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Characterization and biological activity studies on some transition metal complexes of thiosemicarbazide derived from 2-picolinic acid hydrazide

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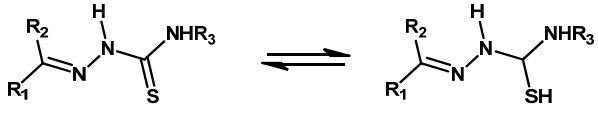
ABSTRACT

Mixed-ligand bivalent transition metal ion complexes with *N*-ethyl-2-picolinoyl hydrazinecarbothioamide (EPHC) and 1,10-phenanthroline (1,10-phen) have been synthesized. The complexes namely [Cu(EPHC)(1,10-phen)(Cl)H_2O] (1), [Ni(EPHC)(1,10-phen)(Cl)H_2O] (2), [Mn(EPHC)(1,10-phen)(Cl)H_2O] (3) and [Co(EPHC)(1,10-phen)(Cl)H_2O] (4) were characterized by elemental analysis, spectral (IR, ^{1}H NMR and UV-Vis) and magnetic moment measurements. The magnetic and spectral data indicates octahedral structure for all complexes. Metal complexes have been modeled using parameterized PM3 semi-empirical method. The free ligand and its M(II)-chelates have been screened for their antimicrobial activities. The antibacterial screening demonstrated that, the Cu(II) complex have the maximum and broad activities among the investigated complexes.

1. Introduction

Thiosemicarbazones have been extensively studied because they have a wide range of actual or potential medical applications [1-3] which include notably antiparasital [3], antibacterial [4] antitumor activities [5], antiviral [6], fungicidal [7] and antineoplastic [8]. Thiosemicarbazones derived from 2-picolinic acid hydrazide and its derivatives are classes of versatile tridentate NNS donors capable of stabilizing both higher and lower oxidation states of transition metal ions [9,10]. In general, thiosemicarbazones are obtained by condensation of the corresponding thiosemicarbazide with aldehydes or ketones. Thiosemicarbazones (TSCNs) exist in the tautomeric thione (A) and thiol (B) forms (Scheme 1).



Scheme 1

The chemistry of transition metal complexes of heterocyclic thiosemicarbazone ligands have been receiving considerable attention primarily because of their bioinorganic relevance [11,12]. There have been attempts to determine structural correlation's between transition metal ion complexes of heterocyclic thiosemicarbazones and their wide spectrum of biological applications [13]. In several cases, the pharmacological action of the thiosemicarbazons is enhanced due to their ability to chelate transition metal ions [14,15]. It is well authenticated that a NNS tridentate system is present in most of the thiosemicarbazones having carcinostatic potency and possessing substantial *in vitro* activity against various human tumor lines [16,17]. In the past, it has been shown that the metal complexes are more effective than their parent ligands in anticancer activity [18,19]. The inhibitory action of these compounds is attributed to their chelating properties to different metal ions that can be found in biological systems [20]. Additionally, one of the many reasons is that the binding affinity of metals to proteins or enzymes will change the interaction process of them with DNA, thereby affecting the DNA replication and cell proliferation [19].

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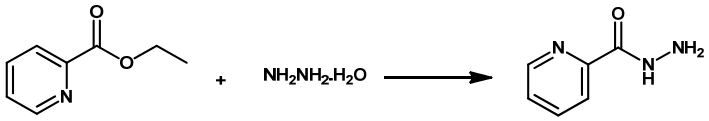
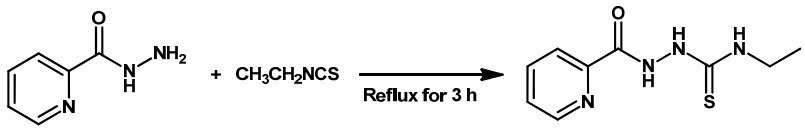


Scheme 2



Scheme 3

Earlier studies on the biological properties of thiosemicarbazones and their metal complexes have concluded that the biologically active thiosemicarbazone molecules are planar and contain a pyridine ring or derivatives giving rise to NNS tridentate system [21,22]. 1,10-Phenanthroline is the parent of an important class of chelating agents. The choice of phenanthroline is mainly due to two factors. This hetero-aromatic moiety can provide a further binding site for metal cations. It is rigid, and provides two aromatic nitrogens whose unshared electron pairs can act co-operatively in binding cations [23]. Moreover, 1,10-phenanthroline, the ligand moiety of the ternary complexes presented in this work is of considerable interest also according to the biological or pharmacological properties (antifungal, antimycoplasma and antiviral) of some of its metal complexes [24].

