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Synthesis, Characterization and Antifungal Studies of Transition Metal Complexes of Dimethylketone Thiosemicarba zone with 1, 10-Phenanthroline

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Abstract: Dimethylketone thiosemicarbazones (DMKT);a Schiff base ligand was synthesized by simple condensation reaction between propan-2-one and thiosemicarbazide, the reaction was carried out in the presence of hydrochloricacid. 1,10-phenanthroline (phen) was introduced as a second ligand and the basic coordination chemistry of the mixed ligand with copper(II), zinc(II) andiron(III) were explored. The derivatised DMKT alongside the mixed ligand metal complexes were characterized by Elemental Analysis (EA)and various spectroscopic techniques such as Fourier Transform Infrared (FT-IR), UV/visible and Nuclear Magnetic Resonance (^{1}H-NMR).They were also screened for their antifungal activities against four pathogenic fungi: *Aspergillusniger, Penicillium species*, *Rhizopus* and *Candida albicans* using disc diffusion method. The antifungal studies of the present complexes show that they are good antifungal agents.

Keywords: Dimethylketone, Thiosemicarbazones, 1,10-phenanthroline,Synthesis, Spectroscopy, Pathogenic fungi

1 Introduction

The rapid increase in the number of multidrug-resistant bacteria is fast becoming a global concern. Thus; the discovery of novel active compounds against new targets is a matter of urgency. This problem has magnetized attention of the scientific community in general to consider and investigate transition metal complexes as alternative. Metal based drugs represent a novel group of antifungal agents with potential applications for the control of fungal infections [1].

The chemistry of thiosemicarbazone has received considerable attention because of their variable bonding modes, promising biological implications, structural diversity and ion–sensing ability. Thiosemicarbazones are a wide group of organic derivatives whose biological activities are a function of the parent aldehyde or ketone and of the coordination metal type.These sulphur-containing organic substances exhibit an interesting biological activity, which has been studied for more than fifty years [2-9]. Thiosemicarbazones are biologically active pharmacophores, besides having good complexing ability and their activity enhances on complexation with metal ions [10-13].

The depro metallo-enzymes. tonated thiosemicarbazon eligands usually coordinate to transition metals like platinum, palladium, copper, ruthenium, and osmium through oxygen, nitrogen, and sulphur donor atoms in their (N, S) bidentate form or (N, N, S or O, N, S) tridentate form, to form metallic complexes of different molecular geometry [14-16]. Thiosemicarbazone metal chelates have broad applications in biological and industrial fields and their metal chelates find important applications in the fields like pharmacology as well as medicine [17-18].

On the other hand, derivatives of 1, 10-phenanthroline are very important ligands in organ metallic chemistry, systematic studies of substituted derivatives of1, 10-phenanthroline have been successfully undertaken.1, 10-phenanthroline as well as some of its derived complexes do exhibit antimicrobial properties.1, 10-phenanthroline has a rigid framework and possesses a superb ability to chelate many metal ions via its two nitrogen centers. The resulting complexes show potential for various applications due to their high charge transfer mobility, among other attractive properties [19].Mixed ligand complexes with metal ion bound to two different and biochemically important ligands have aroused interest as model for metallo-enzymes. Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic

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complexes.

2 Experimental

2.1 Materials and Methods

Analytical grade chemicals and solvent were used in this study. Thiosemicarbazideand 1, 10-phenanthrolineare both products of Sigma Aldrich. The metal salts used for the synthesis were obtained from British Drug House (BDH). Other reagents and solvents like methanol, ethanol, acetone, chloroform, dichloromethane, dimethylsulphoxide (DMSO) and concentrated hydrochloric acid were all products of BDH and used without purification. The mixed ligand complexes were synthesized using standard procedure. Melting points of the ligand and metal complexes were determined using Optimelt Automated melting point System. The conductivity measurements were taken using Jenway 4510 Conductivity Meter. The CHN Elemental Analysis was done using Thermo Flash 1112 CHNSO Elemental Analyzer. Electronic spectra of the ligand and the complexes were recorded in Dimethylsuphoxide (DMSO) solution on Shimadzu 10UV scanning Uv-Visible spectrophotometer in the range 200 – 800 nm. The infrared (IR) spectra were recorded on Shimadzu 8400S FTIR spectrophotometer as KBr pellets in the range 4000 – 400 cm^{-1}.

