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Synthesis, Characterization and Antibacterial Activity Studies of Cobalt(II), Nickel(II),Copper(II) and Zinc(II) Complexes with (3-(4-bromophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-methylcarbothioamide Ligand

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Abstract

A series of bi nuclear transition metal complexes of Co(II), Ni(II) ,Cu(II) and Zn(II) of the general composition ($ML(H_2O)_2Cl_2$) where (M=Co(II), Ni(II) and Cu(II), L=(3-(4-bromophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-methylcarbothioamide). The new ligand was synthesized *via* ring closure of ((E)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one) with the excess of thiosemicarbazide. The new 2-pyrazoline was identified by MS, NMR,FT-IR spectra in addition the elemental microanalyses were carried out to elucidate the chemical structure after adjusting the thin-layer chromatography in (3:1) volume ratios of eluent solvents of ethylacetate and chloroform. The solid metal complexes of the new ligand were prepared and isolated in their solid state by direct reactions of their metal chlorides with the ethanolic solution of the ligand (L). The new metal complexes of cobalt(II),nickel(II),copper(II) and zinc(II) were fully characterized by elemental analysis (C.H.N.S), FT-IR, molar conductivity measurements in DMF solvent, electronic spectra and magnetic susceptibility *via* Farady's method. As well as the ionization mass spectra was assigned for some complexes to investigate the expected skeletal of the complexes. The data observed from elemental analyses, flame atomic absorption and spectroscopic techniques afforded the octahedral environment around cobalt(II),nickel(II) and copper(II) ions whereas the tetrahedral geometry was adopted for $ZnLCl_2$.The anti-microbial activities of these derivatives have been studied by screening them against bacteria like *Staphylococcus aureus* and *Escherichia Coli* and fungi like *Aspergillusnidulece* and *Condida albicance* by Serial dilution method.

Key words: 2-Pyrazoline complexes, antibacterial activity of pyrazole, polydentate ligands of 1-thiocarbamoyl-2-pyrazole derivatives.

1. Introduction

The discovery of bio-inorganic chemistry in the recent years encouraged the researchers to enhance attention in the field of pyrazole derivatives synthesis [1, 2]. Recently, the considerable evidence has been accumulated to demonstrate the efficiency of 3, 5-disubstituted-2-pyrazoline derivatives as potential antibacterial ,antifungal, herbicides , antitumor , and flower control agent [3,4]. The anticancer activity of dioxo vanadium (IV) complexes with poly dentate ligands have described and intensively studied by N.JParmer *e tal* [5].The literature study obtained have referred to the that 1-thiocarbamoyl pyrazole derivatives have exhibited a variety of such bioactivities , as an antimicrobial agent [6], ant tubercular agent [7] , anticonvulsant [8, 9] and anti-inflammatory agents [10]. Furthermore, the applications of green-analytical chemistry for 2-pyrazoline complexes have investigated through the significant kinds of hybrid inorganic-organic species which are employed in the catalysis processes [11]. The poly dentate ligands of pyrazole are considered to be good chelating agents through sulfur and immine groups [12]. There are studies of the coordination behavior of pyrazoline ligands with SNO donation sites, derived from 5-phenyl-5-phenyl-4*H*-3-thiophene-2-pyrazoline beside that their biological activities against certain micro-organisms have scanned and exhibited wide range of inhibition [13, 14].The utilities of pyrazoline encouraged synthesis through condensation acetylpyrrole chalcone with 4-methylthiosemicarbazide has recently reported by Rusul,SD. *E etal* [15] and the

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researchers have reported the Otimism Neurodegenerative applications with novel studies of bio-inorganic chemistry. These interested literature about pyrazoline ligands and their complexes encouraged us in the recent paper to synthesize and characterize new ligand from ring closure of (*E*)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one with alkaline solution of thiosemicarbazide and its complexes with cobalt(II), nickel(II),copper(II) and zinc(II) in addition general scanning their biological activity toward some bacteria and fungi.