With this in mind, it seems therefore of considerable interest to synthesize and characterize M(II) complexes with the novel *N*-ethyl-2-picolinoylhydrazinecarbothioamide (EPHC) and 1,10-phenanthroline (1,10-phen) with different bivalent transition metal ions Co(II), Cu(II), Mn(II) and Ni(II). Additionally, our objective is also to study the antibacterial, antifungal and antitumor activities of the synthesized compounds.

2. Experimental

2.1. Materials and instrumentation

All starting materials were purchased from Fluka, Riedel and Merck and used as received. The analyses were performed twice to check the accuracy of the analyses data. Infrared spectra were recorded on FT-IR Shimadzu spectrophotometer (8001-PC) using KBr pellets. The solid reflectance spectra were measured on a Shimadzu 3101 PC spectrophotometer. The room temperature magnetic susceptibility measurements for the complexes were determined by the Gouy balance using $Hg[Co(SCN)_4]$ as a calibrant. Electron paramagnetic resonance (EPR) has matured into a powerful, versatile, non-destructive, and non-intrusive analytical method. EPR signals were recorded at room temperature by using a Bruker EMX spectrometer (X-band) product of Bruker, Germany. The operating conditions are, microwave power = 0.201 mW, modulation amplitude = 4.00 Gauss, modulation frequency = 100 kHz, sweep width = 200 Gauss, microwave frequency = 9.775 GHz, time constant = 81.92 ms and sweep time = 20.97 s. The detection limits of EPR technique depends on the type of sample, sample size, detector sensitivity, frequency of the incident microwave radiation.

2.2. Synthesis

2.2.1. Synthesis of N-ethyl-2-picolinoylhydrazine carbothioamide (EPHC)

N-Ethyl-2-picolinoylhydrazinecarbothioamide (EPHC) is prepared in two steps as follow:

Step 1: Preparation of 2-picolinic acid hydrazide

2-Picolinic acid hydrazide was prepared by refluxing ethyl picolinate and hydrazine hydrate as shown in Scheme 2.

Step 2: Preparation of N-ethyl-2-picolinoylhydrazine carbothioamide (EPHC)

EPHC was synthesized by boiling 1 mmol of 2-picolinic acid hydrazide with 1 mmol ethyl isothiocyanate in ethanol under reflux for 3 h as given in Scheme 3.

2.2.2. Synthesis of thiosemicarbazone complexes

All complexes were prepared by refluxing an ethanolic solution of the thiosemicarbazone (EPHC) ligand (1 mmol; 0.224 g) and 1,10-phenanthroline heterocyclic base (1 mmol; 0.1982 g) with an ethanolic solution of metal salt (1 mmol, $CuCl_2.2H_2O$, 0.1702 g; $CoCl_2.6H_2O$, 0.238 g; $NiCl_2.6H_2O$, 0.237 g; $MnCl_2.4H_2O$, 0.1979) in the molar ratio 1:1:1 (*w*:*w*:*w*). The reaction mixtures were refluxed on a water bath for 4 h and allowed to cool to room temperature overnight. The precipitated complexes were then filtered off, washed with petroleum ether and dried overnight in a vacuum desiccator.

2.3. Molecular modeling

An attempt to gain a better insight on the molecular structure of these synthesized thiosemicarbazone compounds and their M(II)-complexes, geometric optimization and conformation analysis has performed using semiempirical parameterized PM3 method as implemented in HyperChem 7.5 [25]. Convergence criteria were set to 0.01 kcal/mol.Å for PM3 calculations.

