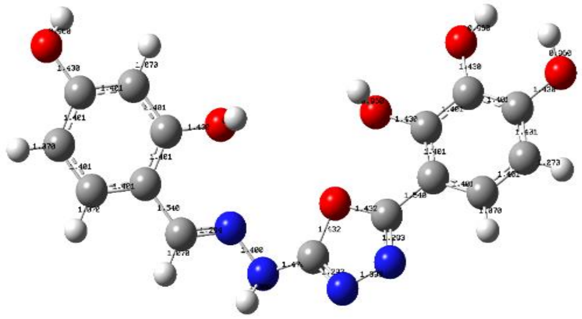


Figure 4. Bond lenght of L

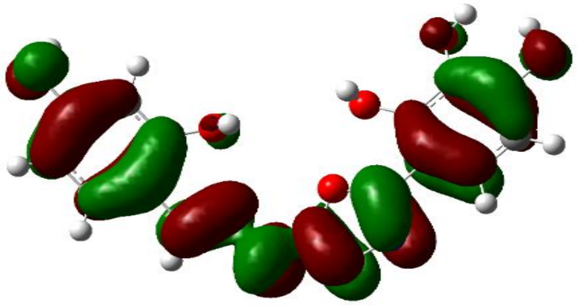


Figure 5. HOMO of L

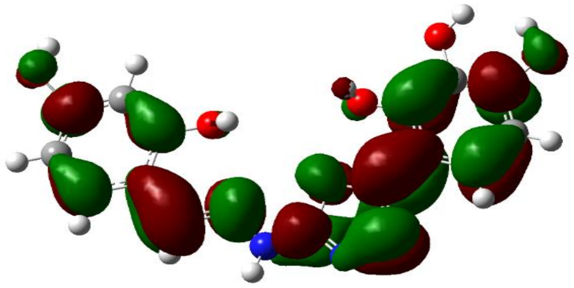


Figure6. LUMO of L

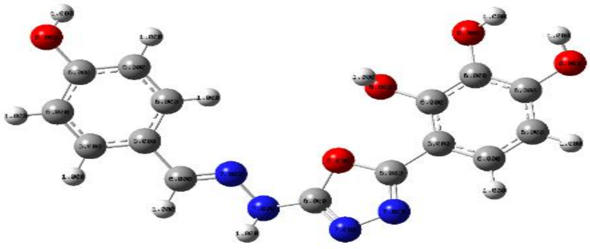


Figure 7. Atomic number of L

3.6 Biological activity

The ligand and its transition metal ions complexes were evaluated for antimicrobial activity against gram positive bacteria such as Staphylococcus aureus and gram-negative bacteria 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 solution.The area of inhibition was measured in millimeter. nutrient agar used as culture medium (table3 and figure 8).

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

Compound	Staphylococcus aureus Inhibition zone(mm)	Pseudomonas Inhibition zone(mm)
L	8	15
[Cr(L) Cl3]	17	25
[Ni(L)Cl2]	14	15
[Fe(L)Cl3]	15	20

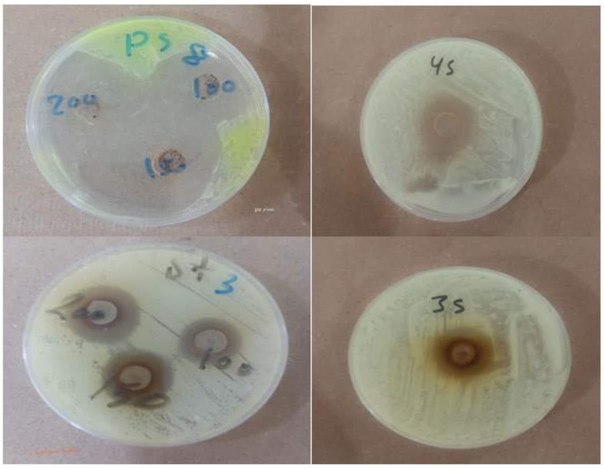


Figure 8. Biological activity of ligand and its complexes

3. Conclusion

A new ligands (E)-4-(5-(2-(2, 4- dihydroxy benzy lidene) hy draziny l)- 1,3,4-oxadiazol-2-y l) benzene-1,2, 3-triol and their Fe (III) and Cr(III) complexes were successfully synthesized. The ligands were bonded to different transition metals to form the corresponded complexes. The FTIR, III) and Cr (III) complxes. The structure chemical were studied of the Frontier Molecular Orbitals (FMOs) of ligands were computed by using density functional theory (DFT) methodat the B3LYP/6-31G(d,p) level of theory. The ligand and its complexes has shown moderate to good activity as antimicrobial.

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