



Synthesis, Characterization and Biological Studies of Some Transition Metal Complexes with 5-(4- bromophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H- pyrazole-1-carbothioamide Ligand

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Authors' contributions

This work was carried out in collaboration between both authors. Author MNAA designed the study and wrote the protocol. Author GKN preformed the statistical analysis, managed the literature search and wrote the first draft of the manuscript with the help of co author GKN. Both authors read and approved the final manuscript.

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ABSTRACT

A 2-pyrazoline based bi dentate ligand 3-(2-thiophen-2-yl)-5-(4-bromophenyl)-1-carbothiomyl-2-pyrazoline has been synthesized by Claisen-Schmidt condensation of 2-acetylthiophene with 4-bromo benzaldehyde followed by cyclization of the resulting chalcone with thiosemicarbazide. The chromium(III), manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes of the new pyrazoline based-ligand were prepared by the direct reaction of their hydrated metal chlorides with the free ligand and separated in solid state. The metal complexes were characterized by (C.H.N.S) elemental analysis, FT-IR, UV-Vis, ¹H, ¹³C NMR and mass spectra. As well as the molar conductance measurements in DMSO solutions suggested non-electrolytic nature of all complexes except chromium(III) complexes which was electrolyte in 1:1 ratio supporting the proposed formula

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of the complexes $[ML_2Cl_2]$ M= Mn, Co, Ni, Cu, Zn(II) and $[CrL_2Cl_2]Cl$. The solution of ligand and its metal complexes were investigated for their ability to kill *Esherichia coli* and *Staphylococcus aureas* bacteria, *Candida albicans* and *Burkholderia cepacia* via diffusion method. It is found from biological results that the copper(II) and zinc(II) complexes showed high inhibition for bacteria growth with compared to the antibiotic drug. However, the free ligand in DMSO exhibited highest inhibition in 12 mm zone compared with its complexes. The resulted obtained showed that the Mn(II), Co(II), Cu(II) and Ni(II) complexes showed medium activity whereas the chromium(III) complex showed inhibition zone toward in the range (18-22) against *Esherichia coli* and *Burkholderia cepacia*.

Keywords: Metal complexes of 2-pyrazoline; biological study of 2-pyrazoline-based ligands; spectroscopic study of 2-pyrazoline complexes.

1. INTRODUCTION

Pyrazole and pyrazolines are well-known important heterocyclic bioorganic molecules [1,2]. The region selective preparation of 2-pyrazoline derivatives have been done by the reaction of substituted hydrazine with unsaturated ketones [3,4]. The 2-pyrazoline derivatives and their metal complexes have been exhibiting various pharmacological activities [5-7], antimicrobial [8,9], hypoglycemia [10], pesticide [11], antibacterial [12] and anticonvulsant activities [13,14]. The hemolysis assays and anticancer studies of copper(II), nickel(II) and iron(III) complexes with pyrazoline-based ligand has indicated quite good binding with DNA [15]. The copper(II) complexes of 1-phenyl-4,5-diacetyl-2-pyrazoline has attracted extensive attention due to their applications in the field of molecular biological technology and drug development [16]. The luminescence properties of aluminum(III) and copper(II) complexes with bi dentate pyrazoline ligand showed models in electronic sensors [17]. The presence of pyrazoline moiety besides other heterocyclic rings like benzothiazole and thiophene might have given industries wide applications in drug chemistry and light emitting diodes [18]. In the present work the metal complexes of chromium(III), manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) with bi dentate ligand of derived from ring closure of thiosemicarbazide with (Z)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one in methanol solvent were prepared, characterized and biologically screened against some negative and positive gram bacteria and *Candida albicans* fungus.

2. EXPERIMENTAL

2.1 Instrumentations

Melting points are determined in open capillary tubes in a Gallen Kamp MFB-600-Melting Point

apparatus and are uncorrected. The mass spectra of the organic compounds were carried out by using SHIMADZU GC- DIMS QP 2010 Ultra and Orbitrap LTQ XL- Thermo Fisher scientific mass spectrometer in the AL-Mustansiriyah University. Elemental analyses (CHNS) of the new ligand and its metal(II) complexes were determined using Carlo-Erba 1106 Elemental analyzer and Perkin-Elmer CHNS240 elemental analyzer at Al-Mustansiriya university, college of science, chemistry department and laboratories of ministry of science and technology respectively. The UV-Visible spectra of the compounds were measured in the region (200–1000) nm (concentration of each sample solution in $C=5 \times 10^{-5}$ M, path length= 1.0 cm) at room temperature by using (Varin Cary 100 Conc. UV-Vis) spectrophotometer. The 1H and ^{13}C NMR spectra were carried at Albait University, Jordan on Bruker 300 MHz spectrometer in DMSO- d_6 solvent. Infrared spectra were recorded using a SHIMADZU FT-IR 8400S in the range (4000–600) cm^{-1} . The molar conductivity ($S \cdot cm^2 \cdot mol^{-1}$) of the complexes solution were recorded at 25°C for (1×10^{-3} M) solution of dimethylsulfoxide (DMSO) using a (WTW 740) terminal conduct meter. The percent of metal contents of the complexes were determined by the Analytik Jena / A Spect LS /FL 1.3.0.0, Abn Sina Center, Ministry of Industry.