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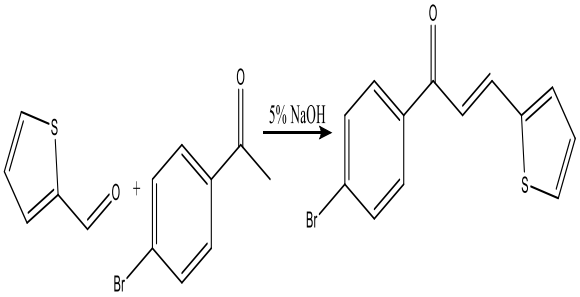
2. Chemicals and Instrumentation:

All reagents and chemicals were commercially were used as received from suppliers. The starting materials; 4-methylthiosemicarbazide (Merck), 4-bromoacetophenone and thiophene-2-carboxaldehede were supplied from Sigma-Aldrich company without purification. The salts of transition metals: $CuCl_2.2H_2O$, $ZnCl_2$, $CoCl_2.6H_2O$ and $NiCl_2.6H_2O$ were supplied from Merck, chemistry department, college of science, Mustansiriyah University. The thermal decomposition of chalcone, ligand and metal complexes were determined in open capillaries and are uncorrected. The conductivity of the complexes were measured on Philips digital conductivity meter with dip type cell at 27^0C in 10^{-3} M solution in DMF. The low values of conductivity suggest the non-electrolytic in nature. The vibration absorptions spectra were recorded on Shimadzu FT-IR spectrometer at Mustansiriyah University, College of Science. The electronic spectra of the prepared. compounds were measured in the region (200–800) nm by using Varian Cary 100 Conc. UV–Vis. The ^{1}H and ^{13}C-NMR spectra were acquired in-d*6*-DMSO solution using a 500 MHZ with tetra methyl silane (TMS) as an internal reference for H-NMR on Shimadzu were recorded at Kashan University, Iran. The magnetic moments were measured by Farady's method on Sherewood magnetic balance at 300 K temperature. The metal contents are determined using standard methods; the analytical data, color, conductivity measurements, magnetic moment, electronic spectra and decomposition temp of complexes have been recorded in (Table1).

2.1 Synthesis of (*E*)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one

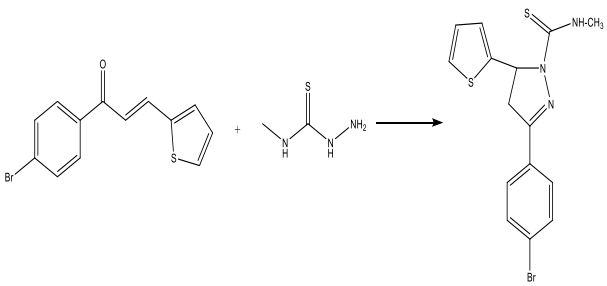
The ά-β-unsaturated carbonyl compound was prepared according to the modified procedure established in literature [15]. (1.99 g, 10 m moles) of 4-bromoacetophenone dissolved in (20 mL) hot methanol was added gradually to (1.13 g, 10 m moles) of thiophene-2-carboxaldehyde then 5% NaOH solution was added with stirring at room temperature for three hours. The pale yellow precipitate was formed, collected by filtration and the re crystallization from chloroform afforded deep-yellow crystals of the novel chalcone, Scheme(1).The analytical data of the prepared chalcone was estimated after carrying out TLC technique; Color: Pale yellow; yield% : 88 ; M.P=120-122 ^{0}C; TLC: R_f=0.65(ethyl acetate/benzene, 7/3). Anal.calc.for $C_{13}H_9BrOS$: C: 53.26, H: 3.09, S: 10.94. Found C: 52.88, H: 2.77, S: 10.31). IR (KBr) υmax cm^{-1}: 3070 (C-H), 1658 (-C=O), 1525(-CH=CH-),808 (bending A-H) and 675 (C-S, thiophene).^{1}H NMR(500 MHz, d_6-DMSO): d-d 7.12-7.15(4H, Ph-Br), 6.25-6.80 (m,3H, thiophene-H), 2.5 (m,1H,CH-Pz), 3.78 (d, 2H, CH_2-Pz).



