Egypt. J. Chem. **Vol. 65**, No. 5 pp. 635 - 645 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis, Characterization, Biological Activity and Quantum Chemical Calculations of New Oxadiazole Derivatives

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Abstract

The two ligands (E)-3-(2-(5-(2-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)hydrazineyl)-1,3,4-thiadiazol-2-yl) hydrazineylidene) indolin-2-one (L1) ,(E)-5-(5-(2-(5-(2-((1H-pyrrol-2-yl) methylene hydrazinyl)-1,3,4-thiadiazol-2-yl) hydrazinyl)- 1,3,4-oxadiazol-2-y1) benzene-1,2,3-triol (L2) and their Fe(III) and Ni(II) complexes were synthesized by addition and elimination reactions. The ligands and their complexes characterized by spectroscopic methods (FTIR , ^{1}H-NMR , MS). The ligand acts as a bidentate ligand coordinating through the nitrogen atom of the oxadiazole ring and the nitrogen atom of amino group. This view is further supported by the appearance of a band corresponding to the metal-nitrogen and vibration at 454–688 cm^{-1} and 314-466 cm^{-1} in the complexes, respectively. The magnetic studies suggest a octahedral and square planar geometry of the complexes. The complex of Fe (III) have shown octahedral geometry, the complex of Ni (II) has shown square planar geometry with prepared ligands.HOMO-LUMO molecular orbitals analysis of these ligands (L1,L2) and some quantum chemical parameters derived from frontier molecular orbitals were studied. The new ligands and their complexes has shown moderate to good activity against three type fungi .

Keywords :1,3,4-oxadiazol, transition metal complexes, IR spectra, mass spectra,^{1}H-NMR spectra, Frontier molecular orbitals.

1. Introduction

The chemistry of five□membered heterocyclic rings in the last few decades , has received considerable attention owing to their synthetic and effective biological importance. Among these, Triazoles and in particular 1,2,4-triazole nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, antianxiety, and antimicrobial agents [1-3]. Furthermore, The thiadiazolesulfur atom in 1,3,4-thiadiazoles and 1,3,4-Thiadiazoles revealed better liposolubility, and these compounds exhibited the ability to cross cellular membranes and interact with biological targets with prominent affinities due to the mesoionic nature of 1,3,4-thiadiazoles. 1,3,4-Thiadiazoles have been characterized by important biological activities, such as anticancer, antiepileptic, antiviral, antibacterial, antifungal, antidiabetic, analgesic, antiprotozoalgenotoxic , anti-tubercular , virucidal, antimalarial , insecticidal , herbicidal , analgesic,muscle relaxants, anticonvulsant, sedative, hypnotic , anticancer and lipid peroxidation inhibitorand anti-inflammatory activities [4–8]. Interesting research investigations have indicated that 1,3,4-thiadiazole is a promising motif of great significance in drug discovery research including divers cancer cell lines by inhibition of diversified molecular targets for cancer medication [4–14]. As another remarkable hetrocyclic scaffold, 1,3,4-oxadiazole, has extensive important applications in designing promising agrochemicals in addition to the recently reported various bioactivities of related derivatives [15–19]. In addition, Schiff bases have been the focus of numerous studies due totheir wide spectrum of biological activities [15]. Moreover, azomethine Schiff bases linkages, as attractive connecting units that could bind two pharmacophores to generate an innovative bifunctional drug, have rapidly emerge as one of the most challenging and attractive topics in drug design for the constructing of novel bioactive molecules. Based on all above considerations and as an extension of our studies on the developments of novel azoles antimicrobial agents [16,17].

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Receive Date: 18 October 2021, Revise Date: 13 November 2021, Accept Date: 15 November 2021

DOI: 10.21608/ejchem.2021.101574.4720

2. Experimental

2.1Materials

Methyl 2-hydroxybenzoate, hydrazine hydrate**,** Ethanol(CH_3CH_2OH), Methanol(CH_3OH), Potassium hydroxide(KOH), Carbon disulfide, 3,4,5-trihydroxybenzoate, Indoline2,3-dione, Hydrochloric acid (HCl), Iron (III) Chloride($FeCl_3$)and Nickel(II) Chloride ($NiCl_2.6H_2O$) were used B.D.H

2.2Instrumentation

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) .

2.3Preparation of the ligands

2.3.1Preparation of L1

A mixture of methyl 2-hydroxybenzoate **(**15.2ml, 0.1mol) and hydrazine hydrate (10ml, 0.2mol) was dissolved in (100 ml) ethanol were refluxed for 8 hours. The mixture (A1) was evaporated to half, cooled, filtered and re-crystallized in methanol [18, 21,22], the solid (A1) was white, melting point 148 °C, yield 95% .

