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3D Series Metal Complexes Containing Schiff Base Ligand with 2,2'-Bipyridine: Synthesis, Characterization and Assessment of Antifungal Activity

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The rapid increase in the number of multidrug-resistant of most pathogenic organisms is fast becoming a global concern, thus, the discovery of novel active pharmacological compounds against new targets is a matter of urgency. The incorporation of metal ions into organic ligands has introduced metal-organic drugs framework with synergistic effects for novel applications in the biological system. In this research work, metal(II) chloride complexes of copper, nickel and zinc containing methylphenylketone thiosemicarbazone (MPK-TSC) with 2,2'-bipyridine (bipy) were synthesized; they were further characterized by satisfactory microelemental analysis, Fourier Transform InfraRed (FTIR) spectra as well as electronic spectra study. The complexes are proposed to have the formulae $[L_1ML_2(Cl_2)]$ where M=metal ion, L_1=methylphenylketone thiosemicarbazone L_2=2,2'-bipyridine. The complexes are of 1:2 (metal:ligand) stoichiometry and non-electrolytes in solution, the bidentate nature of the two ligands was evident from the FTIR spectra. The compounds were screened for their antifungal activity against four pathogenic fungi: *Aspergillus niger, Penicillium Species, Rizopus and Candida albicans* using disc diffusion method. The activities of the complexes have been found to be greater than those of the metal salts and the uncoordinated ligands.

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1. INTRODUCTION

Thiosemicarbazones are very good Schiff base ligands that provide bidentate N, S'- donor sites for chelation with metal ions. Metal complexes of thiosemicarbazones have been explored for nearly 50 years because of their versatile biological activity and prospective use as drugs [1]. Owing to the interest they generate through a variety of biological properties, thiosemicarbazones metal complexes have been employed in medicinal applications ranging from anticancer [2], antitumor [3], antifungal [4, 5], antibacterial [6], antmalarial [7,8], antitilarial, [9], antiviral [10,11], antineoplastic [12,13], antileprotic [14], trypanocidal [15,16] and anti-HIV activities [17]. It has been proved that thiosemicarbazones block DNA synthesis in mammalian cells by inhibiting the enzyme, ribonucleoside diphosphate reductase, presumably either via chelation with iron(III) required by the enzyme or because a preferred metal chelate of the inhibitor interacts with the target enzyme [18,19]. Metal-based drug is seen as promising alternatives for possible replacement for some of the current drugs.

2,2'- bipyridine and its derivatives on the other hand play important roles for supermolecular assemblies because they can also provide bidentate N-donor site for chelating with metal ions to form bridge ligands. The efficacies of some therapeutic agents are known to increase upon coordination, the lipophilicity, which controls the rate of drug entry into the cell, is modified, and some side effects may be decreased [20-22]. Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. This work is the result of our systematic studies in this field; we report the synthesis, spectral and biological activities of mixed ligand complexes of methylphenylketone thiosemicarbazone with 2, 2'-bipyridine.

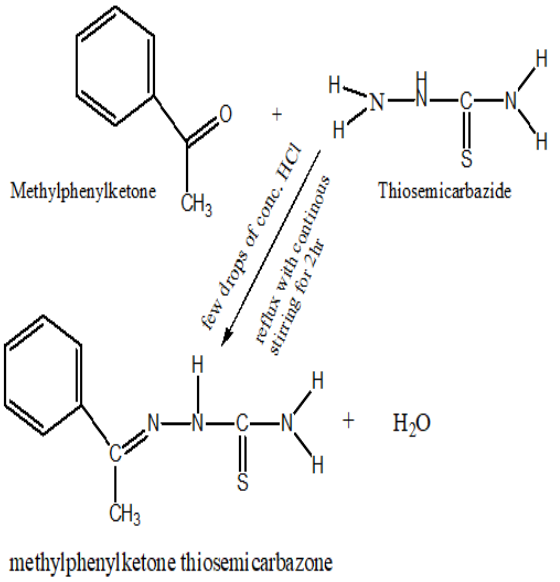
2. MATERIALS AND METHODS

The ligand and complexes were synthesized using standard procedure. Melting points of the compounds 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 Analyser. Electronic spectra of the ligand and the complexes were recorded in Dimethylsuphoxide (DMSO) solution on Shimadzu 10UV scanning Uv-Visible spectrophotometer in the range 200-800nm. The infrared (IR) spectra were recorded on Shimadzu 8400S FTIR spectrophotometer as KBr pellets in the range 4000–400 cm^{-1}. All the synthesized compounds were screened for their antifungal activity using sensitivity disc method. All chemicals used were of A.R grade.