Scheme 1. Synthesis of chalcone

2.2. Synthesis of 3-(4-bromophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

The target 2-pyrazoline ligand was prepared according to the modified procedure established in literature [12]. The mixing a solution (2.94 g, 10 m moles) of (*E*)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one in a solution of sodium hydroxide (0.5 g, 5 m moles) in hot ethanol (25 ml). An excess of 4-methylthiosemicarbazide (1.5 g, 2 m moles) in ethanol (15 ml) was then added, and the reaction mixture was stirred and refluxed for 18 hours. The dark yellow solid of the 2-pyrazoline ligand obtained after cooling the reaction was filtered off under Buckner suction. Bright yellow shaped crystals of the ligand suitable for the spectroscopic and analytical methods were recrystallized from hot methanol to afford pure compound which then was dried on anhydrous $CaCl_2$ pellets, Scheme (2).



Scheme 2. Synthesis of (L) ligand

2.3. Synthesis of Metal Complexes:

A mixtures (1 m mole) of metal chlorides (0.34 g.$CuCl_2.2H_2O$),(0.257 g, $NiCl_2.6H_2O$), (0.22 g $CoCl_2.6H_2O$), and (0.18 gm of $ZnCl_2$) dissolved in (10 mL.) of hot methanol with (0.365g g, 10 m moles) of the ligand dissolved in (15 ml) of hot ethanol was heated and stirred on water bath for (30-45) minutes, then add drops of 5% NH_3 solution to maintain the pH to ≈6-7) .On cooling the complex precipitated out, which filtered with ethanol and dried in vacuum desiccator, aver anhydrous $MgSO_4$. The complexes of NiL and ZnL were isolated in their solid state up on refluxing the mixture for about 3 hours and residue was precipitated after keeping them overnight to afford yellow and off white of complexes, Table(1).

3. Results and Discussion:

3.1. Characterization of ligand and its complexes:

Table (1) shows main physical properties of chalcone, ligand and its complexes. The observed elemental micro-analyses are in well- agreement of the calculated values then they supports the chemical formula of all the prepared compounds. As well as the % yield of almost complexes are good since they have prepared in isolated solid state with adjusting the precipitation conditions such as temperature and time of complexation. Furthermore, the molar conductivity of complexes solutions in DMF recorded values of (10-22) $S.mole^{-1}.cm^{-1}$ indicating non electrolytic properties of complexes then supports the neutral inner sphere structure of all complexes [11, 13].

Table (1) . Some physical properties and elemental analysis of the prepared complexes

Compound	Λ $S.cm^2/mole$	%Yield	M.P ^0C	%Found % (Calculated)				
				C	H	N	S	M
A		88	120-122	52.88	2.77	-	10.31	-
Deep yellow	-			(53.26)	(3.09)		(10.94)	
L		75	180-182	45.10	3.30	10.86	17.51	-
Dark yellow	-			(45.91)	(3.07)	(11.47)	(16.58)	
$[CoLCl_2(H_2O)_2].2H_2O$	10	85	212-214	34.06	3.01	18.71	4.837	10.00
Olive				(35.87)	(3.70)	(18.59)	(3.38)	(11.22)
$[NiLCl_2(H_2O)_2].2H_2O$		75	287 dec.	33.32	2.95	10.73	10.94	12.54
Pale yellow	30			(34.22)	(3.39)	(11.66)	(11.80)	(11.12)
$[CuLCl_2(H_2O)_2].H_2O$		72	327 dec,	40.06	3.49	17.33	11.15	10.50
Green	18			(40.87)	(4.02)	(17.50)	(11.64)	(11.09)
$ZnLCl_2$	22	96	322 dec	37.06	3.90	16.33	15.99	14.78
Off white				(36.80)	(4.12)	(17.22)	(16.96)	(15.45)

3.2. Mass spectra

The mass spectrum of the (E)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one showed molecular ion at *m/z*=294 with 100 % relative abundance conforming the expected molecular ion ($C_{13}H_{14}BrSO^+$), Figure(1). As well as the base peak at *m/z*=79 and *m/z*=81 is normally strog evidence of the $Br^{+\cdot}$ due to the high stability of bromine isotopes.