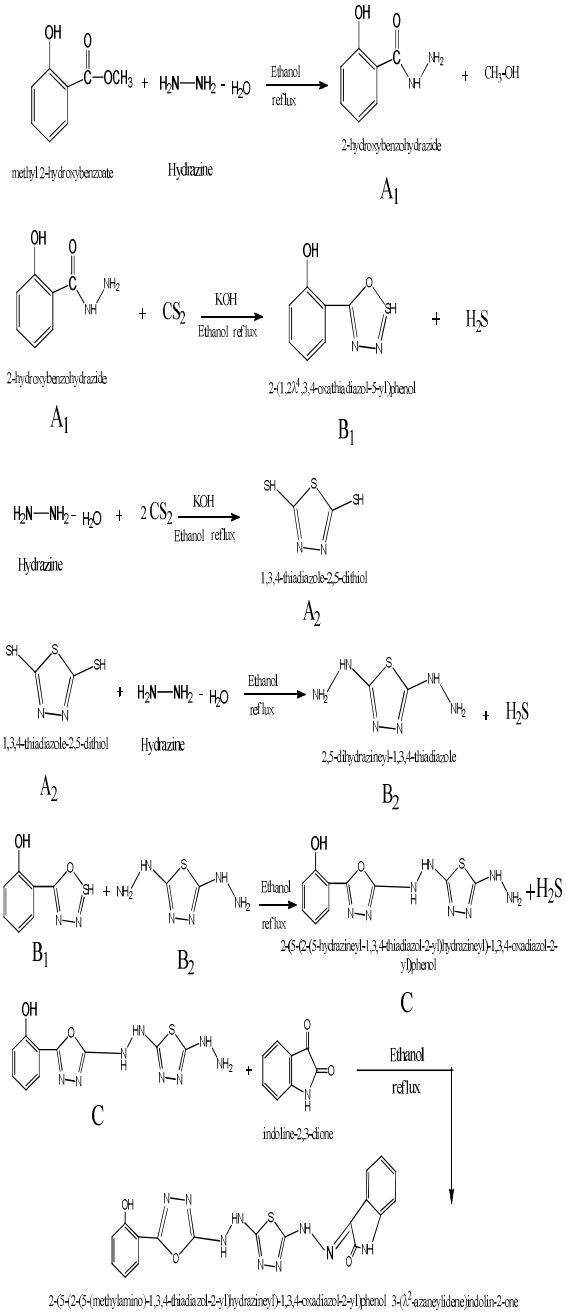
2-hydroxybenzohydrazide (A1) (15gm, 0.1mol), potassium hydroxide (5.6gm, 0.1mol) and carbon disulfide (6ml 0.1mol) were refluxed in (100 ml) ethanol. The solvent was evaporated and acidified with HCl (25%) then the precipitated was filtered and the result solid was recrystallized from ethanol absolute [19]. The solid (B1) was white, melting point 222 °C, yield 83%.

potassium hydroxide (12gm, 0.1mol), carbon disulfide (15ml 0.2mol) and hydrazine hydrate (5ml) were refluxed in ethanol (100 ml) ethanol. The solvent was evaporated and acidified with HCl (10%). Then the precipitated was filtered and the result solid was recrystallized from ethanol absolute. The solid thiadiazole (A2), was yellow, melting point 165 °C, yield 87%.

1,3,4-thiadiazole-2,5-dithole (A2) (15 gm, 0.2mol) and hydrazine hydrate (8 gm ,0.1mol) in ethanol as solvent (50 ml) were refluxed for 20 hours. The mixture (B2) was concentration and then cooled [20]. was yellow, melting point 130 °C, yield 77%.

2-hydroxyphenyl-1,3,4-oxadiazole-2(H) thion(4gm) and 2.5-dihydrazinyl-1,3,5 thiadiazole (3.2gm) were refluxed in ethanol (100 ml) ethanol refluxed for 8 hours. The mixture was evaporated to half, cooled, filtered and recrystallized in methanol [7], the solid was violet, melting point298 °C, yield 69%.

The ligand was synthesized by condensation of amine (2gm) and 1H-indol-2,3-dione(1.02gm) 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 58%.



Scheme 1. Preparation of L1

2.3.2Preparation of L2

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 refluxed for 8 hours. The mixture (A1) was evaporated to half ,cooled, filtered and re-crystallized in methanol [18,21,22], the solid (A1) was white, melting point 158 °C, yield 85%.

3,4,5-trihydroxybenzohydrazide (A1) (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 [19].The solid (B1) was white, melting point 222 °C, yield 83%.

potassium hydroxide (12gm , 0.1mol),carbon disulfide(15ml 0.2mol) and hydrazine hydrate (5ml) were refluxed in ethanol (100 ml) ethanol. The solvent was evaporated and acidified withHCl (10%) .Then the precipitated was filtered and the result solid was recrystallized from ethanol absolute .The solidthiadiazole (A2) , was yellow, melting point 169 °C, yield 88%.