2.4. Biological activity

The antibacterial investigation of the free (EPHC) ligand or its Mn(II), Co(II), Cu(II) and Ni(II) complexes was carried out using a modified Kirby-Bauer disc diffusion method [26]. The test was done against filamentous fungi as (*Aspergillus flavus* RCMB 02568, *Pencicillium italicum* (RCMB 03924), *Aspergillus flavus* (RCMB 02568)) at 30 °C for 24-48 hours; Gram (+) bacteria as (*Bacillus subtillis* RCMB 010067, *Staphylococcus aureus* RCMB 010028); Gram (-) bacteria as (*Pseudomonas aeuroginosa* RCMB 010043, *Escherichia coli* RCMB 010052). The standard antibacterial agents used are Gentamicin for G^-, Ampicillin for G^+ and Amphotericin B (Antifungal agent) served as positive controls while DMSO, which exhibited no antimicrobial activity, was used as a negative control. The agar used is Mueller-Hinton agar that is rigorously tested for composition and pH.

Table 1. Analytical and physical data of synthesized compounds.

Compound	Formula	Yield (%)	% Calculated (Found)				
			C	H	N	S	Cl
EPHC	$C_9H_{12}N_4OS$	77	48.20 (48.18)	5.39 (5.36)	24.98 (24.82)	14.30 (14.28)	- (-)
[Cu(EPHC)(1,10-phen)Cl] (1)	$C_{21}H_{19}N_6OSCuCl$	85	50.15 (50.21)	3.78 (3.80)	16.71 (16.70)	6.36 (6.47)	7.06 (7.09)
[Ni(EPHC)(1,10-phen)Cl].H_2O (2)	$C_{21}H_{19}N_6OSNiCl.H_2O$	82	48.93 (48.98)	4.07 (4.09)	16.31 (16.35)	6.21 (6.25)	6.89 (6.91)
[Co(EPHC)(1,10-phen)Cl].H_2O (3)	$C_{21}H_{19}N_6OSCoCl.H_2O$	79	48.84 (48.89)	4.07 (4.11)	16.28 (16.31)	6.20 (6.25)	6.88 (6.91)
[Mn(EPHC)(1,10-phen)Cl].$2H_2O$ (4)	$C_{21}H_{19}N_6OSMnCl.2H_2O$	81	47.54 (47.59)	4.34 (4.40)	15.84 (15.89)	6.04 (6.08)	6.70 (6.76)

Table 2. Tentative assignment of the important infrared bands of the synthesized complexes.

Compounds	υ_{H2O}	$\delta_{(C=N)\,py}$	$\upsilon_{(C=N)py}$	$\upsilon_{C=S}$	υ_{N-N}	$\upsilon_{(N=C)}$*	$\upsilon_{(M-N)py}$	$\upsilon_{(C=N)phen}$	υ_{M-N}	υ_{M-S}	υ_{M-Cl}
EPHC/Phen	-	615	1608	1290, 830	1115	-	-	1570	-	-	-
[Cu(EPHC)(1,10-phen)Cl] (1)	-	638	1580	1265, 805	1170	1630	290	1546	444	325	240
[Ni(EPHC)(1,10-phen)Cl].H_2O (2)	3450	633	1585	1265, 810	1185	1625	278	1550	438	323	238
[Co(EPHC)(1,10-phen)Cl].H_2O (3)	3428	625	1590	1250, 805	1191	1623	280	1551	431	333	222
[Mn(EPHC)(1,10-phen)Cl].$2H_2O$ (4)	3460	623	1592	1249, 802	1177	1619	282	1554	430	335	225

* A new band appears in the complexes due to the thiolating of the (C=S) group.

Plates were incubated with filamentous fungi at 30 °C for 24-48 hours and with bacteria at 35-37 °C for 24-48 hours [27] and then the diameters of inhibition zones were measured in millimeters using slipping calipers of the National Committee for Clinical Laboratory Standards (NCCLS) [28,29].

3. Results and discussion

The isolated thiosemicarbazone compound is formed by the interaction of 2-picolinic acid hydrazide with ethyl isothiocyanate under reflux conditions (Scheme 3). The formulation of the isolated compounds based on the elemental analysis (Table 1), IR, and electronic spectra. The solid compounds are air stable. These compounds are colored, insoluble in H_2O and other common organic solvents like methanol and ethanol but soluble in dimethylformamide (DMF) and dimethylsulphoxide (DMSO). Attempts to obtain single crystal suitable for X-ray determination were unsuccessful, thus molecular modeling for EPHC thiosemicarbazone compound and its M(II)-complexes were investigated.