2.2 Inorganic Synthesis

2.2.1 Synthesis of DMKT

Thiosemicarbazide (0.01 mol 0.182 g) was dissolved in ethanol (30 ml) by refluxing at 50 °C.In the refluxing solution; dimethylketonein (30 ml) ethanol was added, this was then followed by the addition of few drops of concentrated HCl. The reaction mixture was continuously stirred and refluxed for 4 h at 60 °C. The volume of reaction mixture was reduced and then cooled on ice water. The crystals of DMKT precipitated out. The crystals was washed with ethanol and dried in the desiccator over silica gel [20-23].

2.2.2 Synthesis of Mixed Ligand Complexes of DMKT with phen

To refluxing 2 mmol (0.27 g) in 30 ml methanolic solution of dimethylketone thiosemicarbazone, 1 mmol of the corresponding metal salts in 15 ml methanolic solution was added slowly in the molar ratio of 2:1. The reacting mixture was continuously stirred and refluxed for 30 minutes and the reaction mixture precipitated. Subsequently, 2 mmolmethanolic solution of 1, 10-phenanthrolinewas then added slowly to the refluxing mixture. On addition of the methanolic solution, the reaction mixture became clear and was continuously stirred and refluxed for another 3 h at 60 °C. The resultingsolution was concentrated by evaporation and left overnight in refrigerator.Complexes which separated out were collected by filtration, washed with distilled water and cold methanol then dried over silica gel in a desiccator [24-25].

2.3 Antifungal Activity Test

The antimicrobial activities of the compounds were screened by adapted qualitative diffuse metric methods (i.e. distribution of the tested solutions on filter paper discs, or in spots on solid media that have been inoculated with test microbial strains). Media plates of sensitivity test agar (STA) were prepared and inoculated from overnight slant cultures of the test organisms and spread as uniformly as possible throughout the entire media. Discs impregnated with 60 µg/ml solution of the antimicrobial sample were then placed on the inoculums media. Blank paper discs of dimethylsulphoxide were used as control. The plates were filed with the SDA agar (two-thirds) and the fungi specie inoculated into it and the sample solutions added as in the antibacterial sensitivity test above except that the inoculated plates were incubated at 37 ^{o}C for 72 hours. The activities of the compounds were represented by size of the diameter in mm, this size also known as inhibition zones were measured using the zone reader. In all experiments, results were recorded in triplicate and mean of each triplicate were calculated [26].

2.4 Statistical Analysis

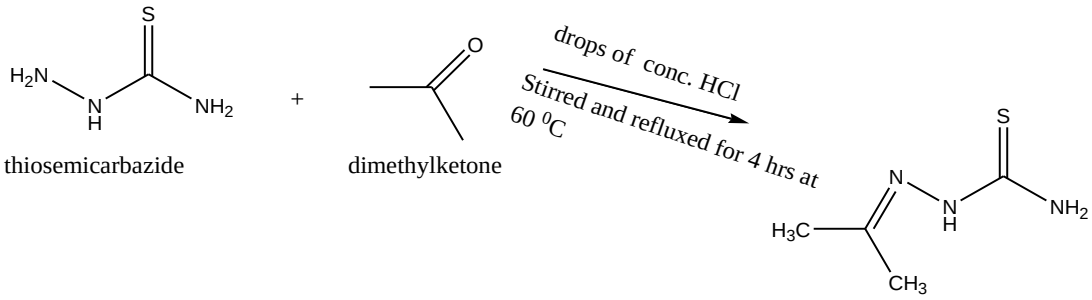
Data are expressed as the mean of three replicates ± standard deviation, means were analyzed using One Way Analysis of Variance (ANOVA) Posthoc(Turkey), $P<0.05$ were considered as statistically significant. Descriptive statistics (Frequency count, simple percentage) was also used. All statistical analysis was done using Statistical Package for Social Science (SPSS) version 16.