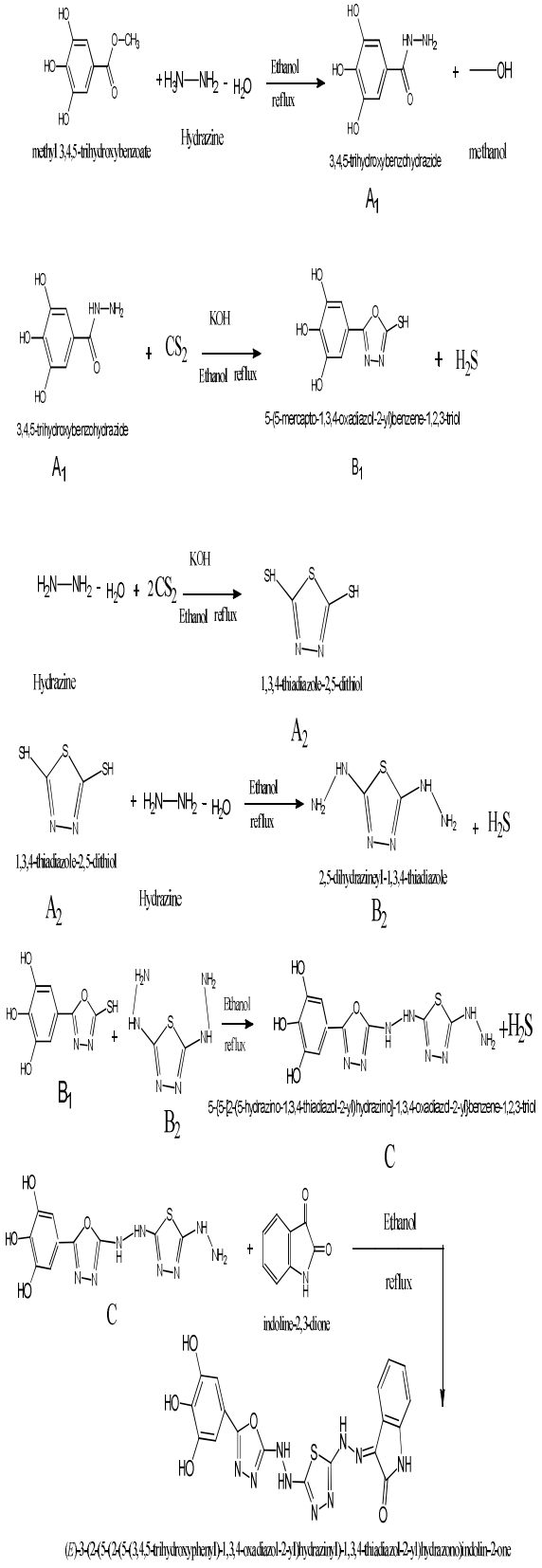
1,3,4-thiadiazole-2,5-dithole (A2) (15gm , 0.2mol)and hydrazine hydrate (8 gm ,0.1mol) in ethanol as solvent (50 ml) were refluxed for 20 hours. The mixture (B2) was concentration and then cooled[20]. was yellow, melting point 125 °C, yield 72%

5-(5-mercpto-1,3,4-oxadiazole-2yl)benzene-1,2,3-triol (4gm) and2.5-dihydrazinyl-1,3,5 thiadiazole (2.6gm) were refluxed in ethanol (100 ml) ethanol refluxed for 8 hours. The mixture was evaporated to half ,cooled, filtered and recrystallized in methanol [7], the solid was violet, melting point289 °C, yield 69%.

The ligand was synthesized by condensation of amine(2gm) and indline-2,3-dione (0.8gm) in ethanol (30 ml). Then the mixture refluxed for 4 hours. The ligand was precipitated, filtered and recrystallized from ethanol to getyellowligand , melting point 289 °C, yield 57% .

2.2.3 Preparation of complexes

The complexes were synthesized by mix (0.001mol) from ligand with (0.001mol)from salts[$FeCl_3$and $NiCl_2.6H_2O$] both alone in (50ml) ethanol and refluxed for 3 hours (monitored by TLC) .Then the precipitate was filtered and wash with ethanol oraqueous ethanol to removed unreacted salts or ligand ,then precipitated complexes was dried [23] . Physical properties data of the ligands and its complexes was tabulated in Table (1)



Scheme 2. Preparation of L2

3. Results and Discussions

3.1 FT-IR Spectra

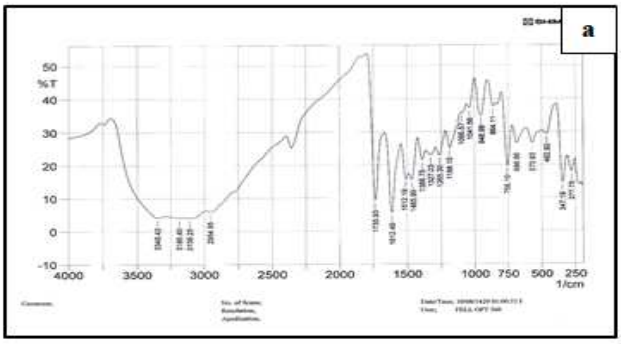
FT-IR of the synthesized ligands and their complexes were carried out KBr disc to ligands and CsI disk for complexes. The results show in Table (2) and Figure (1) [24-32].