3.1. Infrared spectra

The tentative assignments of the significant IR spectral bands of the free EPHC thiosemicarbazone compound and its metal(II) complexes are listed in Table 2. The characteristic IR peaks reveal each of the following:

In the spectra of EPHC, the band observed at 1115 cm^{-1} is assigned to ν(N-N). The increase in frequency of this band in the spectra of complexes due to the increase in the double bond character of N-N [30] is an evidence for the enethiolization of the thiosemicarbazone ligand and the coordination via the azomethine nitrogen. The IR spectrum of EPHC ligand exhibits a band at 3510 cm^{-1} due to ν(OH) in addition to ν(CO) at 1665 cm^{-1} suggested the *keto-enol* tautomerism. On complexation the band due to ν(CO) is absent indicating the coordination of EPHC ligand in *enol* form. The pyridine in-plane deformation mode at 615 cm^{-1} in the spectrum of the ligand shifts to 623-638 cm^{-1} in spectra of the above complexes, suggesting coordination of the heteroaromatic nitrogen. In the spectra of all complexes, the bands assigned to the newly formed (N=C)* band due to the thiolating of the (C=S) groups are located in the range 1619-1630 cm^{-1}. The two bands assigned to δ(C=S) and ν(C=S) appear at the frequencies 1290 and 830 cm^{-1} respectively [31,32]. In all complexes, these two bands undergo weakness and shift to lower frequencies appearing in the range (1249-1260 cm^{-1}) and (802-810 cm^{-1}), respectively, confirming the coordination via the thiolate sulfur atom [33,34]. The IR spectrum of the free 1,10-phen ligand shows a very stronger bands at ~1570 cm^{-1} due to stretching frequency of >C=N present in 1,10-phenanthroline moiety. This band was shifted to lower frequencies in the complexes ~16-24 cm^{-1}, which clearly indicate that the coordination of the two nitrogen atoms of the neutral 1,10-phen ligand to M(II) ion upon complexation [32]. The coordination positions of the EPHC thiosemicarbazone in the M(II) complexes are confirmed by assigning the strong bands observed in the far IR spectra of the complexes. The bands observed at (430-444) and (323-335) cm^{-1} are assigned to ν(M-N) [35] and ν(M-S) as suggested by Lever [36], respectively. The broad band centered at 3428-3460 cm^{-1} in the spectra of complexes may be due to hydrated water. In the literature, the bands appearing between 160 and 300 cm^{-1} are allotted to the vibration of the M-X bonds where M = Metal and X = Cl or Br [37,38]. In our case the ν(M-Cl) frequencies appearing between 225-240 cm^{-1} are in good agreement with the reported values in the literature. Based on the above spectral evidences, it is confirmed that the thiosemicarbazone ligands lost the NH proton attached to C=S and coordinated to the M(II) ion as mononegative tridentate anion, coordinating via the azomethine and pyridine nitrogen atoms and the thiolate sulfur atom after deprotonation.

3.2. Electronic spectra

The probable assignments for the bands in the region 28150 and 33242 cm^{-1} are due to the n → π* and π → π* transitions of thiosemicarbazone compound respectively. Always n → π* transitions occurs at a lower energy than π → π* transitions [39]. In the spectra of M(II) complexes the bands observed in the region 27320-27880 cm^{-1} are assigned to S → M charge-transfer band [40]. The bands in the range 31260-31588 cm^{-1} observed in the spectra of all M(II) complexes are assigned as Cl → M charge-transfer transitions [41]. The shift of the π → π* bands to the longer wavelength region is the result of the C=S bond being weakened and conjugation system being enhanced after the formation of the complex [42]. The magnetic moment of Mn(II) complex (6.11 B.M.) is corresponding to five unpaired electrons, as expected for high spin $3d^5$ system [43]. The electronic spectrum of this complex show two bands at 20,250 and 24,850 cm^{-1} attributable to $^6A_{1g} \rightarrow {}^6T_{1g}(G)$ and $^6A_{1g} \rightarrow {}^6T_{2g}(G)$, respectively, suggesting an octahedral structure [43].

The Co(II) complexes generally give rise to three absorption bands in the visible region under the influence of the octahedral field by the excitation of the electron from the ground state $^4T_{1g}$ (F) to the excited states $^4T_{2g}$ (F), $^4A_{2g}$ (F) and $^4T_{1g}$ (P).