3 Results and Discussion

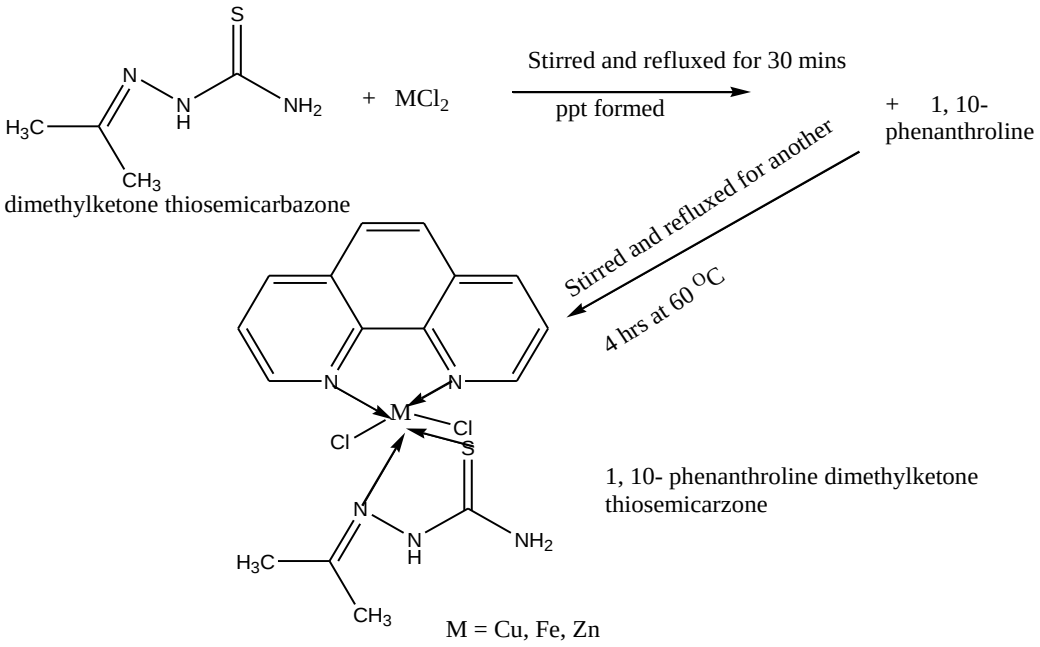
3.1 Physical Characteristics of Mixed Ligand Complexes of DMKT with phen

The colour exhibited by the metal complexes in Table 1 may be due to d-d electron transition or as a result of electron transfer (lone pair) from the ligand to the central metal [27-28]. The higher melting point of the complexes observed when compared with the ligand could be attributed to the increase in molecular mass of the resulting complexes, enhanced stronger lattice structure and stronger interaction which accompanied the coordination of the ligand to the central metal ions in the complexes.

The molar conductance measurements of the complexes in DMSO determine the non-electrolytes and electrolytes nature of the complexes based on their molar conductance



Scheme 1: Synthetic Preparation of DMKT



Scheme 2: Synthetic Preparation of Mixed Ligand Complexes of DMKT with phen.

value, higher value indicates the electrolytes nature of the complexes while lower values are attributed to non-electrolytes nature. The molar conductance values of the complexes fall in the range 9 to 21 $\Omega^{-1}cm^2\ mol^{-1}$ indicating that they are non-electrolytes. The higher conductivity observed in the complexes as compared to the ligand is also another indication of complex formation between the ligand and the respective metal ions. The results of partial elemental analysis are in good agreement with assigned formulations [27-28].

3.2 Electronic Spectra (cm^{-1}) of Mixed Ligand Complexes of DMKT with phen

Generally, upon complexation some changes in the UV-Vis spectra can be noticed in the ligand bands arising from the donor groups which are involved in bonding to the metal. The colour of transition metal compounds results from d-orbital splitting. As a consequence, the metal complexes absorb visible light and thus are colored. The shift in these bands to visible region may be attributed to complexation [29-30].