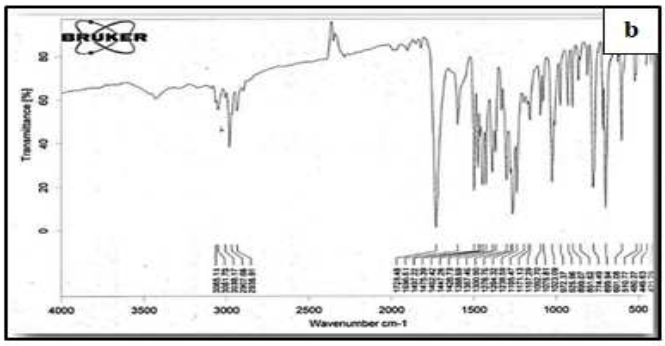
Table 1. Physical properties of the ligands and their complexes

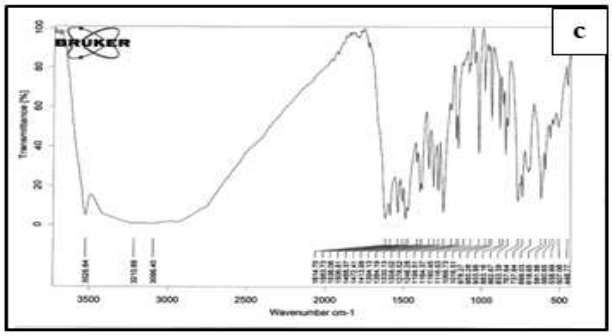
Symbol	Chemical Formula	M.Wt g\mol	M.P. (°C)	Color	Λm(S.cm2. mole-1)	Yield
L1	$C_{18}H_{13}N_9O_3S$	433	284	Brown	-	58%
L1M1	[Fe(L1) Cl_3]	596	320	Light green	14	72%
L1M2	[Ni(L1)Cl_2]	564	337	Black blue	13	83%
L2	[$C_{18}H_{13}N_9O_5S$]	467	289	Yellow	-	57%
L2M1	[Fe(L2) Cl_3]	627	364	Dark green	17	70%
$L2M_2$	[Ni(L2)Cl_2]	596	345	Greenish blue	18	83%

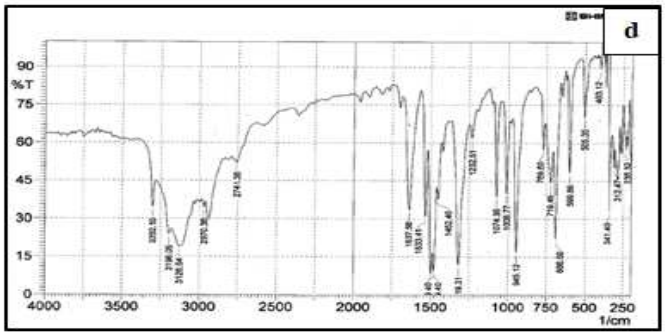
Table 2. Physical properties of the ligands and their complexes

Compound	υ(NH) cm^{-1}	υ(O-H) cm^{-1}	υ(C═N) imine cm^{-1}	(C-S-C) υ cm^{-1}	υ (C−O−C) cm^{-1}	(C=O) cm^{-1}υ	Struc. Movement cm^{-1}	υ(M−N) cm^{-1}	(M−O) υ cm^{-1}	υ(M−Cl) cm^{-1}
$C_{18}H_{13}N_9O_3S$(L1)	3200	3348	1612	1465	1327(Asy), 1265(sy)	1735	1095	-	-	-
[Fe(L1)Cl_3]	3210	3526	1614	1472	1338(Asy),1308(sy)	-	1095	538	507	448
[Ni(L1) Cl_2]	3361	3361	1635.6	1479	1400(Asy),1319(sy)	-	1008	567	410	374
$C_{18}H_{13}N_9O_5S$(L2)	3200	3450	1696	1388	1367(Asy),1300(sy)	1723	1171	-	-	-
[Fe(L2)Cl_3]	3196	3392	1633	1479	1452(Asy),1419(sy)	-	1074	505	403	312
[Ni(L2) Cl_2]	3210	3336	1608	1477	1384(Asy),1267(sy)	-	1033	567	520	500









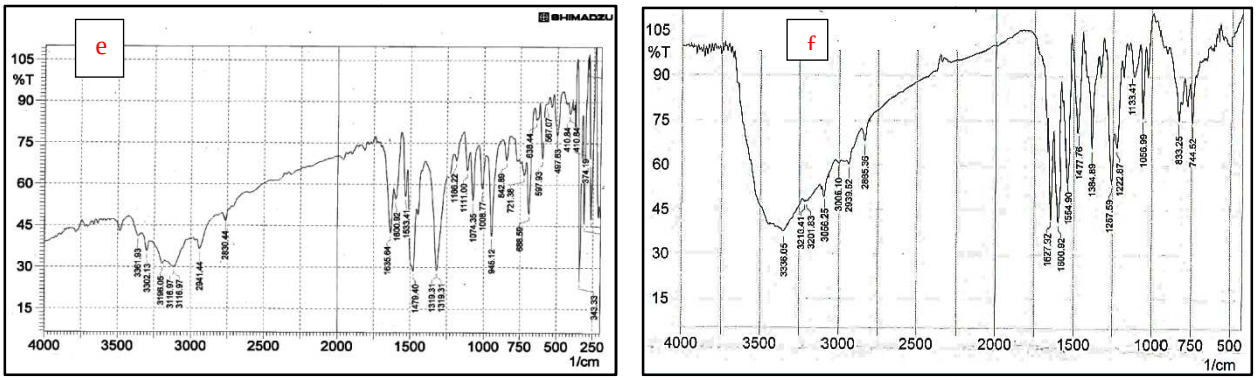


Figure 1. FT-IR Spectra of
(a) $C_{18}H_{13}N_9O_3S$(L1) , (b) $C_{18}H_{13}N_9O_5S$(L2) ,(c-f) their complexes