Table 3. Molar conductance, magnetic moment and electronic spectral data (cm^{-1}) of the complexes.

Compounds	Λ_M[a]	$\mu_{eff.}$ (B.M.)	*d-d*	Transitions
[Cu(EPHC)(1,10-phen)Cl] (1)	3.15	1.82	14585	$^2B_{1g}\rightarrow{}^2E_g$
[Ni(EPHC)(1,10-phen)Cl] (2)	4.99	3.11	10265	$^3A_{2g}\rightarrow{}^3T_{1g}(F)$
			16940	$^3A_{2g}\rightarrow{}^3T_{1g}(P)$
[Co(EPHC)(1,10-phen)Cl].H_2O (3)	5.35	4.63	9725	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$
			21010	$^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$
[Mn(EPHC)(1,10-phen)Cl].H_2O (4)	6.97	6.11	20250	$^6A_{1g}\rightarrow{}^6T_{1g}(G)$
			24850	$^6A_{1g}\rightarrow{}^6T_{2g}(G)$

[a] Molar conductance measured for 10^{-3} M DMSO solution, Ω^{-1} cm^2 mol^{-1}.

In the Co(II) complex, only two bands are observed at 9725 cm^{-1} $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$ (ν_1) and 21,010 cm^{-1} $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$ (ν_3) as reported in many octahedral cobalt(II) complexes [44,45]. The ν_2 transition was not observed due to very weak intensity. The value of the magnetic moment 4.63 B.M. (normal range for octahedral Co(II) complexes is 4.3-5.2 B.M.) is an additional evidence for an octahedral geometry around the Co(II) ion [46].

The copper(II) complex exhibit magnetic moment of 1.82 B.M. at room temperature. This value is quite close to the spin allowed values expected for a S = 1/2 system and may be indicative of a distorted octahedral geometry around copper(II) ion. This copper(II) complex displays a broad band at 14,585 cm^{-1} due to $^2B_{1g}\rightarrow{}^2E_g$ assigned to *d-d* transitions of a distorted octahedral environment [47,48].

The electronic spectra of the nickel(II) complexes exhibited absorption bands at 10,265 and 16,940 cm^{-1}, attributable to $^3A_{2g}\rightarrow{}^3T_{1g}(F)$ and $^3A_{2g}\rightarrow{}^3T_{1g}(P)$, transitions, respectively, in an octahedral geometry [44,48]. Also, the value of the magnetic moment (3.11 B.M.) may be taken as additional evidence for their octahedral structure. On the basis of the above observations, it is tentatively suggested that all of the complexes show an octahedral geometry in which the EPHC thiosemicarbazone ligand act as monoanion tridentate ligand, 1,10-phen acts as bidentate ligand and in addition to the monodentate chloride ion. These possibly accommodate themselves around the metal atom in such a way that a stable chelate ring is formed giving, in turn, stability to the metal complexes.

3.3. ESR spectrum of [Cu(EPHC)(1,0-phen)Cl] complex

ESR spectroscopy is a direct measurement of electron spin when there are unpaired electrons within a chemical structure and thus provides a way to investigate the electronic spin state and oxidation state of the coordinated metal ion. Also, the ESR spectra of the complexes is important in studying the metal ion environment in the complexes, such as geometry, nature of ligation sites from the ligand to the metal, and the degree of covalence of the metal-ligand bonds. The room temperature powder ESR spectrum of [Cu(EPHC)(1,10-phen)Cl] exhibits an axial signal with two g values ($g_{||}$ = 2.281, $g_{\perp}$ = 2.065). The $g_{||}$ and $g_{\perp}$ values are computed from the spectrum using DPPH free radical as "g" marker. The ordering of g values ($g_{||} > g_{\perp} > 2.003$) observed for copper(II) complex indicates that the unpaired electron is localized in (d_{x2-y2}) orbital [49] of the Cu(II) ion (spectroscopic state $^2B_{1g}$) and the spectral features are characteristics of axial symmetry [50]. $g_{||}$ is a moderately sensitive function for M-L bond nature. The $g_{||}$ value is a moderately sensitive function for M-L bond nature i.e., the $g_{||}$ value < 2.3 $g_{||}$ value > 2.3 are characterized for covalent and ionic metal-ligand bonds respectively. By applying this criterion, the $g_{||}$ value is less than 2.3 is an indication of significant covalent bonding in copper(II) complex. Based on elemental analysis, IR, electronic spectra and ESR data, Cu(II) complex has octahedral structure. The geometric parameter G, which is a measure of the exchange interaction between copper centers in the polycrystalline compound, is calculated using Hathway expression ($G = g_{||}-2.0023/g_{\perp}-2.0023$) [51]. According to Hathway, if the value of G > 4, the exchange interaction is negligible in solid complexes but G < 4 indicates considerable interaction in solid complexes [51]. In the Cu(II) complex reported in this paper, the G value (4.445) > 4, suggesting the absence of copper-copper exchange interactions in the solid state.