2.1 Inorganic Synthesis

2.1.1 Synthesis of methylphenylketone thiosemicarbazone (MPK-TSC)

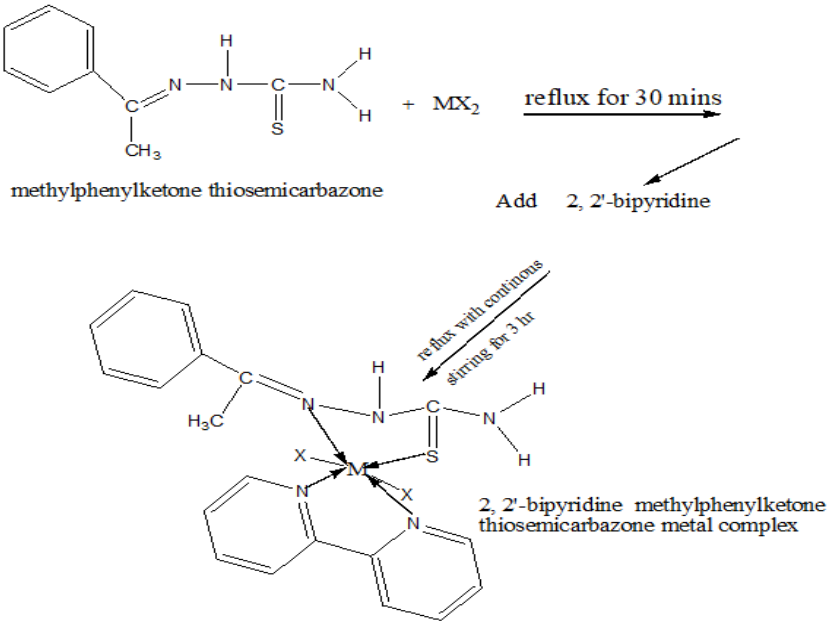
5 mmol, (0.46 g) thiosemicarbazide was dissolved in methanol (30 mL) by refluxing at 50°C. In the refluxing solution, 5 mmol, (0.60 g) methylphenylketone solution in methanol (30 mL) was added; this was then followed by the addition of few drops of conc. HCl. The reaction mixture was continuously stirred and refluxed for 4 h at 60 °C. The volume of reaction mixture was reduced and kept in the refrigerator overnight. White crystals of MPK-TSC precipitated out, the crystals was washed with methanol and dried in the desiccator over silica gel [23, 4].



Scheme 1. Synthetic procedure of the ligand methylphenylketone thiosemicarbazone through condensation reaction

2.1.2 Synthesis of Complexes of (MPK-TSC) with 2,2'-bipyridyine (bipy)

To refluxing (30 mL) methanolic solution of 2mmol (0.387 g) **(**MPK-TSC), was added slowly 15 mL hot methanolic solution of the metal salts e.g. for copper complex 1 mmol (0.170 g) of $CuCl_2.2H_2O$ was used. The reacting mixture was constantly stirring and refluxed for 30 min. The reaction mixture precipitated. Subsequently, 2mmol (0.312 g) methanolic solution of 2,2'-bipyridine, was then added slowly. On addition of the methanolic solution of 2,2'-bipyridine, the reaction mixture became clear and was continuously stirred and refluxed for another 4 h at 60^{o}C [23,4].



Scheme 2. Synthetic procedure of metal complex of methylphenylketone thiosemicarbazone with 2, 2'-bipyridine
M=Cu, Ni and Zn
X=C1

2.2 Antifungal Sensitivity Tests (Sensitivity Disc Test)

The antimicrobial activity of the complexes and ligands were screened by adapted qualitative diffusmetric 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 organisms and spread as uniformly as possible throughout the entire media. The antimicrobial sample solutions (60 µg/mL) impregnated discs were then placed on the inoculums media. Blank paper discs of dimethylsulphoxide were used as control. The plates were filled with 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 [24]. The activity of the compounds was 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.