3.2. ^{1}H-NMR spectra

The ^{1}H-NMR spectra of L1 and L2 was recorded in DMSO as solvent in Figure (2,3). The ^{1}H-NMR (DMSO-d6) spectral information was given extra support for the proposition of the structure L1 and L2 . The 1H-NMR spectrum of L1 exhibit in Figure (2a) the chemical shifts δ ppm at 6.90-6.96 (3H, s, NH protons) [33] , 6.97-7.65(8H, m, aromatic protons) [34,35] , 11.6 (1H,s, OH protons) ,10.45 (1H,s, NH protons) [36,37], 2.5(s, DMSO) ,while the 1H-NMR spectrum for L2 exhibit in Figure (2b) the chemical shifts δ ppm at 10.06 (3H,s,OH), 9,41(H,s,NH) [33], 6.37-8.02(6H,m,armatic protons, 3H,s,NH) [34,35], 2.5(s,DMSO).

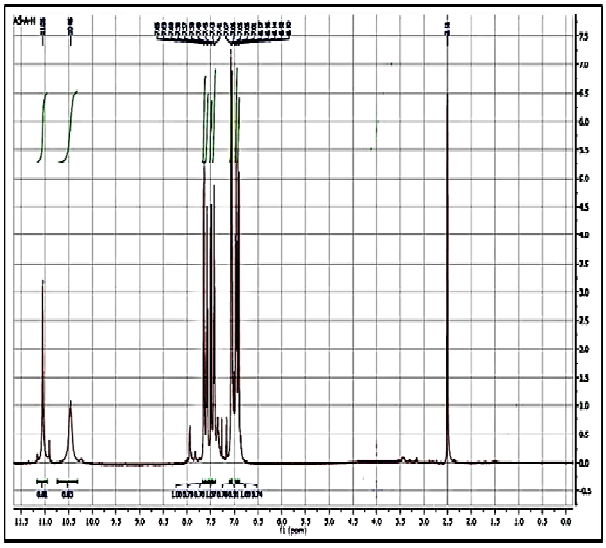


Figure 2. 1H-NMR spectra of L1

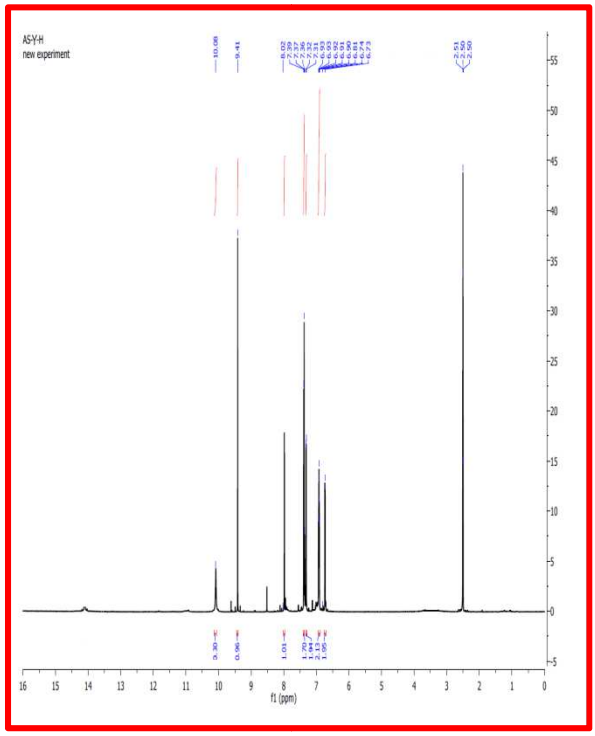


Figure 3. 1H-NMR spectra of L2

3.3. Mass spectra

3.3.1. Mass spectra of L1and their complexes

The mass spectrum of the ligand (L1) exhibits a molecular ion peak $[M]^+$.at 434 m/z ,the ligand spectra shows fragments at (434 ,369, 314, 236, 109, 84, 69, 43,….) m/z as shown in Figure (4a).

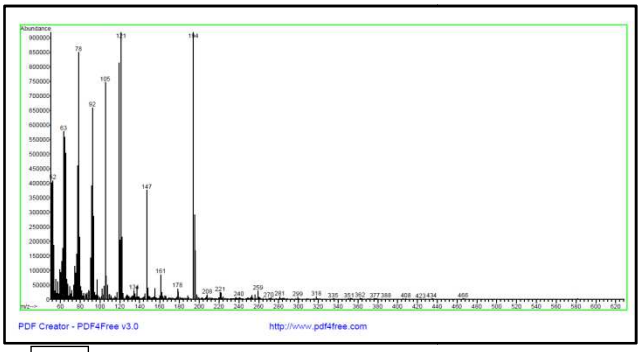
The mass spectrum of the complex $[Fe(L1)Cl_3]$ spectra shows fragments at (466,408,259,147,194,105,92,78,62,52,…) m/z