3.4. Conductivity measurements

Conductivity measurements in non-aqueous solutions have frequently been used in structural studies of metal chelates within the limits of their solubility. These measurements were provided a method for testing the degree of ionization of the complexes, the molar ions that a complex liberates in solution, the higher will be its molar conductivity and vice versa. The non-ionized complexes have negligible value of molar conductance. It is clear from the conductivity data (Table 3) that the complexes present seem to be nonelectrolytes (3.15-6.97 $\Omega^{-1}.cm^2.mol^{-1}$). Also the molar conductance values indicate that the anions were existed inside the coordination sphere, which was also confirmed from the chemical analysis and also Cl^- ion is not precipitated by addition of $AgNO_3$ solution. Hence, the conductivity measurements of the metal(II)-chelates confirm the proposed general formulae of those chelates as suggested depending upon the results of elemental analyses, UV-Vis, ESR and IR spectra.

3.5. Antimicrobial activity

To assess the biological potential of the synthesized compounds, the thiosemicarbazone ligands and their metal complexes were tested against different species of bacteria and fungi. The parent (EPHC) ligand and its complexes are water insoluble; therefore, the antimicrobial test was carried out in DMSO. The results of the antimicrobial test of the parent ligand and its metal complexes against Gram positive and Gram negative are given in Table 4 while the results of the antifungal activity against was given in Table 5. In testing the antimicrobial activity of these compounds, we used more than one test organism to increase the chance of detecting antibiotic principles in tested materials. The organisms used in the present investigations included two Gram positive (*Staphylococcus aureus* and *Bacillus subtillis*) and two Gram negative (*Pseudomonas aeruginosa* and *Escherichia coli*). The diffusion agar technique was used to evaluate the antibacterial activity of the synthesized mixed ligand complexes [52-55]. The medium used for growing the culture was nutrient agar. The results of the antibacterial activity of the synthesized compounds are recorded in Tables 4 and 5. Metal ions are adsorbed on the cell walls of the microorganisms, disturbing the respiration processes of the cells and thus blocking the protein synthesis that is required for further growth of the organisms. Hence, metal ions are essential for the growth-inhibitory effects [56]. The synthesized compounds were found to be more toxic compared with their parent free ligands against the same micro-organism and under the identical experimental conditions.

Table 4. Antibacterial activity of thiosemicarbazone ligand and its metal complexes.

Compounds	Diameter of inhibition zone (in mm) [a]			
	(G^-)		(G^+)	
	Escherichia coli (RCMB 010052)	*Pseudomonas aeuroginosa* (RCMB 010043)	*Staphylococcus aureus* (RCMB 010028)	*Bacillus subtillis* (RCMB 010067)
EPHC	11.2±0.52	12.2±0.34	20.1±0.45	19.9±0.79
[Cu(EPHC)(1,10-phen)Cl] (1)	19.9±0.47	17.1±0.19	31.2±0.25	26.7±0.62
[Ni(EPHC)(1,10-phen)Cl].H_2O (2)	16.4±0.44	16.4±0.22	28.7±0.24	25.3±0.32
[Co(EPHC)(1,10-phen)Cl].H_2O (3)	15.8±0.53	13.8±0.34	24.9±0.65	22.3±0.69
[Mn(EPHC)(1,10-phen)Cl].$2H_2O$ (4)	14.5±0.25	13.1±0.25	23.8±0.39	20.8±0.87
Standard [b]	22.3±0.18	17.3±0.15	32.4±0.10	27.4±0.18

[a] Mean zone of inhibition in mm±standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (1 mg/mL) concentration of tested samples.
[b] The standard antibacterial agents used are *Gentamicin* for G^- and *Ampicillin* for G^+.