3 RESULTS AND DISCUSSION

3.1 Statistical Analysis

Data are expressed as the mean of five (5) replicates ± standard deviation, One Way Analysis of Variance (ANOVA) Posthoc (Turkey), was used to analyse the means and $P<0.05$ 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.

Table 1. Analytical Data for Complexes of Methylphenylketone Thiosemicarbazone with 2, 2'-Bipyridine

S/N	Ligands/ Complexes	Appearance/ Colour	Yield (%)	Molecular Weight g/mol^{-1}	Melting Point (^{O}C)	Elemental Analysis (%) Found (Calc.d)		
						C	H	N
1	2,2'-Bipyridine $C_{10}H_8N_2$	Amorphous Powder/ White	-	156.19	72.56			
2	MPK- TSC $C_9H_{11}N_3S$	White Crystal	89	193.27	198.70	55.97 (55.93)	5.89 (5.74)	21.56 (21.74)
3	[Cu(MPK-TSC) (Bipy)Cl_2] $C_{19}H_{19}Cl_2CuN_5S$	Black Powder	57	482.00	250.18	47.57 (47.16)	4.08 (3.96)	14.86 (14.47)
4	[Ni(MPK-TSC) (Bipy)Cl_2] $C_{19}H_{19}C_{l2}N_5NiS$	Dark Green Powder/	54	477.01	310.4DT	47.70 (47.64)	4.11 (4.00)	14.79 (14.62)
5	[Zn(MPK-TSC) (Bipy)Cl_2] $C_{19}H_{19}C_{l2}N_5SZn$	White Powder	75	483.00	210.10	48.12 (46.98)	4.06 (3.94)	14.51 (14.42)

Table 2. The Main IR in (cm^{-1}) of Complexes of (MPK-TSC) with 2, 2'-Bipyridine

IR Band Assignment (KBr, cm^{-1})	MPK-TSC	bipy	Ni(MPK-TSC) $(bipy)Cl_2$	Cu(MPK-TSC) $(bipy)Cl_2$	Zn (MPK-TSC) $(bipy)Cl_2$
ν(OH)				3736 b	3728 br
ν(N-H)	3373 s		3119 s	3308 s	3495 br
	3263 s			3169 s	3296 s
	3184 s			3103 s	3173 s
Ar(C-H)		3054	3064	3062	3095s
			3061s		3060
ν(C=N)	1645 s		1615 s	1641s	1627 s
n(C-S)+n(C-N)	1286 s	-	1257 m	1232 w	1199 w
Ar(C=C)		1556	1423	1492	1433
Ar(C=N)		2291	2063	2074	2070
ν(N-N)	1001 s		1035 s	1037 s	1068 s
			1064 s	1076 s	
ν(C=S)	800 s		767 s	700 s	700 s
Ar(C-H) Bending			852	723	725
Ar(C-C) Bending		752	741	670	683
M-N_{Azo}			583	473	466
M-N			512 w	468	563 w
M-S			431 w	418	437 w
			416 w		

Table 3. Electronic Spectra nm, (cm^{-1}) of Complexes of (MPK-TSC) with 2, 2'-Bipyridine

Compound	d^n Configuration	n→π* Transition nm (cm^{-1})	π→π* Transition nm (cm^{-1})	Charge Transfer nm (cm^{-1})	d–d Transition nm (cm^{-1})
MPK-TSC		199 (50251) 207 (48309) 223 (44843)	294 (34103)	-	-
2,2'-bipy	-	226 (44247) 288 (34722)			
Cu (MPK-TSC) (bipy)Cl_2	d^9	207 (48309) 224 (44642)	-	-	407 (24570) $^2B_{1g} \rightarrow {}^2E_g(V_3)$
Ni (MPK-TSC) (bipy)Cl_2	d^8	215 (46511) 224 (44642)	-	342 (29239) 356 (28089)	598 (16722) $^3A_{2g} \rightarrow {}^3T_{1g}$ (P)
Zn (MPK-TSC) (bipy)Cl_2	d^{10}	200 (50000) 223 (44843) 228 (43859)	297 (33670)	-	-