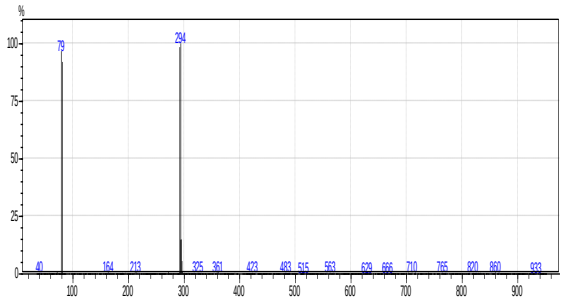


Figure 1. MS spectrum of chalcone at 7 ev bombardment

The MS spectrum of the 2-pyrazoline based ligand showed high intense absorption at *m*/z=374 and 375 with relative intensity 100% and 95% due to the high stability of molecular ion of $[C_{16}H_{17}BrN_4S_2^+]$. As well as the effect of bromine isotope was remarkably observed from the vicinal peaks at *m*/z=79 and *m*/z=81 due to fragmentation of $[L\text{-}Br]^{+\cdot}$, Figure (2). However, the appearance of peak at *m*/z=325 and *m*/z=327 may be assigned to cleavage of hydrogen sulfide gas from the thiocarbamoyl moiety in order to give the molecular ion $[C_{15}H_{13}BrN_4S^+]$ with relative intensity of (90-93 %) [8, 12].

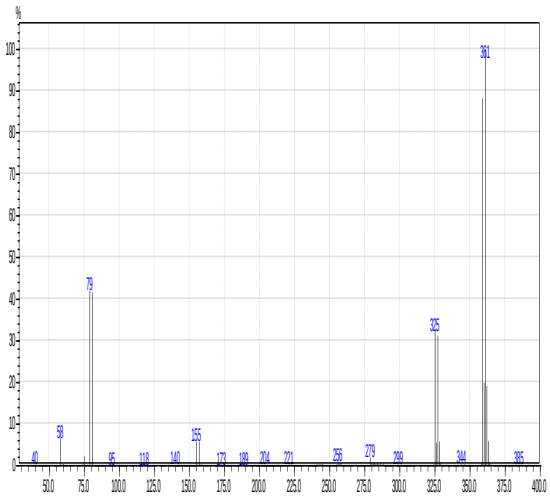


Figure 2. MS spectrum of ligand at 7 ev bombardment

The electron spray ionization mass spectra for zinc(II) complex was carried out at soft conditions at 10 electron volts to elucidate the proposed chemical structure of [$ZnLCl_2$] and to optimize the mole ratio 1:1 in complex. Figure (3) exhibits high resolution vicinal peaks at *m*/z=515.9 and *m*/z=515.9 which are consistent with isotopic effect of stable $Br^{+\cdot}$ with $C_{15}H_{14}BrCl_2N_3S_2Zn$ chemical formula. The variable peaks at around *m*/z=301.2 , *m*/z=265.9 and *m*/z=251.3 are already assigned to fragmentations of thiophene, 4-bromophenyl and chloride ions that is breaked out from the weak points of complex structure [9,10].

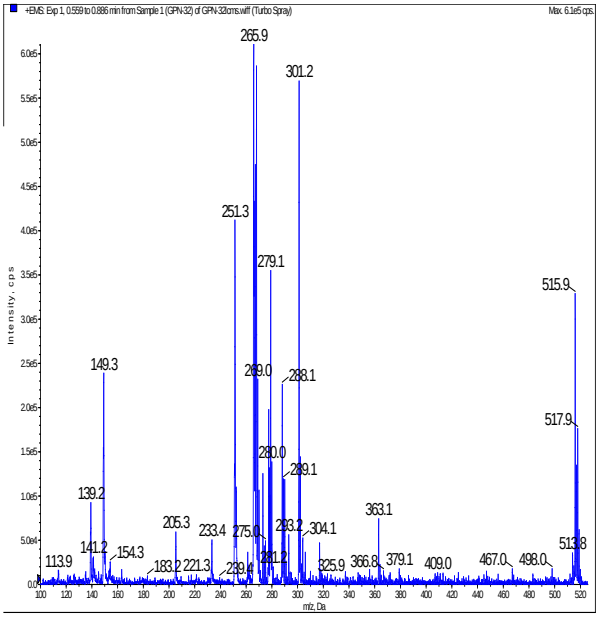


Figure 3. MS spectrum of CuL complex

3.3.NMR spectra:

The H NMR spectrum of the free ligand in d*6*-DMSO showed singlet peak at 8.75 ppm assigning to the nuclear spin of acidic –HN-C=S [10, 11] . The aromatic protons of thiophene and 4-bromophenyl rings were resonated at (6.5-7.75) ppm with arear under peaks equals to the seven protons and the doublet-doublet peaks at 7.25-7.74) ppm are attributed to spin-spin coupling of protons of 1,4-disubstituted aromatic ring. The strong evidence for ring closure of thiosemicarbazide with chalcone derivative is mainly cleared from showing new peaks at (3.65-4.25) ppm which are assigned to –CH-CH_2 of vicinal and germinal protons formed in the 2-pyrazoline ring [11,16, 17].

3.4. Infrared Spectra:

The main absorptions of FT-IR spectra of the prepared compounds are discussed in order to prove the ring closure of chalcone ά-β unsaturated carbonyl derivative (*E*)-1-(4-bromophenyl)-3-(thiophen-2-yl) prop-2-en-1-one with the thiosemicarbazide [15,18], Figure(4). The strong absorptions at around 1683, 1642 and 1594 cm^{-1} are consistent with carbonyl and –CH=CH- groups respectively. Figure(4) exhibits new bands at (3422-3251) , 1581 and 1065 cm^{-1} which are corresponded to asymmetric vibration of –NH_2 ,immine –C=N- moiety of 2-pyrazoline ring and thioamide one –C=S respectively. However the absorptions located at 811 and 671 cm^{-1} are assigned to bending of C-H aromatic and C-S of thiophene ring respectively [19, 20]. Up on coordination the metal ions under study with the 2-pyrazoline ligand, the active sites of thioamide –C=S and –C=N- were shifted to lower wavenumbers in the IR spectra of all complexes due to the donating the lone pairs to the empty orbitals of the metal ions and these changes were observed from the strong bands at around (1550-1530) cm^{-1} and (1035-1075) cm^{-1} of immine and thiocarbamoyl moieties [21] with formation five-membered chelate ring [23]. Furthermore, the new weak to medium bands at region (550-510) and (420-450) cm^{-1} are assigned to (M-N) and (M-S) coordination bonds [22]. The broadening bands at around (3400-3500) cm^{-1} beside medium bands at (1637-1622) and (890-855) cm^{-1} revealed the presence of coordination water molecules in the structure of CoL,NiL and CuL complexes [21, 22], Figures(5 & 6).