Table 5. Antifungal activity of thiosemicarbazone ligand and its metal complexes.

Compounds	Diameter of inhibition zone (in mm) [a]		
	Aspergillus flavus (RCMB 02568)	*Pencicillium italicum* (RCMB 03924)	Geotricum candidum (RCMB 05097)
EPHC	12.6±0.58	13.2±0.24	15.7±0.29
[Cu(EPHC)(1,10-phen)Cl] (1)	22.9±0.50	18.2±0.38	26.5±0.18
[Ni(EPHC)(1,10-phen)Cl].H_2O (2)	21.2±0.58	16.9±0.54	24.4±0.32
[Co(EPHC)(1,10-phen)Cl].H_2O (3)	20.6±0.25	14.7±0.24	21.7±0.75
[Mn(EPHC)(1,10-phen)Cl].$2H_2O$ (4)	18.6±0.47	14.1±0.37	19.8±0.53
Amphotericin (B)	23.7±0.10	21.9±0.12	28.7±0.22

[a] Mean zone of inhibition in mm±standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (1 mg/mL) concentration of tested samples.

According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid-soluble materials, so lipophilicity is an important factor controlling the antifungal activity. Upon chelating, the polarity of the metal ion will be reduced due to the overlap of the ligand orbitals and partial sharing of the positive charge of the metal ion with donor groups. In addition, chelation allows for the delocalization of π-electrons over the entire chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity facilitates the penetration of the complexes into lipid membranes, further restricting proliferation of the microorganisms. The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the microbial cells or on differences in the ribosomes of the cells [57-59]. All of the metal complexes possess higher antifungal activity than the ligand [60-63]. Although the exact biochemical mechanism is not completely understood, the mode of action of antimicrobials may involve various targets in the microorganisms. These targets include the following.

(i) The higher activity of the metal complexes may be due to the different properties of the metal ions upon chelation. The polarity of the metal ions will be reduced due to the overlap of the ligand orbitals and partial sharing of the positive charge of the metal ion with donor groups. Thus, chelation enhances the penetration of the complexes into lipid membranes and the blockage of metal binding sites in the enzymes of the microorganisms [64].

(ii) Tweedy's chelation theory predicts that chelation reduces the polarity of the metal atom mainly because of partial sharing of its positive charge with donor groups and possible electron delocalization over the entire ring. This consequently increases the lipophilic character of the chelates, favoring their permeation through the lipid layers of the bacterial membrane [65].

(iii) Interference with the synthesis of cellular walls, causing damage that can lead to altered cell permeability characteristics or disorganized lipoprotein arrangements, ultimately resulting in cell death.

(iv) Deactivation of various cellular enzymes that play a vital role in the metabolic pathways of these microorganisms.

(v) Denaturation of one or more cellular proteins, causing the normal cellular processes to be impaired.

(vi) Formation of a hydrogen bond through the azomethine group with the active centers of various cellular constituents, resulting in interference with normal cellular processes [66-68]. The tested complexes were more active against Gram-positive than Gram-negative bacteria, it may be concluded that the antibacterial activity of the compounds is related to cell wall structure of the bacteria (Figure 1 and 2).

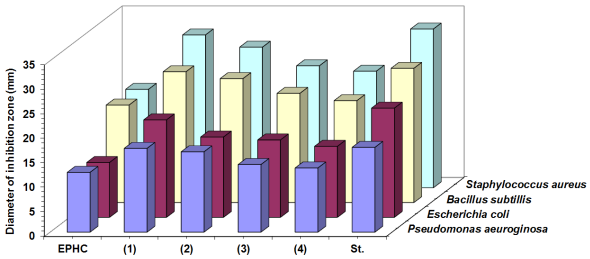


Figure 1. Antibacterial activity of M(II)-complexes towards different types of bacterial strains.