Table 4. Antifungal Activity Data for Mixed Ligands Complexes of (MPK-TSC) with 2, 2'- Bipyridine after 72 Hours Using Sensitivity Disc (60 µg/mL). Zone of Inhibition in (mm)

Test Samples	*Aspergillus niger*	*Penicillium Species*	*Rizopus*	*Candida albicans*
CONTROL (5% DMSO)	0.00 ± 0.00*	0.00 ± 0.00*	0.00 ± 0.00*	0.33 ± 0.58*
MPK-TSC	13.67 ± 1.15**	12.00 ± 1.00**	11.33 ± 1.15**	10.67 ± 1.15**
bipy	09.67 ± 1.00**	08.00 ± 1.00**	08.33 ± 1.00**	07.67 ± 0.00**
Ni (MPK-TSC)(bipy)Cl_2	40.60 ± 2.08**	41.00 ± 1.00**	42.00 ± 0.00**	35.33 ± 1.53**
Cu (MPK-TSC)(bipy)Cl_2	46.00 ± 2.08**	40.67 ± 0.60**	41.00 ± 1.00**	39.00 ± 2.00**
Zn (MPK-TSC)(bipy)Cl_2	39.67 ± 0.58**	36.00 ± 1.00**	31.33 ± 1.15**	32.76 ± 1.15**
$NiCl_2 .6H_2O$	0.00 ± 0.00**	0.02 ± 0.10**	0.07 ± 0.58**	0.00 ± 0.58**
$CuCl .2H_2O$	0.01 ± 0.58**	0.00 ± 0.58**	0.05 ± 0.58**	0.00 ± 0.58**
$ZnCl_2$	0.04 ± 0.00**	0.05 ± 0.00**	0.09 ± 0.58**	0.02 ± 0.58**

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

3.2 Physical Characteristics of Complexes of Methylphenylketone Thiosemicarbazone with 2,2′-Bipyridine

The colour exhibited by the Copper and Nickel complexes in Table 1 may be attributed to d-d electron transition [25, 26]. The higher melting point observed in the complexes compared to the ligands are as a result of increased molecular mass, enhanced stronger lattice structure and stronger interaction which accompanied the coordination of the ligands to the central metal ions. Partial elemental analysis results are in good agreement with assigned formulations.

3.3 IR Spectra of Complexes of Methylphenylketone Thiosemicarbazone with 2,2′-Bipyridine

The IR spectra of complexes of methylphenylketone thiosemicarbazone with 2,2′-bipyridine are presented in Table 2. The presence of v(OH), band in the copper and zinc complexes was suggested by broad absorption around 3736-3728 cm^{-1} [27]. The strong bands observed at 3495-3119 cm^{-1} region in MPK-TSC are assigned to v (N-H) vibrations. The most notable change in MPK-TSC spectra when coordinated to metal ion is the v(C=N). strong band at 1645 cm^{-1}, in the spectrum of MPK-TSC exhibited a blue shift at ca 30-04 cm^{-1} to 1615 cm^{-1}, 1641 cm^{-1} and 1627 cm^{-1} in the spectra of Ni, Cu and Zn complexes respectively. This finding may be taken as an evidence for the participation of v(C=N) azine group in coordination to the metal ions [28-31].