2.2 Materials

The hydrated metal chlorides $CrCl_3 \cdot 6H_2O$, $MnCl_2 \cdot 4H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$ and $ZnCl_2$ were supplied from Sigma-Aldrich company and used without purification. The 2-acetyl-thiophene and 4-bromobenzaldehyde were supported by Sigma-Aldrich Company (99% purity). The other organic starting materials were supplied from Sigma-Aldrich company and used without purification.

2.3 Methods

2.3.1 Synthesis of (Z)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one

A considerable variety of methods are available in literature for the synthesis of chalcones. The most convenient method is the one, that involves the Claisen-Schmidt condensation of equimolar quantities of an aryl methyl ketones with arylaldehyde in presence of alcoholic alkali. A mixture of 2-acetyl thiophene (0.01 mol) 1.26 gm and the corresponding 4-bromobenzaldehyde (0.01 mol) 1.85 gm was dissolved in 20 ml ethanol. Then, an ethanolic solution of sodium hydroxide (0.025 mol, 20 ml) was added drop wise to the reaction mixture during a period of 0.5 h with vigorous stirring. The mixture was stirred vigorously for further 24 h until the mixture became thick. The product was filtered under vacuum, washed with ice water until the filtrate be neutral to litmus, washed several times with n-hexane to remove the un reacted materials and finally re crystallized from ethanol. The physical properties of chalcone (A), (Scheme 1).

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

A mixture of (0.01 mole, 2.29 gm) of (Z)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one and thiosemicarbazide (0.012 mole, 0.94 gm) with sodium hydroxide (1 g in 5 ml, water) was refluxed in 50 ml absolute ethanol for 12 hours. The product was poured into ice water and the crude product, which was separated out(L), was filtered and re crystallized from methanol then dried in *vacuum* desiccators. The physical properties and elemental analyses of ligand were shown in Table 1.

2.4 Synthesis of the Metal Complexes

A methanolic solution (100 mL) of (1 mmole) from hydrated metal chloride ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.237 g), ZnCl_2 (0.135 g), $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.233 g), $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.171 g) and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.322 g)) was added with constant stirring to an ethanolic solution of the ligand (0.365 g, 2 mmol) followed refluxing the mixture on water bath for 1.5 hours except the manganese(II) and zinc(II) which required stirring on water bath for 2-3 h. then keep the mixture in ice bath with stirring to yield colored precipitates of complexes. The

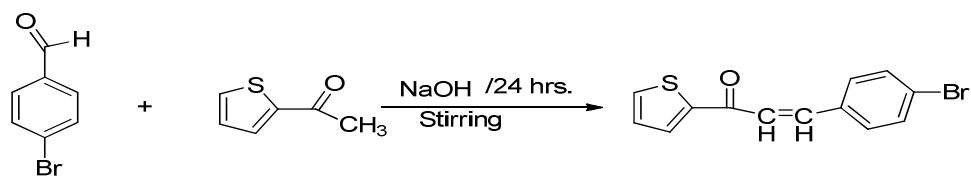
obtained crudes were separated by filtration under suction, washed with methanol and dried in air overnight then re crystallization from mixture of acetonitrile: absolute ethanol to get purified colored solids, Table 1.

2.5 Biological Activity

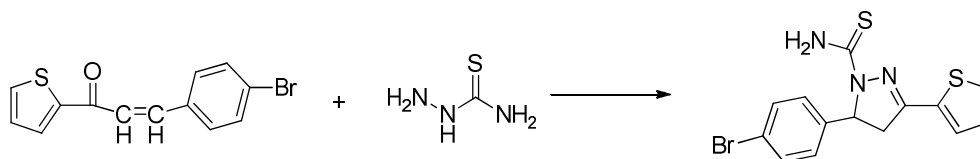
Four kinds of bacteria were used as Gram-negative bacteria *Escherichia coli* and *Bacillus subtilis* and Gram-positive bacteria (*Staphylococcus aureus* (Staph) and *Burkholderia cepacia*. These bacteria were diagnosed and cultured on Eosin methylene blue (EMB) and Mueller-Hinton agar medium for use in this experiment, and in measuring the deactivating capacity of the prepared compounds. The deactivating capacity agent of the isolated bacteria of these compounds was tested by using the holes method. In this method the holes were saturated with 100 μm of $1 \times 10^{-3}\text{M}$ of the given compound and left for about 15 min in order to spread on the medium then incubated at 25°C for 24 hour. The deactivation diameters were measured by special ruler designed for this purpose. Testing was done in the seeded broth (10^{-6} to 10^{-7} cfa/ml). The test complexes were taken at 20 $\mu\text{g/ml}$ and the standard solution of chloromiphenical drug prepared at 20 $\mu\text{g/ml}$ of sterile distilled water and DMSO were maintained throughout the experiment simultaneously as control.