shown in Figure (4b). The mass spectrum of the complex

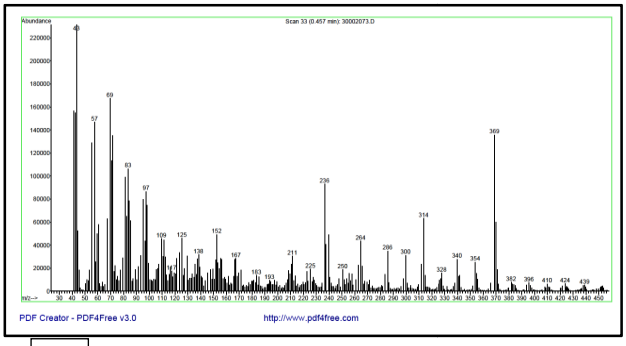
shows (Figure 4b) a molecular ion peak [M]+.(596) m/z which is equivalent to molecular mass of the complex .This complex shows another a fragment ion peak with loss of chlorine atom at (561,526,491) due to $[Fe(L1)Cl_2]$+ [Fe (L1)Cl]+, and [Fe (L1)]+ ,respectively.

The mass spectrum of the complex $[Ni(L1)Cl_2]$ shows (Figure 4c) a molecular ion peak $[M]^{+\cdot}$(564) 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 (529,495) due to $[Ni(L1)Cl]^+$ and $[Ni(L)]^+$ respectively.

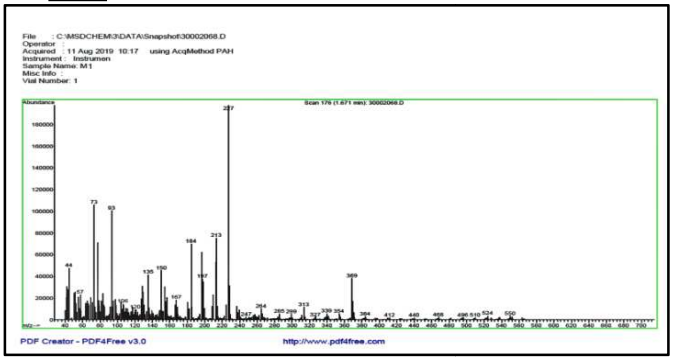
a



b



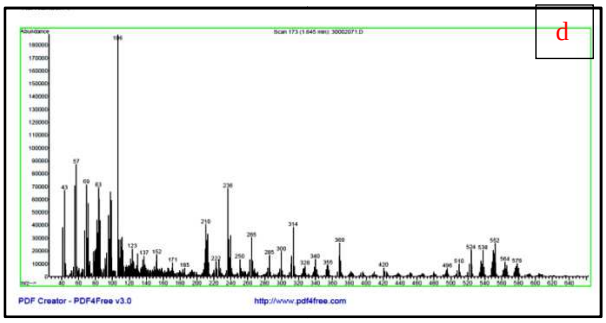
c



3.1. Mass spectra of L2 and their complexes

The mass spectrum of the ligand (L2) exhibits a molecular ion peak $[M]^{+\cdot}$at 466 m/z ,the ligand(L1) spectra shows fragments at (466,408,259,147,194,105,92,78,62,52,…) m/z shown in Figure (4d). The mass spectrum of the complex $[Fe(L2)Cl_3]$ shows a molecular ion peak $[M]^{+\cdot}$ (628) 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 (593,557,522) due to $[Fe(L2)Cl_2]^+$ $Fe(L2)Cl]^+$, and $[Fe(L2)]^+$ respectively [Figure (4e)]. The mass spectrum of the complex $[Ni(L2)Cl_2]$ shows a molecular ion peak $[M]^{+\cdot}$ (597) 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(561,529) due to $[Ni(L2)Cl]^+$ and $[Ni(L2)]^+$ respectively[Figure (4f)].

d



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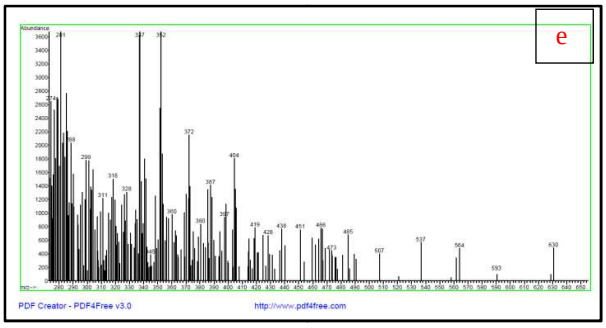

f

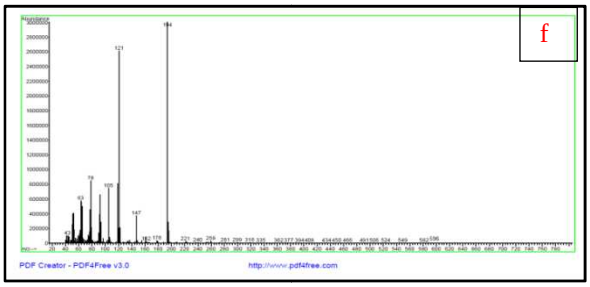

Figure 4. Mass spectrum of Ligands and their complexes

3.4. Magnetic Susceptibility

The magnetic susceptibility data (μeff B.M) for metal complexes (L1) give an information about the electronic state of central ion (transition metal ion) of the complexes. The magnetic studies shown low values of μeff B.M (low spin) of the complexes because the ligands are strong, which leads to electron pairs and also suggested a octahedral and square planar geometry of the complexes . Where the complex of Fe (III) have shown octahedral geometry, while the complex of Ni (II) has shown square planar geometry with prepared ligands [36,37] .The results show in Table (3).