The bands at 1286 and 800 cm^{-1} in the free MPK-TSC due to n(C-S)+n(C-N) and v(C=S) stretching vibrations are shifted to lower frequencies at 1257–1199 and 767–700 cm^{-1} in the spectra of the complexes, suggesting coordination through the thioketo sulphur with the metal ion [32,29]. Strong bands found at 1001 cm^{-1} in MPK-TSC is assigned to v(N–N) vibration, this band is found at higher frequencies of 1076-1035 cm^{-1} in the spectra of the complexes, this increase is due to the increase in the bond strength. The absorption frequency of all characteristic bands of MPK-TSC decreases upon complexation except the hydrazinic v(N-N) band [33]. This is due to the donation of the unpaired electrons from one of the nitrogen atom to the metal ion, incidentally deflating the repulsion force between the two adjacent nitrogen electrons. This decreases the distance between the two nitrogen atoms, subsequently, shifting the absorption frequency to a higher value [34]. This again confirms the coordination via the azomethine nitrogen [35]. Evidence of bonding of the ligand to the central metal ion is provided by the appearance of new bands observed at 563-413 cm^{-1} which are tentatively assigned to v(M-N) and v(M-S) (metal-ligand) stretching bands supporting the coordination of the ligand as bidentate N-S chelating agent [36,37,38, 28].

Conclusively, the coordination of 2,2′–bipyridine is indicated by the positive shift of v (C=C), v (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 2,2′–bipyridine has been completely changed in the spectra of the complexes where it is used as co-ligand, and new bands appeared at 1492-1423 and 2075-2063 cm^{-1} confirming the coordination nature of bipyridine ligand. Some new non-ligand bands appearing in the far ir region around 583-466 cm^{-1} have been noticed in the spectra of the metal complexes, these are assigned to $v(M\text{-}N_{Azo})$ [39].

3.4 Electronic Spectra (cm^{-1}) of Complexes of (MPK-TSC) with 2,2′-Bipyridine

Electronic spectra data are presented in Table 3. Methylphenylketone thiosemicarbazone showed four absorption bands in the region 199 nm (50251 cm^{-1}), 207 nm (48309 cm^{-1}), 223 nm (44843 cm^{-1}) and 294 nm (34103 cm^{-1}) corresponding to n→π* and π→π* transitions respectively. Upon complexation a blue shift was observed due to the polarization of the C=N bond caused by the metal ligand electron interaction during the chelation. This is an indication of coordination of azomethine nitrogen to the metal atom.

$Cu(MPK\text{-}TSC)(bipy)Cl_2$ complex exhibited n→π* transitions at around 207 nm (48309 cm^{-1}) and 224 nm (44642 cm^{-1}), but no band represent π→π* transition . The d-d band of Cu(II) complex is observed at 407nm (24570 cm^{-1}). This shows square planer structure, [40].

In octahedral Ni(II) complexes, three spin-allowed transitions are expected because of the free-ion ground ^3F term and the presence of ^3P

term. The d-d transition: $^3A_{2g}(F) \rightarrow {}^3T_{lg}(P)$ occurred at 598nm (16722 cm^{-1}). In addition, the electronic spectrum of the Ni(MPK-TSC)(bipy)Cl_2 complex shows four bands: 215 nm (46511 cm^{-1}), 224 nm (44642 cm^{-1}) and 342 nm (29239 cm^{-1}), 356 nm (28089 cm^{-1}) assigned to n→π* and LMCT.

Zn (MPK-TSC)(bipy)Cl_2, complex exhibited n→π* and π→π* transitions at around 200nm, (5000 cm^{-1}), 223nm (44843 cm^{-1}), 228nm (43859 cm^{-1}), and 297nm (33670 cm^{-1}) but no band represents LMCT. Zinc has an electronic configuration of d^{10} and a spectroscopic ground state term symbol of 1S. The S-orbital here are non-degenerate and cannot be split by either octahedral or tetrahedral field [41]. Hence no d-d transition is expected in the spectrum Zn(MPK-TSC)(bipy)Cl_2, therefore the bands observed have been interpreted to be charge transfer transition.

3.5 Antifungal Activity of Mixed Ligands Complexes of (MPK-TSC) with 2, 2'- Bipyridine

The result of fungicidal screening in Table 4 shows that the complexes were more active than the free ligands against all pathogenic fungi: *Aspergillus niger, Penicillium Species, Rizopus and Candida albicans.* The mode of action may involve the formation of a hydrogen bond through the azomethine nitrogen atom with the active centers of the cell constituents, resulting in interference with the normal cell process [4, 42]. The increased activity of the mixed ligand complexes might be due to the combined activity effect of both ligands present in the metal complexes. The complexes could act through a dual mechanism of action combining the pharmacological properties of both ligands and the metal salt [43, 44]. This suggests that, mixed antibiotics metal complexes are 50% higher in fungal resistance than ordinary antibiotics and therefore are better potential antifungal drugs.