3. RESULTS AND DISCUSSION

The new metal complexes prepared in this research were non-hygroscopic (stable at the room temperature) and in the form of amorphous solids. These are soluble easily in DMSO, DMF and sparingly in ethanol and methanol whereas they are insoluble in chlorinated hydrocarbons. The elemental analysis data of the ligand and its metal complexes along with molar conductivity values are shown in Table 1. In this study, the chalcone (Z)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one. was synthesized by literature methods as described [14] and treated with thiosemicarbazide to obtain 5-(4-bromophenyl)-3-(2-thienyl)-2-pyrazolines, (Scheme 2). This reaction probably involved in the intermediate formation of thiosemicarbazone and subsequent addition of N-H on the olefinic bond of the propenone moiety. Condensation of chalcone with thiosemicarbazide can lead to the free ligand of pyrazoline, Scheme (3).



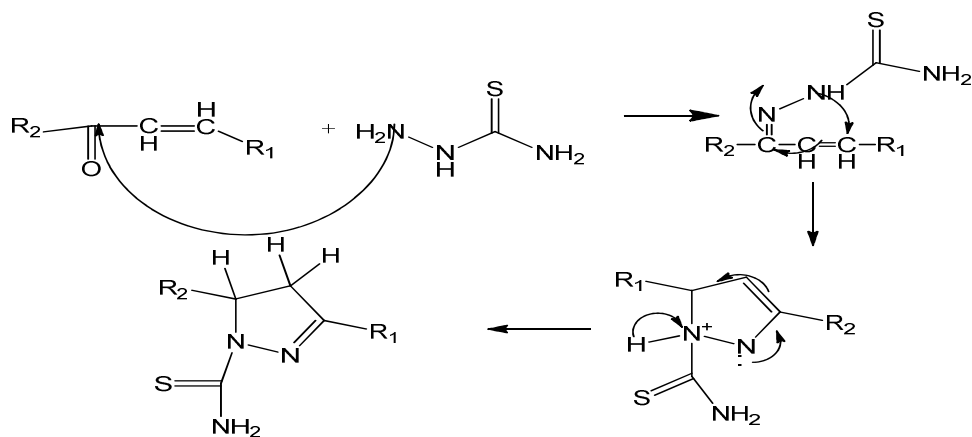
Scheme 1. Synthesis of chalcone [A] derivative



Scheme 2. Synthesis of ligand L

Table 1. Some physical properties and elemental analyses of the ligand and its complexes

Molecular formula	Color	M.P (°C)	Yeild (%)	Elemental analysis (%)				
				Found (calc.)				
				C	H	N	S	M
L	Cream	205-207	70	(45.91)	(3.33)	(11.47)	(17.55)	
				44.98	3.00	10.66	16.84	
[CrL ₂ Cl ₂]Cl	Deep Green	> 253	72	(52.91)	(3.20)	(10.15)	(7.75)	(6.35)
				51.98	2.05	11.09	6.79	5.22
[MnL ₂ Cl ₂]	Brown	272 (dec)	68	-	-	-	-	(6.70)
								6.01
[CoL ₂ Cl ₂]	Greenish-blue	245	80	-	-	-	-	(7.12)
								6.988
[NiL ₂ Cl ₂]	Green	220	89	-	-	-	-	(6.88)
								6.22
[CuL ₂ Cl ₂]	Green	265	80	-	-	-	-	(7.50)
								6.66
[ZnL ₂ Cl ₂]	Off white	225	72	-	-	-	-	(7.62)
								7.11



R1=4-bromophenyl and R2=2-thienyl

Scheme 3. Proposed mechanism of Pyrazoline ligand formation

3.1 IR Spectra Studies

Selected diagnostic bands of the IR spectra of the cyclised pyrazoline analogues of thiosemicarbazones showed useful information about the structure of the compounds. The free ligand (Z)-3-(4bromophenyl)-1-(thiophen-2-yl)-prop-2-en-1-one showed intense bands in the region 1093cm^{-1} due to the $\nu(\text{C}=\text{S})$ stretch of the thiocarboxamide group [2,15]. The IR spectra of the ligand showed $\nu(\text{C}=\text{N})$ stretch at 1616cm^{-1} because of the ring closure. In addition, the absorption bands at $1003\text{--}1424\text{cm}^{-1}$ were attributed to the $\nu(\text{N}=\text{C}=\text{S})$ stretch vibrations, which also confirm the formation of desired pyrazoline ring in all the compounds. The ligand also showed additional sharp bands in the region 3383cm^{-1} due to the $\nu(\text{NH})$ stretching [14,15]. As

well as the medium intensity band at 619cm^{-1} reveals the C-S bond of thiophene ring [3,16]. The lowering in wave numbers of $\nu(\text{C}=\text{S})$ and $\nu(\text{C}=\text{N}-\text{Pz})$ in all complexes in the region $1040\text{--}1184$ and $1610\text{--}1583\text{cm}^{-1}$ confirms the coordination of thioamide sulphur and nitrogen of pyrazoline moiety with the metal ion [17]. Moreover, (N-C=S) undergoes strong vibrational coupling and exhibits two to three bands around 1005 , 1190 and 1424cm^{-1} respectively, whereas the IR spectra of all complexes reveal slight but specific changes from the spectrum of the free ligand. Furthermore, the spectra of all complexes showed weak to medium absorptions around $400\text{--}460$ and $490\text{--}577\text{cm}^{-1}$ which are attributed to the vibrations of M-S and M-N respectively [16-18].