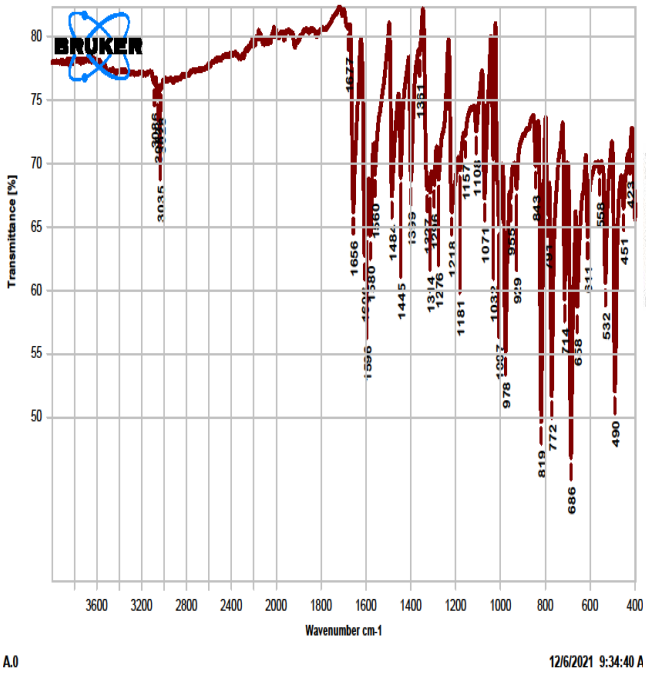


Figure 4. FT-IR spectrum of chalcone in KBr disc

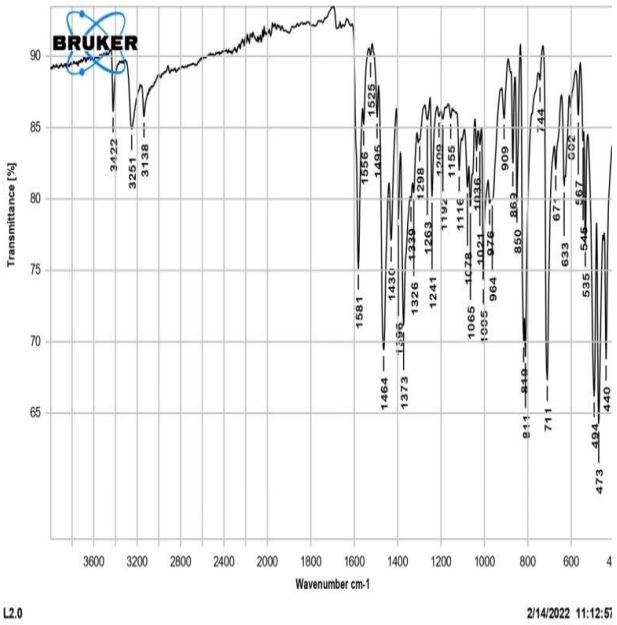


Figure 5. FT-IR spectrum of ligand (L) in KBr disc.

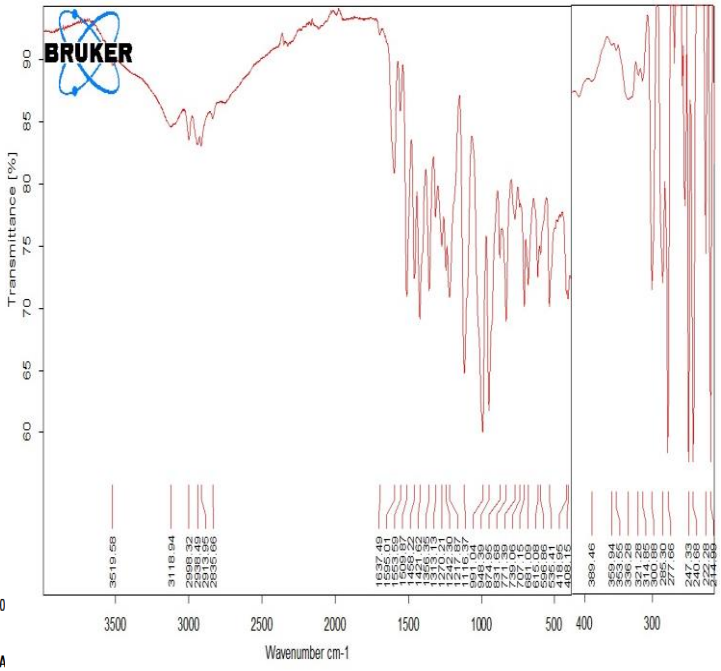


Figure 6. FT-IR spectrum of $[CuLCl_2(H_2O)_2].2H_2O$ complex

3.5. Electronic Spectra and Magnetic Susceptibility measurements:

The electronic spectra were recorded on spectrophotometer in the range (10,000-25,000) cm^{-1}. The cobalt (II) complex display three bands in the regions (12,000-29,000) cm^{-1} which may be assigned $^4T_1g(F) \rightarrow {}^4T_2g(F)$, $^4A_2g(F)$ and $^4T_1g(P)$ indicating the octahedral geometry [10,23].The proposed geometry is further confirmed by high magnetic moment value in the range 4.85 B.M. due to the spin-orbital coupling[20, 23]. The electronic spectra of NiL complex displays three bands in the region 16,400, 21,700 and 25,300 cm-1 which may be assigned $^3A_2g(F) \rightarrow {}^3T_2g(F) \rightarrow {}^3T_{12}g(F)$ and $^3T_1g(P)$ transitions respectively suggesting the octahedral environment around nickel(II) ion [24]. As well the magnetic moment of solid NiL at 300 K^0 temperature was 3.25 BM, Table(2) presents the magnetic moments of complexes at room temperature, and the observed value for the Ni(II) complex in 3.25 BM is consistent with the presence of two odd electrons in its outer shell, The olive solution of copper(II) complex in DMF showed two electronic spectral bands in the regions 13,400 and 28,600 cm^{-1} which may be assigned to the $^2Eg \rightarrow {}^2T_2g$ and LMCT transitions respectively confirming the distorted octahedral geometry which is further confirmed by the μ_{eff} in the range 1.82 B.M [15, 25].