TABLE 3. Magnetic Susceptibility Values

Complex	μ (B.M.)
[Ni(L1)Cl_2]	**0.11**
[Fe(L1) Cl_3]	**2.08**
[Ni(L2)Cl_2]	**0.13**
[Fe(L1) Cl_3]	**2.11**

3.5. Quantum chemical calculations:

Quantum chemical methods are useful in determining the molecular structure as well as elucidating the electronic structure and reactivity (43). The interaction of two atomic or molecular orbitals produces two new molecular orbitals. One of the new orbital is termed LUMO (lowest unoccupied molecular orbital) and other is HOMO (highest occupied molecular orbital), are shown in Figures (5-7) of L1 and L2 .These orbitals are sometimes referred as frontier molecular orbitals (FMOs), because they lie at the furthermost borders of the compound's electrons. HOMO and LUMO figure how the molecule interacts with other species. Highest occupied and lowest unoccupied orbitals in atoms participate in the bonding more than any other levels. The energy difference between frontier molecular orbitals is known as the HOMO-LUMO energy gap (ΔE) .The frontier orbitals energy gap helps individualize the chemical reactivity of molecule. The lower the energy of the HOMO and the higher the energy of the LUMO , the more stable the species is thermodynamically. A molecule which have more orbital gap is less polarized and less chemically reactive [40,41]. According to the present DFT calculations, among aimed molecules L2 have the biggest ΔE value from L1. The hard-soft-acid-base (HSAB) principle was used by Pearson to rationalize a variety of chemical information. The qualitative definition of HSAB was converted to a quantitative one by using the idea of polarizability. L1 less polarizable molecule or ion is "hard" and a more easily polarized species are "soft". The quantitative definition of hardness is the average of ionization potential and electron affinity. The concepts of hardness and softness of molecules are intimately linked with their polarizabilities and also the sizes. Softness and polarizability are assumed to be related "a soft species is also more polarizable." Global hardness and softness are important properties to measure the molecular stability and reactivity. Evaluating the values of the hardness in Table (4) shows that L2 is harder, this means that L1 has the largest potential chemical resistance to change the number of electrons among the other molecules. Also, it can be seen in Table of L1 have thehigh value of global softness that show the greater reactivity in relationship to the others. One can relate hardness to the gap between the HOMO and LUMO: The energy gap (ΔE) is directly involved with hardness/softness of a chemical species. Soft molecules are more reactive than hard ones because they could easily offer electrons to an acceptor[39]. The IP is the ionization potential (E_{LUMO}) and EA (E_{HOMO}) is the electron affinity of the system. The low IP creates a better electron donor, and the large EA makes a better acceptor Chemical potential measures the escaping tendency of an electron cloud, while the electrophilicity index (ω) which represents the measure of the energy reduction caused by the maximum electron flow between acceptor and donor and The negative of the chemical potential is expressed as electronegativity (χ), which represents a measure for the power of a molecular system to attract electrons). The values highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), HOMO–LUMO energy gap (ΔE_{H-L}), electronegativity (χ), electron affinity (A), global hardness (η), softness (σ), ionization potential (I), chemical potentials (μ), The global electrophilicity (ω), the ionization potential (I) and the electron affinity of the system (A) of the prepared L1 and L2, are collected in Table 4.

TABLE 4. The calculated quantum chemical parameters of L1and L2

Parameters (eV)	L1	L2
E_{HOMO}	**-7.17**	**-8.95**
E_{LUMO}	**-1.74**	**-1.75**
Energy bandgap (Eg) = $E_{LUMO} - E_{HOMO}$	**5.43**	**7.20**
Ionization potential (I = $-E_{HOMO}$)	**7.17**	**8.95**
Electron affinity (A = $-E_{LUMO}$)	**1.74**	**1.75**
Electronegativity (χ = (I+A)/2)	**4.45**	**5.35**
Chemical hardness (η = (I–A)/2)	**2.71**	**3.60**
Chemical potential (μ = - (I+A)/2)	**-4.45**	**-5.35**
Electrophilicity index (ω = μ 2 /2η)	**3.65**	**4.67**
Chemical softness (σ = 1/η)	**0.36**	**0.27**