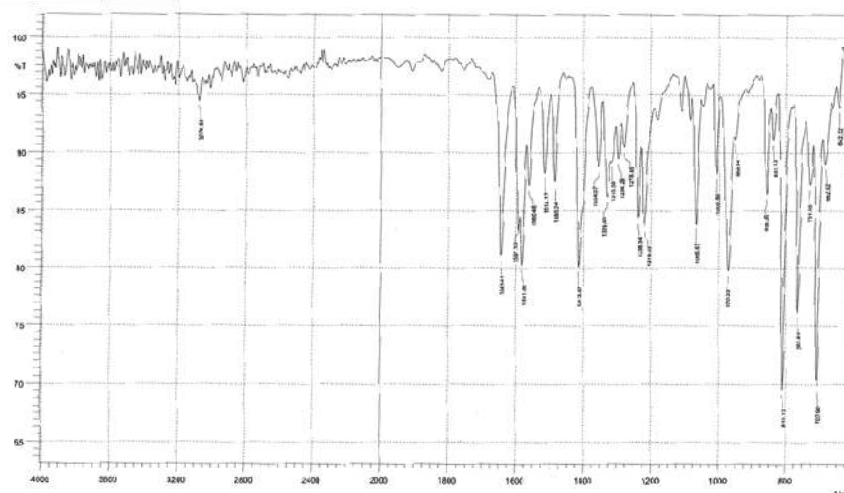


Fig. 1. FT-IR spectra of chalcone in KBr disc

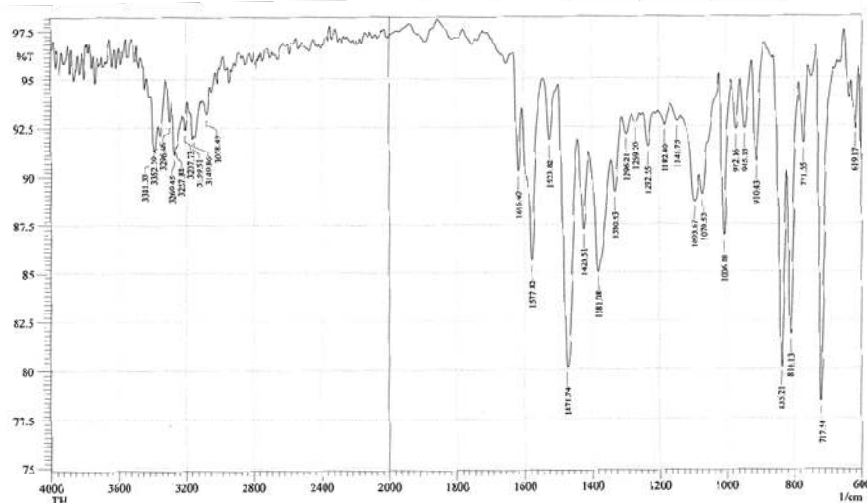


Fig. 2. FT-IR spectra of ligand in KBr disc

Table 2. FT-IR absorptions of the pyrazoline L ligand and its metal complexes in cm^{-1}

Compound	νNH_2	$\nu\text{C=S}$	$\nu\text{C=N}$	$\nu\text{N-C=S}$	$\nu\text{C-N}$	$\nu\text{M-N}$	$\nu\text{M-S}$	$\nu\text{C-H}$
L	3383(br)	1093(d)	1616 (s)	1003,1420(m)	1330(s)	-	-	3070(w), 2965
[CrLCl ₂]Cl	3450(m)	1075	1595(s)	1006, 1424(m)	1340(s)	550(w)	410(w)	3050,2978(m) 3100(w)
[MnL ₂ Cl ₂]	3400(br)	1060 (s)	1590 (s)	1005, 1433	1370(s)	510(w)	460(w)	3040(w)
[CoL ₂ Cl ₂]	3384-3267(m)	1040(m)	1610-1583	1003,1473(m)	1390(m)	573(w)	451(w)	3082(w)
[NiL ₂ Cl ₂]	3381-3263(d)	1184(d)	1610-1587 (d)	1007,1469	1377(m)	577(m)	455(w)	3074(w)
[CuL ₂ Cl ₂]	3460(br)	1070(m)	1587 (s)	1003, 1425	1377 (m)	499(m)	424(m)	3089(w)
[ZnL ₂ Cl ₂]	3519(br)	1059(m)	1600-1588 (d)	1005,1437	1375(m)	500(w)	400(m)	3012(w)