Fe(III) has a d^5 configuration like Mn(II) and as such; series of weak transitions are expected. The electronic spectrum of Fe(DMKT) (phen) Cl_2in Table 2 showed bands in the visible region. The broad band's shown at 50251, 48076 and 44843- 46082 cm^{-1} are assigned π -π* transition and n→π* transitions bands at 33003; 19047; 33112 and 27397cm^{-1}. The d-d bands were observed in the range 14,992-14,047cm^{-1} assigned to the transition$^6A_{1g}\rightarrow{}^4T_{1g}(G)$ [31-33]. This shows a square planer structure [34].In the electronic absorption spectra of the copper complex: Cu

(DMKT) (phen) $Cl_2.H_2O$the bands in the range 40983-50761 $cm^{-1}$are assigned to π→π* transition. The n→ π* transition bands were found between the range of 36231 and 29325 cm^{-1}. Band due to charge transfer transition was seen at 29154 cm^{-1}while the d-d transition was also recorded in visible region by concentrating the solution, bands of observed at 20,040 cm^{-1}assigned to ($^2B_{1g}\rightarrow{}^2E_g$). This shows square planer structure [34-38].

Zinc has an electronic configuration of d^{10} and a spectroscopic ground state term symbol of 1S. The S-orbital here are non-degerate and cannot be split by either octahedral or tetrahedral field [38]. Hence no d-d transition is expected in the spectrum of Zn(II) complex; Zn(DMKT)(phen)Cl_2 bands observed have been interpreted to be charge transfer transition [33].

Conclusively, electronic spectral bands of the ligand and the metal complexes studied in methanol and DMSO showed that all complexes show bands at 51813- 42016 and 36231-25445 cm^{-1}assigned to π→π* and n→π* transitions respectively. The d-d bands were only seen in the Fe(III) and Cu(II) complexes around 13966-20040 cm^{-1} are changes of the electron while it moves between two orbitals having different energies in the complex that are present in the Cu(II) and Fe(III) complexes are responsible for their colours which are generally, green-black and brown respectively. Zn(II) have no d-d transition, the bands observed have been interpreted to be charge transfer transition [33].

3.3 IR Spectra of Mixed Ligand Complexes of DMKT with phen

The possibility of thione (H-N-C=S)-thiol (C=N.SH) tautomerism in this ligand has been ruled out from the fact that no band is observed around 2600-2500 cm^{-1} which are characteristic of thiol group in the infrared absorption [39-40] The infrared spectra of dimethylketone thiosemicarbazone in Table 4 showed a strong band at 1658 cm^{-1} attributed to C=N group [41-42].A negative shift of the order 31-50 cm^{-1} was observed for C=N stretching vibration on coordination due to the decrease of the bond order as a result of metal nitrogen bond formation which is in agreement with the work reported by Bermejo *et al.,* (2005)andAguirre *et al.,* (2006)[42-43]. The next strong band at 866 cm^{-1} is attributed to C=S group [42, 43], a negative shift in the region of 32-36 cm^{-1} was observed in the complexes on coordination thereby indicating the involvement of thiosulphur in the coordination the metal ion [42-44]. The bands found at 3537 and 3370-3419$cm^{-1}$are attributed to ν(H_2O) and ν(NH, NH_2) respectively. The negligible effect on these frequencies after complexation precludes the possibility of complexation at this group. The presence of these bands supported the formation of the complexes. The coordination of 1,10- phenanthroline is indicated by the positive shift of ν(C=C), ν(C=N) ring stretching frequencies and the presence of the deformation modes at around 1556 and 2291 cm^{-1} respectively. The position of the bands found in the spectrum of 1, 10-phenanthroline has been completely changed in the spectra of the complexes where it is used as co-ligand, and new bands appeared at 1492 and 2190 cm^{-1} confirming the coordination nature of pyridyl ligand.Some new non-ligand bands appearing in the far IR region around 438 - 476 cm^{-1}have been noticed in the spectra of the metal complexes, these are assigned to ν(M–N) and ν(M–S) vibrations [42-45].An additional non-ligand band at ~ 418-425 cm^{-1} has also been observed in all the complexes indicating pyridyl-nitrogen coordination with the metal ion [35]. Based on the above spectral evidences, it is confirmed that the ligandsare bidentate, coordinating via the azomethine nitrogen and thiosulphur and the two pyridyl nitrogenatoms of dimethylketonethiosemicarbazoneand 1, 10-phenanthroline respectively.