Table 2.Distinct electronic bands λ(nm) in DMF and magnetic susceptibility of complexes

Compounds	Molar Conc.	Nmλ	ε_o L.mol^{-1} cm^{-} $_1$	Assignment	μeff(BM)
[L]	1x10^{-3}	325 270	1090 17800	$n\rightarrow\pi^*$ $\pi\rightarrow\pi^*$	-
[CoL]	2x10^{-4}	650 520 380 250	179 90 28200 20000	$^4T_1g_{(F)}\rightarrow {}^4T_2g_{(F)}$ $^4T_1g_{(F)} \rightarrow {}^4A_2g_{(F)}$ LMCT $\pi\rightarrow\pi^*$	4.85
[NiL]	1x10^{-4}	725 490 300 233	220 93 21900 18900	$^3A_2g \rightarrow {}^3T_2g$ $^3A_2g \rightarrow {}^3T_1g$ MLCT $\pi\rightarrow\pi^*$	3.25
[CuL]	2x10^{-3}	825 510 345	120 75 2700	$^2Eg \rightarrow {}^2T_2g$ LMCT $\pi\rightarrow\pi^*$	1.82
[ZnL]	2x10^{-3}	370 210	10500 18950	MLCT $\pi\rightarrow\pi^*$	0.00

3.6. Antimicrobial Activity:

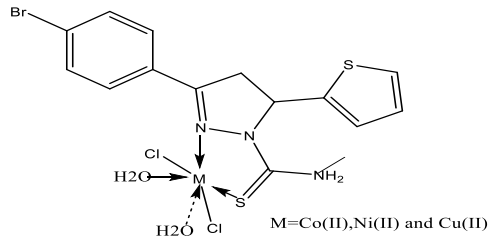
The obtained inhibition zones (mm) values of the ligand and its metal(II) complexes at 10 ppm concentration in DMSO solvent as blank solution are recorded by diffusion method [26, 27].The activity of precursor complexes is listed in parenthesis. Like their precursor complexes the antibacterial activity of ligand has been tested against two fungi, namely *Aspergillusnidulence* and *Candida albicance* and two bacteria namely *staphylococcus aureus* and *Escherichia coli*. The values suggest that all the metal complexes were more biologically active as compared to all the ligands [28]. Almost complexes solutions showed higher activities rather than the free ligand against bacteria whereas showed less inhibition toward the fungi organisms, these data approved the lipophilic penetration of neutral complexes across the layers of proteins wall of bacteria [26]. As well as these data will be encouraged in designing novel 2-pyrazoline complexes possessing active sites to manufacture excellent drugs against these types of micro-organisms [29, 30].

Table 3. Inhibition zones (mm) of ligand and its complexes at 10 ppm concentration

Compound	Bacteria		Fungi	
	S.aureus	*E.coli*	*A.nidulence*	*C.albicance*
L	22	15	5	12
[CoL]	33	45	13	18
[NiL]	35	37	10	10
[CuL]	37	42	17	12
[ZnL]	36	50	18	15

4.Conclusion:

According to the data obtained from elemental analyses, FT-IR spectra and magnetic moments, the octahedral environment was concluded around the cobalt(II), nickel(II) and copper(II) ions whereas the tetrahedral geometry was proposed for zinc(II) complex, Scheme(3).



Scheme3. Geometry of the prepared complexes

Furthermore, the biological activity of complexes solutions have been showed greater inhibition zones at optimized condition of 10 ppm in blank solution of DMOS. The active sites presence of thioamide and immine groups has assisted in penetration the selected solution s across the wall of bacteria rather then fungi according to the observed results from diffusion method.

5.Acknowledgement:

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6.Reference:

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