* s = strong, m = medium, br = broad, w = weak

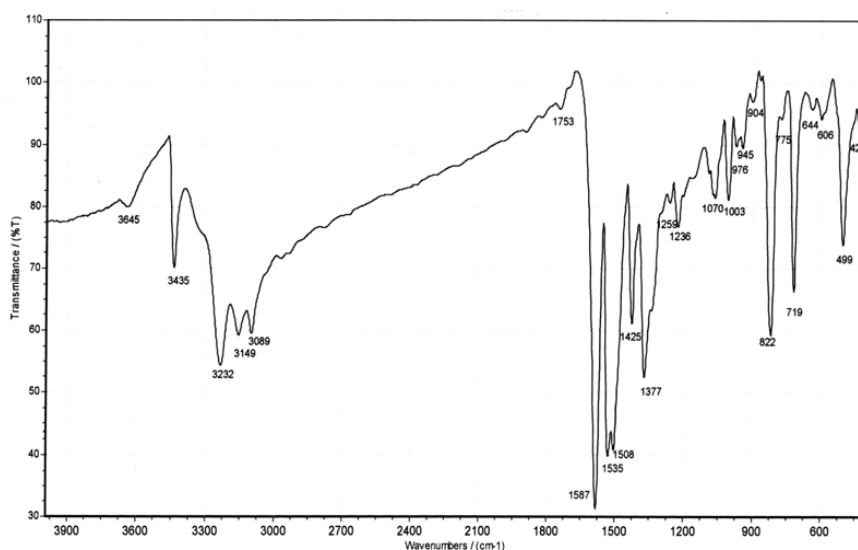


Fig. 3. FT-IR spectra of $[CuL_2Cl_2]$ in CsI disc

3.2 Mass Spectra Study

The mass spectra of compounds showed $[M^{+1}]$ peaks, in agreement with their molecular formula. The Fig. 4 shows the molecular ion $M^+=292$ and 294 which is remarkably investigate the proposed structure of compound (Z)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one

with $C_{13}H_9OSBr$ formula [13]. The Fig. 5 exhibits the molecular ion related to free ligand L that is remarkably observed from the base peak at $M^{+2} = 367$ and 365 which gives strong evidence for isotopic effect of Br substituted in para position of phenyl ring. The other fragments at 333, 332 and 285 may be assigned to cleavage of H_2S gas and $H_2N-C=S$ moiety respectively [18].

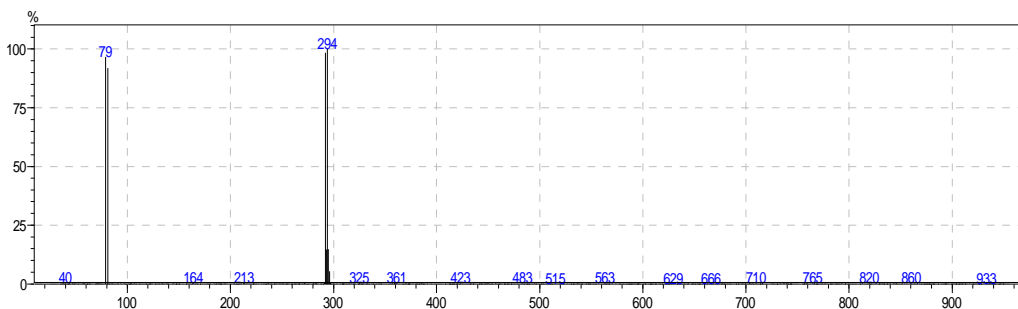


Fig. 4. Mass spectra of A chalcone

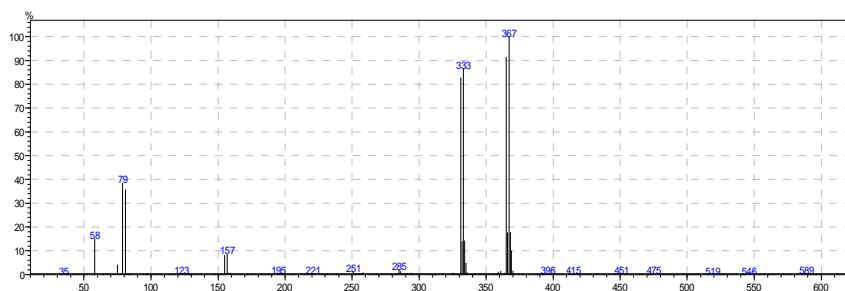


Fig. 5. Mass spectra of the ligand (L)

3.3 Electronic Spectra and Magnetic Moments

The electronic spectral data of the metal complexes in DMSO solution are given in Table 3. The nature of the ligand field around the metal ion has been deduced from the electronic spectra. The UV-Vis spectrum of the ligand in DMF within the range 200-1000 nm, Fig. 6, displays mainly three peaks. These transitions at 250,308,418 nm could be ascribed to the moderate energy $\pi \rightarrow \pi^*$ transition of the aromatic rings. Furthermore, the sharp (λ_{max}) peaks at (308,418 nm) were related to the $\pi \rightarrow \pi^*$ transition of intermolecular charge-transfer taken place through the azo group (-C=N-, -C=C and -C=O) [10,16]. The UV-visible spectra of zinc(II) and cadmium complexes showed high-handed mark absorptions in the regions 240-390 and 322-470 nm, these may be part to LMCT of L→Cd and to zinc(II) respectively [16,17]. The electronic spectra of nickel(II) in DMF solution exhibited spin-allowed d-d transitions at 615 and