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 [45]. Subsequently, this reduces the polarity of the metal ion and which in turn will increase the lipophilic character of the metal chelate and favours its permeation through the lipoid layers of the membrane of the pathogenic organisms [46]. Lipophilicity is a property that has a major effect on absorption, distribution, metabolism, excretion and toxicity properties as well as on pharmacological activity because drugs cross biological membranes through passive transport, and the ablity to do this is strongly dependent on their lipophilicity.

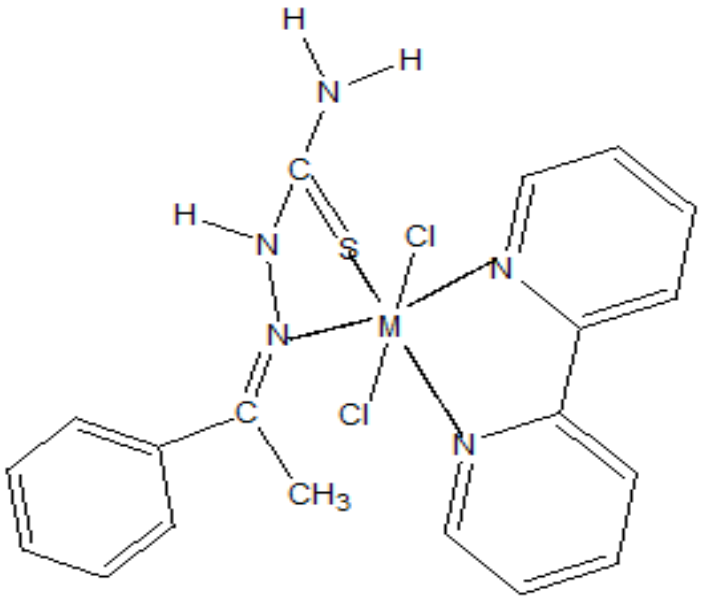


Fig. 1. Proposed structure of metal complex of (MPK-TSC) with 2,2'-bipyridine

4. CONCLUSION

The synthesis and characterization of Cu(II), Ni(II), and Zn(II) complexes containing Schiff base ligand with 2,2'-bipyridine have been achieved with assessment of their antifungal activity. The complexes are proposed to have the formulae $[L_1ML_2(Cl_2)]$ where M=metal ion, L_1=methylphenylketone thiosemicarbazone and L_2=2,2'-bipyridine. The complexes are of 1:2 (metal:ligand) stoichiometry and a non-electrolytes in solution. The bidentate nature of the two ligands was evident from the FTIR spectra. The structural analysis indicates that coordination of the secondary ligand is via the two pyridyl nitrogens while the primary ligand coordinated to the center metal ion via the azomethine nitrogen and thiolato sulphur atom, the fourth coordination site being occupied by chloride ions. All complexes increased the antifungal activity, relative to the ligand alone; but Ni(II) and Cu(II) complexes demonstrated marked antifungal efficacy. For the copper complex, it could be due to copper's affinity for binding sites and flexible Cu(II) redox potentials which help the copper complex to form more potent, clinically effective copper based antifungal drugs of higher growth inhibitory. Additionally, Cu(II) ion forms the active center in a large number of metalloproteins, thereby, making the coordination of Schiff base ligands to the metal ion results in the high extent of increase in antifungal activity. Metal ions play an important role in biochemical processes, they function to facilitate or inhibit biochemical reactions. Coordination of metal ions by different ligands change the reduction–oxidation potentials of a reaction, the change in redox potential finds diverse applications i.e. transport and storage of oxygen and other essential elements, electron transfer etc. Generally, it is suggested that the chelated complexes deactivate various cellular enzymes, which play a vital role in various metabolic pathways of these microorganisms. Thus, the precomplexation of the transition metals increased the intracellular levels of activity of the complexes within the cell, resulting in greater anti-microbial activity.

DISCLAIMER

The products used for this research are commonly and predominantly products use in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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