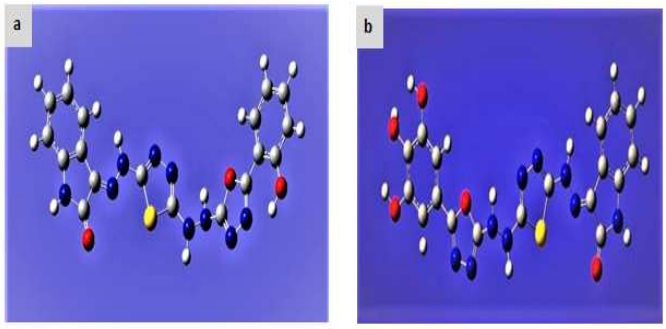

Figure 5. (a) Optimized structure of L1 , (b) Optimized structure of L2

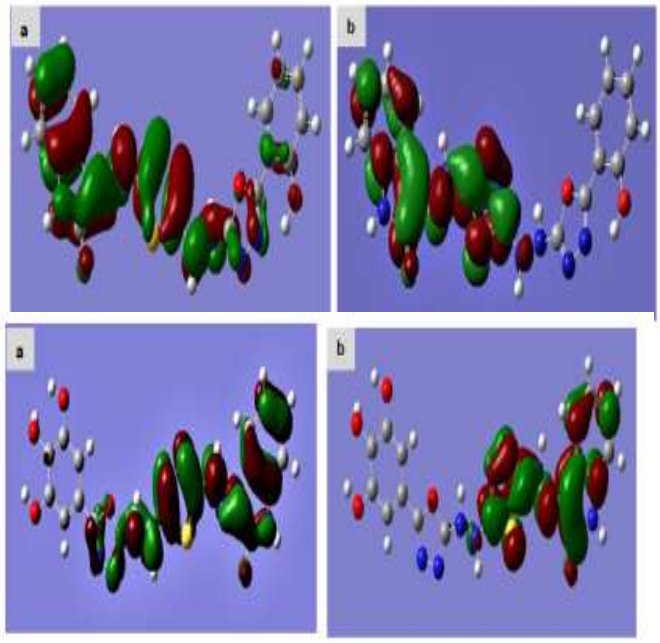

Figure 6.(a) HOMO molecular orbital of L1 , (b) LUMO molecular orbital of L1

Figure 7.(a) HOMO molecular orbital of L2, (b) LUMO molecular orbital of L2

3.6. Biological Activity

The ligands and their transitions metal ions complexes were evaluated for antimicrobial activity against three type funqi(C.Tropicals ,C.Glabrate, C.Kruzei) (Table.5). The higher activity of the metal complexes may be owing to the effect of metal ions on the normal cell membrane [42]. Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues. In addition, chelation may enhance or suppress the biochemical potential of bioactive organic species. Further, lipophilicity, which controls the rate of entry of molecules into the cell, is modified by coordination, so the metal complex can become more active than the free ligand. Therefore, the metal complexes show greater antimicrobial activities than the uncoordinated ligand and free metal ion which in fact is in agreement with the literature [43]. These mixed-ligand complexes have an advantage in that the respective bioactivities of the uncoordinated ligands and metal ions are combined which could make them more potent antimicrobial agents (Figure8).

TABLE 5. Anti-fungi data of ligands and Their complexes

Compound	C.Tropicals (mm)	C.Glabrate (mm)	C.Kruzei (mm)
$C_{18}H_{13}N_6O_3S$ (L1)	10	5	12
$[Fe(L1)Cl_3]$	15	17	11
$[Ni(L1)\ Cl_2]$	14	20	22
$C_{18}H_{13}N_9O_5S$ (L2)	14	12	13
$[Fe(L2)Cl_3]$	20	14	14
$[Ni(L2)\ Cl_2]$	21	30	35

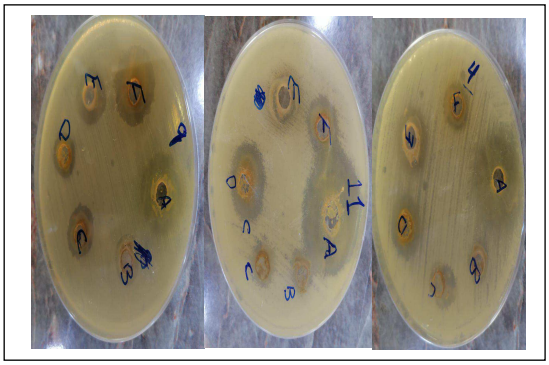

Figure 8. Biological Activity(Anti-fungi of ligands and Their complexes

4. Conclusion

A new ligands (E)-3-(2-(5-(2-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)hydrazineyl)-1,3,4-thiadiazol-2-yl)hydrazineylidene)indolin-2-one (L1) ,(E)-5-(5-(2-(5-(2-((1H-pyrrol-2-yl)methylene hydrazinyl)-1,3,4-thiadiazol-2-yl)hydrazinyl)- 1,3,4-oxadiazol-2-y1) benzene-1,2,3-triol (L2) and their Fe(III) and Ni(II) complexeswere successfully synthesized. The ligands were bonded to different transition metals to form the corresponded complexes . The FTIR,^{1}HNMR, Mass Spectra and Magnetic Susceptibility observations suggest the octahedral geometry for the Fe (III) geometry and square planar geometry for Ni (II)**.** 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 new

ligands and their complexes has shown moderate to good activity against three type fungi (C.Tropicals,C.Glabrate,C.Kruzei)

5. References

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