740nm which are assigned to the ${}^3A_{2g} \rightarrow {}^3T_{2g}$ and ${}^3A_{2g} \rightarrow {}^3T_{1g}$ transitions respectively, suggesting the octahedral geometry around nickel(II) ion [19,20]. At the comparable in like manner, the electronic spectra of cobalt(II) and copper(II) complexes in DMF solvent, the bands showed in the visible region 426-400 and 480-562 nm are assigned to ${}^3T_{1g} \rightarrow {}^3T_{2g}(F)$, ${}^3T_{1g} \rightarrow {}^3A_{2g}(F)$ and ${}^2E_g \rightarrow {}^2T_{2g}$ respectively [21,22]. As well as the green solution of chromium(III) complex in DMF exhibited three spin-allowed transitions at 565,400 and 380 nm which are corresponded to ${}^4A_{2g} \rightarrow {}^4T_{2g}$, ${}^4A_{2g} \rightarrow {}^4T_{1g}(F)$ and LMCT respectively [21], these transitions agree well with the expected spectra of octahedral structure of Cr(III) complex. The magnetic moment data are summarized in Table 3. The effective magnetic moment values for these compounds range from 2.80 to 6.0 BM, clearly indicating that these Cr(III), Mn(II), Co(II), Ni(II), and Cu(II) complexes are high-spin paramagnetic and gives strong proof for their monomer octahedral geometry [23,24].

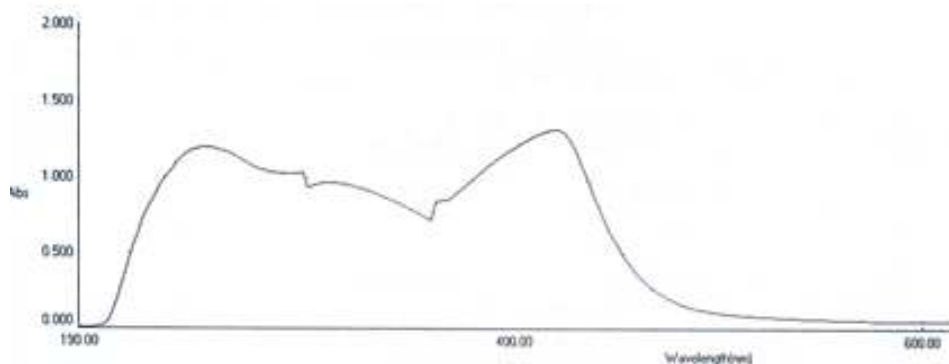


Fig. 6. UV-Visible spectra of ligand in ethanol solution

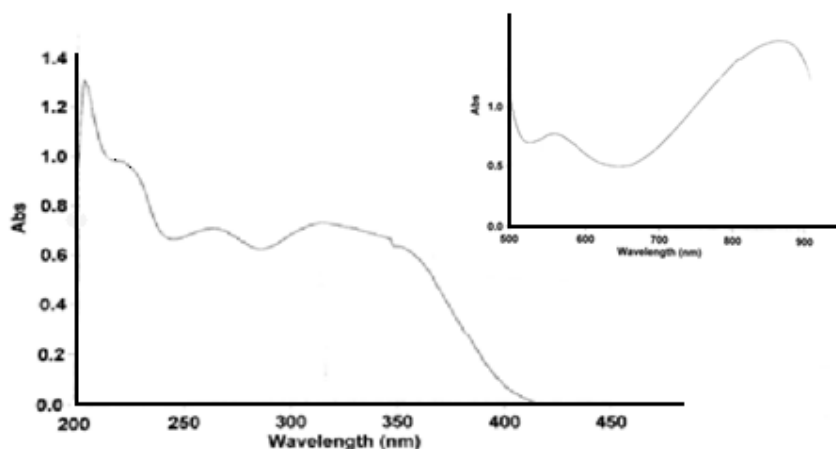


Fig. 7. UV-Visible spectra of $[CuL_2Cl_2]$ in DMSO solution

3.4 ¹H NMR Study

The Fig. 7 shows the proton and C-13 NMR spectra of the chalcone derivative (A) in DMSO-d₆ solution. The geminal coupling –HC=CH– of alpha-beta carbonyl compounds fall in the range 8.1-8.50 ppm. As well as the aromatic protons were shown as doublet-doublet in the region 7.20-7.45 ppm, whereas the multiplet peak at 7.75-7.76 ppm may be attributed to 3H of thiophene moiety [12,17]. Furthermore the resonance spin of C-13 for the chalcone derivative displayed peaks at 181,171,145,141,135,134,131,130,128, 123,122 and 74 ppm which are consistent with the chemical shifts of –C=O,CH=CH-,aromatic C=C- and –C-S of thiophene ring. The ¹H NMR spectra was recorded using d₆-DMSO as the

solvent clearly supports the proposed structure of the new pyrazoline ligand. The protons at C4 and C5 carbons appeared as broad triplets at 3.88 and 5.66 ppm, respectively. The strong deshielding of the C5 protons compared with the C4 protons of the pyrazoline ring can be assumed due to its conformation. The NH proton of thiocarboxamide group(H₂N-C=S) bonded directly to N1 of pyrazoline ring showed a singlet at 8.45 ppm [9,11]. The protons belonging to the phenyl ring and the other C-H of thiophene ring were observed with the expected chemical shift and integral values. The ¹³C NMR spectra of the compound L was taken in DMSO-d₆ and the signals obtained are in good agreement with the proposed structures.