3.4 ^1H NMR Spectra data (δ, ppm) of Mixed Ligand Complexes of DMKT with phen

The ^{1}H-NMR spectral data (δ, ppm) of dimethylketone thiosemicarbazone and its metal complexes is presented in Table 3.The ^{1}H-NMR spectrum of the ligand recorded in DMSO-d6 showed proton signals in the expected regions but showed slight shifts compared to the ligand spectrum. The spectra showed no peak at 4 ppm, that is attributable to SH protons [46], but showed a peak at 7.68-7.99 ppm, which was attributed to the N–H group, indicating that the ligand was in the thione form, which is in conformity with the IR spectrum. The methyl signals from the coordinated thiosemicarbazone in the complexes were observed at around 1.00 -1.98 ppm. A significant azomethine proton signal due to CH=N was observed at 9.15 - 10.94 ppm, the expected signals from the pyridine fragment coordinated to dimethylketone thiosemicarbazone are clearly observed in the aromatic region between 7.00–7.93 ppm. The downfield shifts of the N-H and N_2H signals are attributable to coordination through the azomethine nitrogen and the thiocarbonyl sulfur atoms, which are in consistent with the IR spectral data. These observations are in agreement with the findings of Tameryn,*et al.,* and Gangadharan,*et al.,* [47-48].

3.5 Antifungal Activity of Mixed Ligand Complexes of DMKT with phen

The result of fungicidal screening Table 5 shows that the complexes were more active than the free ligand against pathogenic fungi:*Aspergillusniger, Penicillium species*, *Rhizopus* and *Candida albicans*. The mode of action may involve the formation of a hydrogen bond through the azomethane nitrogen atom with the active centers of the cell constituents, resulting in interference with the normal

cell process [49-50]. The complex that possess the highest activity among the single ligand is the copper(II) complex. This is in accordance with other work done by Dimiza, *et al.*,Miodragovic, *et al.*,Yesilel, *et al.*,Nomiya, *et al.*, Rodriguez-Argüelles, *et al.* ,Segl'a, *et al.* ,Brindha, *et al.*, Navarro, *et al.*,[51- 57].

The activity of the mixed complexes was found to be greater than those of the metal salts and the primary ligands [58], these obtained derivatives could act through a dual mechanism of action combining the pharmacological properties of both ligands and the metal salt [59-60]. The values obtained in this work are lower than that reported by Kpomah*et al.*,[61] in their work where single ligand was used. This increase in the inhibitory activity of the mixed ligands complexes as compared to the ligands is an indication that they are very much effective against the

A possible explanation for the observed increased activity upon chelation is that the positive charge of the metal in chelated complex is partially shared with the ligand's donor atoms so that there is π-electron delocalization over the whole chelate ring [62]. Subsequently, this reduces the polarity of the metal ion and which in turn will increase the lipophilic character of the metal chelate and favors its permeation through the lipoid layers of the bacterial membranes [63].

Lipophilicity is a property that has a major effect on absorption, distribution, metabolism and excretion and toxicity properties as well as on pharmacological activity because drugs cross biological membranes through passive transport, and the ability to do this is strongly dependent on their lipophilicity.