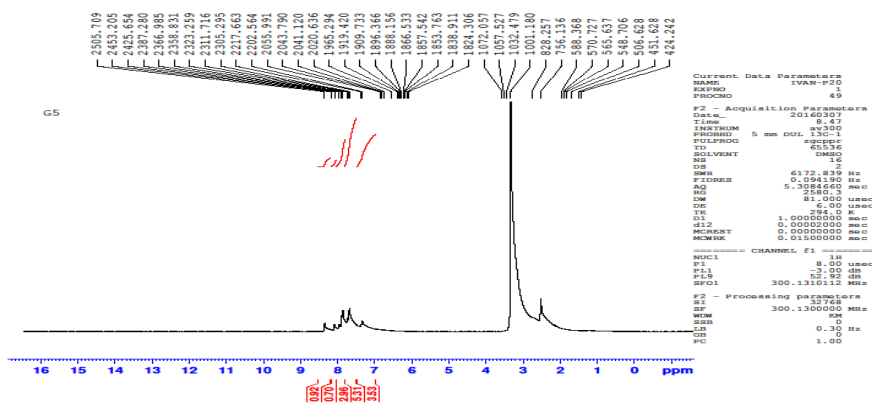


Fig. 8. ¹H NMR A compound chalcone in d₆-DMSO solution

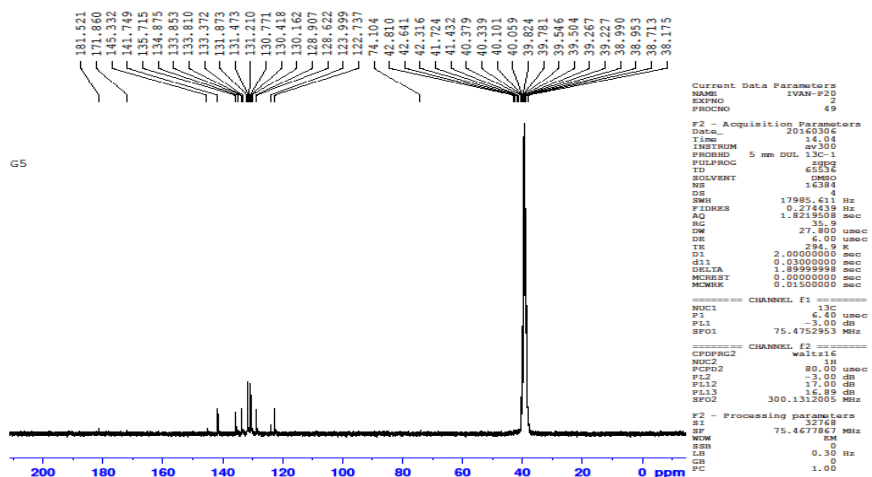


Fig. 9. ¹³C NMR spectra of A compound chalcone in d₆-DMSO solution

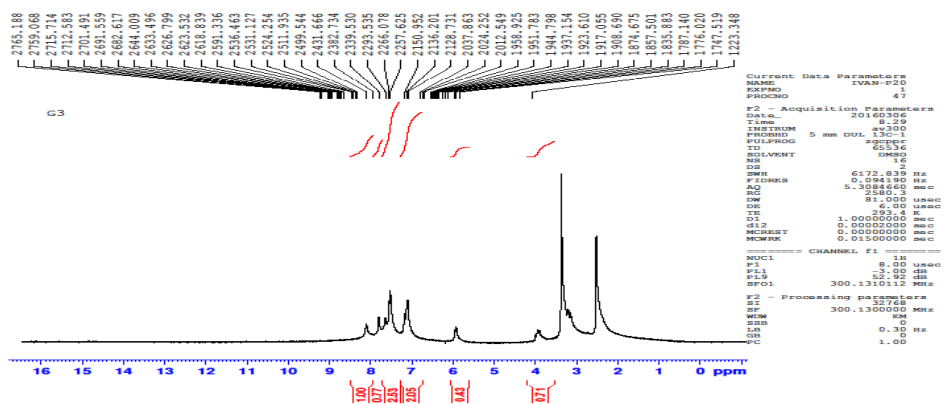


Fig. 10. ¹H NMR spectra of L in DMSO-d₆ solution

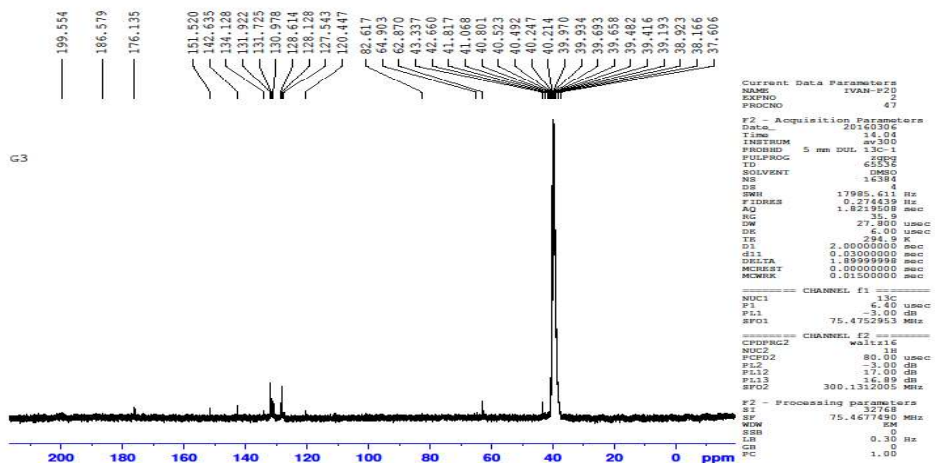


Fig. 11. ¹³C NMR spectra of L in DMSO-d₆ solution

Table 3. The electronic spectra and molar conductance of the prepared complexes

Compound	UV-visible, λ (nm)	μ (BM)	Λ _m (S.mol ⁻¹ .cm ²) *	Geometry
L	250,308,418	-	5	-
[CrLCl ₂]Cl	255,332,380,562	3.80	80	-
[MnL ₂ Cl ₂]	300, 498,509	6.0	20	Octahedral
[CoL ₂ Cl ₂]	259,598,675	5.02	26	Octahedral
[NiL ₂ Cl ₂]	328,615,740	3.34	13	Octahedral
[CuL ₂ Cl ₂]	315,562,873	2.80	28	Octahedral
[ZnL ₂ Cl ₂].H ₂ O	259,345(CT)	0.00	17	Octahedral

*Λ_m = molar conductance was measured in DMF solutions

3.5 Biological Activity

Table 4 listed the deactivation capacity against the bacteria specimen of the prepared compounds under study. The results of the

present study show that the complexes have a relatively moderate inhibition against the *staphylococcus aureus*, *E. coli* and *Bacillus* bacteria, while copper(II) and zinc(II) complexes exhibited the highest inhibition zones

in the range (22-30 mm) against *Burkholderia cepacia* in compared with Fluconazole drug [25]. However, introduction of metal in complexes increase the deactivating capacity of the ligand.

Table 4. Diameters inhibition zone (mm) of the prepared compounds against bacteria and fungi

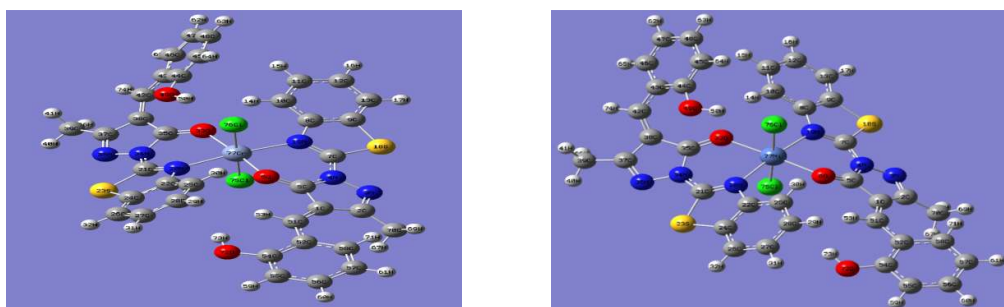
Compound	<i>Candida albicans</i>	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Esherichia coli</i>	<i>Burkholderia cepacia</i>
L	12	-	-	5	6
[CrL ₂ Cl ₂]Cl	-	22	20	20	18
[MnL ₂ Cl ₂]	5	6	10	15	8
[CoL ₂ Cl ₂]	3	-	-	-	12
[NiL ₂ Cl ₂]	1	10	7	10	15
[CuL ₂ Cl ₂]	4	27	17	13	30
[ZnL ₂ Cl ₂]	2	-	-	11	22