Table 1. Physical characteristics, molecular weight, melting point and conductivity data of (DMKT-with-phen) complexes

					Elemental Analysis Found/ (Calcd) (%)			
Formulation and Empirical Formula	M/ Wt. (g/mol)	Colour	Yield (%)	M.p. (°C)	C	H	N	**EC 10^{-3} M (ohm^{-1} cm^{2}mol^{-1})**
DMKT $C_4H_9N_3S$	131.2	White crystals	89	181.9	36.51 (36.62)	6.89 (6.91)	32.25 (32.03)	9.12
Cu(DMKT)(phen)Cl_2.H_2O $C_{16}H_{21}Cl_2CuN_5O_2S$	481.89	Green crystals	51	339	40.34 (39.88)	3.92 (4.39)	12.46 (14.53)	19.11
Fe(DMKT)(phen)Cl_2 $C_{16}H_{17}Cl_2FeN_5S$	438.16	Brown crystals	60	235	43.18 (43.86)	3.54 (3.91)	16.06 (15.98)	16.10
Zn(DMKT)(phen)Cl_2 $C_{16}H_{17}Cl_2N_5SZn$	447.70	White crystals	63	248	42.71 (42.92)	3.95 (3.83)	16.48 (15.64)	12.10

EC = Electrical Conductance, 10^{-3} M solution in DMSO, Ohm^{-1}

Table 2. Electronic Spectra (cm^{-1}) of Mixed Ligand Complexesof (DMKT) with (phen)

Compound	Type	π -π*	n- π *	Charge Transfer	d–d
DMKT	-	207 (48309) 215 (46511) 236 (42372)	304 (32894)	-	-
Cu (DMKT) (phen)Cl_2.H_2O	d^9	197 (50761) 210 (47619) 222 (45045) 244 (40983)	276 (36231) 296 (33783)	343 (29154)	499 (20040) ($^2B_{1g}\rightarrow{}^2E_g$)
Fe (DMKT) (phen)Cl_2	d^6	199 (50251) 208 (48076) 223 (44843)	302 (33112) 365 (27397)		667 (14992) $^6A_{1g}\rightarrow{}^4T_{1g}$(G)
Zn (DMKT) (phen)Cl_2	d^{10}	199 (50251) 207 (48309) 223 (44843)	294 (34013)	362 (27624)	-

Table 3.[1]H NMR Spectra data (δ, ppm) of Mixed Ligand Complexes of (DMKT) with (phen)

COMPOUNDS	**-CH_3 (METHYL PROTON)**	**CH (AROMATIC PROTON)**	**-$^4NH_2$ (IMINO PROTON)**	**-^{2}NH (AZOMETINE PROTON)**	**-0H (ALCOHOL)**
DMKT $C_4H_9N_3S$	6H, (s), 1.91 2.00-3.40	-	2H, 8(s), 7.68- 7.99	1H, 5(s), 10.00	
Cu(DMKT) (phen)Cl_2.H_2O $C_{16}H_{21}Cl_2CuN_5O_2S$	6H, 0.95, (d) 3.03-4.36, (d)	8H, (m), 7.55 - 8.03	2H, (s), 8.20-8.59	1H, (s), 9.15- 10.94	4H, (d), 11.01
Zn(DMKT) (phen)Cl_2 $C_{16}H_{17}Cl_2N_5SZn$	6H,(s), 0.91-1.98 3.00 - 4.29	8H, (m), 7.00 -7.29	2H, (s), 8.10-8.24	1H, (s), 9.87	
Fe(DMKT) (phen)Cl_2 $C_{16}H_{17}Cl_2FeN_5S$	6H (s), 1.00- 1.72 3.09-4.50	8H, (m), 7.55 - 7.93	2H, (s), 8.31-8.61	1H, (s), 9.87	

Table 4. The Main IR in (cm^{-1}) of Mixed Ligand Complexes of(DMKT)with (phen)

	COMPOUNDS				
IR Band Assignment (KBr, cm^{-1})	**DMKT**	**phen**	**Cu (DMKT) (phen)Cl_2.H_2O**	**Zn(DMKT) (phen)Cl_2**	**Fe (DMKT) (phen)Cl_2**
v(OH), H_2O			3537		
v(N-H)	3377 3230		3419	3423 3068	3370
Ar v(C-H)		3061	3047	3010	3060
v(C=N)	1658		1627	1624	1603
n(C-S)+n(C-N)	1251	-	1205 1309	1222	1219
Ar(C=C)		1504	1491	1492	1414 1515
Ar(C=N)		2359	2098	2087 2061	2044
v(N-N)	1028		1043	1101	1135
v(C=S)	866		844	846	831
Ar V(C-H)Bending	839	839	781	763 723	715
Arv(C-C) Bending	696 700 719	731 738	719	669	628
M-N_{Azo}			461	476	459
M-S			440	438	437
M-N_{Aro}			422	418	425

S = strong, w = weak, m = medium, br. = broad

Table 5. Antifungi activity Data for Complexes of (DMKT) with (phen) after 72 Hours Using Sensitivity Disc (60 µg/mL). Zone of Inhibition in (mm)

Test Samples	Aspergillusniger	Penicillium Species	Rizopus	Candida albicans
DMKT	$11.33 \pm 1.47^{**}$	$10.23 \pm 0.58^{**}$	$10.00 \pm 2.00^{**}$	$9.00 \pm 1.00^{**}$
$Cu(DMKT)(phen)Cl_2.H_2O$	$40.67 \pm 1.15^{**}$	$41.70 \pm 2.18^{**}$	$43.67 \pm 2.52^{**}$	$32.13 \pm 1.53^{**}$
$Fe(DMKT)(phen)Cl_2$	$33.00 \pm 1.73^{**}$	$30.80 \pm 2.02^{**}$	$31.33 \pm 0.58^{**}$	$28.00 \pm 1.00^{**}$
$Zn(DMKT)(phen)Cl_2$	$32.33 \pm 2.08^{**}$	$31.00 \pm 2.00^{**}$	$29.66 \pm 2.52^{**}$	$23.00 \pm 1.00^{**}$
$FeCl_2.6H_2O$	$0.00\pm0.00^{*}$	$0.00\pm0.00^{*}$	$0.00\pm0.00^{*}$	$0.00\pm0.00^{*}$
$ZnCl.7H_2O$	$0.00\pm0.00^{*}$	$0.09 \pm 0.58^{*}$	$0.13 \pm 0.58^{*}$	$0.00 \pm 0.58^{*}$
$CuCl.2H_2O$	$0.33\pm0.00^{*}$	$0.67 \pm 0.58^{*}$	$0.57 \pm 0.58^{*}$	$0.27\pm0.00^{*}$

All values are mean of triplicate determinations ± standard deviation, values in the same column with different superscript letters (**) are significantly different from the control (*) ($P< 0.05$), one way analysis of variance (ANOVA) followed by post hoc LSD.

4 Conclusions

The IR data of the ligands and the mixed ligand complexes shows that are coordinated to the metal ions through nitrogen atoms of the C=N (phenanthroline ring) groups. The results obtained from this research demonstrated that all synthesized compounds have antifungal activities against the fungal strains.The increased activity of the mixed ligand complexes might be due to the combined activity effect of both the ligands present in the metal complexes. Copper is one of the metals acting as an essential trace element involved in cellular respiration, antioxidant defense, neurotransmission, connective tissue biosynthesis and cellular iron metabolism [64-65]. Moreover, several investigations provide evidence that copper ions are capable of interacting directly with nuclear proteins and DNA, causing site-specific damage [66-67]. In addition, it has been reported that copper compounds delay cell-cycle progression and increase cell death in different cell cultures [68]. Copper(II) ions binding to specific sites can modify conformation of proteins, polynucleotides, or membranes. [69-71]. Complexes of copper containing 1, 10-phenanthroline as a ligand mixed with other types of ligands stirred great interests since they exhibit numerous biological activities such as antitumor, antibacterialand anti-candida activity [72]. The excellent antifungal activity of the copper complex shows that ithas promising future in the medical field.

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