Control	-	-	-	-	-
Chlormphenicol	-	28	30	25	15
Flucanazole	80	-	-	-	-



Fig. 12. Inhibition zone of complexes against *Staph. aureus* and *B. capacia*



Fig. 13. Inhibition zone of complexes against *Candida albicans*



Scheme 3. 3D-optimized structure of the prepared complexes

The inhibition zone (mm) for all solutions were recorded as minimum inhibition concentration (MIC) so the values are generally within the range 10-20 ppm against all evaluated strains. The antifungal activity of the ligand and its metal complexes was studied with one pathogenic fungi. The results obtained in Table 4, showed that the ligand in DMSO solution showed inhibition for growing the *Candida albicans* at 12 mm value whereas its complexes could not give any activity in comparing with *Chloromphenicol* drug [26].

4. CONCLUSIONS

According to the results obtained from elemental analyses, NMR, Mass, IR and UV-Visible spectra, the complexes of manganese, cobalt, nickel(II), copper(II), zinc(II) and chromium(III) with the new pyrazoline based-ligand were octahedral in $[MLCl_2]$ formula. The vibration frequencies of the metal complexes were compared with the IR spectra of the free L ligand and it is found that L behaved as neutral bidentate Lewis base via nitrogen of pyrazoline ring besides the sulphur atom of thione moiety. The solutions of L and its complexes in DMSO were screened their biological activity against some bacteria and *Candida albicans* fungus and it is found that the complexes of copper(II) and zinc(II) have greater activity than the free ligand due to the lipophilicity of their structure which make them more penetrate to cell wall of these bacteria. However the free ligand showed good inhibition zone against the *Candida albicans* verse no activity of the complexes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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