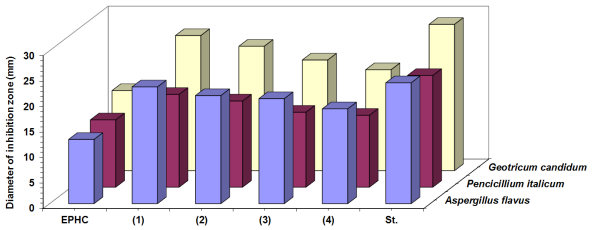


Figure 2. Antifungal activity of M(II)-complexes towards different types of fungal strains.

It is possible because the cell wall is essential to the survival of bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan. Gram-positive bacteria possess a thick cell wall containing many layers of peptidoglycan and teichoic acids, but in contrast, Gram negative bacteria have a relatively thin cell wall consisting of a few layers of peptidoglycan surrounded by a second lipid membrane containing lipopolysaccharides and lipoproteins.

Table 6. Some energetic properties of EPHC thiosemicarbazone and its complexes calculated by PM3 method.

Ligand	Total energy (kcal/mol)	Binding energy (kcal/mol)	Electronic energy (kcal/mol)	Dipole moment (Debye)	HOMO (eV)	LUMO (eV)
EPHC	-54843.90	-2698.41	-322610.60	1.95	-9.02	-0.90
[Cu(EPHC)(1,10-phen)Cl] (1)	-132278.40	-5495.28	-1119311.52	5.25	-3.62	-0.96
[Ni(EPHC)(1,10-phen)Cl].H_2O (2)	-128997.47	-5624.97	-1128540.07	11.91	-6.21	-2.18
[Co(EPHC)(1,10-phen)Cl].H_2O (3)	-123307.98	-5800.93	-1102050.97	5.50	-3.52	-1.73
[Mn(EPHC)(1,10-phen)Cl].$2H_2O$ (4)	-114017.78	-5553.96	-1054657.86	2.95	-3.71	-1.15

Table 7. Bond distances (Å) and angles (°) for EPHC compound.

Atoms	Bond distances (Å)	Atoms	Angle (°)
C(13)-C(15)	1.5142	C(15)-C(13)-N(12)	111.1151
N(12)-C(13)	1.4836	C(13)-N(12)-C(11)	120.7721
C(11)-S(14)	1.6607	S(14)-C(11)-N(12)	124.3345
C(11)-N(12)	1.3900	S(14)-C(11)-N(10)	123.1882
N(10)-C(11)	1.4266	N(12)-C(11)-N(10)	112.4562
N(9)-N(10)	1.4474	C(11)-N(10)-N(9)	118.9549
C(7)-N(9)	1.4543	N(10)-N(9)-C(7)	115.3396
C(7)-O(8)	1.2126	N(9)-C(7)-O(8)	120.8053
C(5)-C(7)	1.4997	N(9)-C(7)-C(5)	114.2262
C(5)-C(6)	1.3976	O(8)-C(7)-C(5)	124.8760
N(4)-C(5)	1.3581	C(5)-C(6)-C(1)	118.6875
C(3)-N(4)	1.3496	C(7)-C(5)-C(6)	121.1215
C(2)-C(3)	1.3972	C(7)-C(5)-N(4)	117.1474
C(1)-C(6)	1.3934	C(6)-C(5)-N(4)	121.7192
C(1)-C(2)	1.3902	C(5)-N(4)-C(3)	119.4206
		N(4)-C(3)-C(2)	121.5728
		C(3)-C(2)-C(1)	119.1281
		C(6)-C(1)-C(2)	119.4708

These differences in cell wall structure can produce differences in antibacterial susceptibility and some antibiotics can kill only Gram-positive bacteria and is ineffective against Gram-negative pathogens [69,70]. It is worth noting that the comparison of antimicrobial activities of the compounds against the selected types of microorganisms indicate that Cu(II) > Ni(II) > Co(II) > Mn(II).

3.6. Molecular modeling

The atomic numbering scheme as given in Figure 3-5 and the theoretical geometry structures for the ligand and some of its metal complexes are calculated. The molecular parameters: total energy, binding energy, isolated atomic energy, electronic energy, heat of formation, dipole moment, HOMO and LUMO were calculated and represented in Table 6. A comparison between the bond length of the ligand and its complexes is illustrated. All the active groups taking part in coordination have bonds longer than that already exist in the ligand (like C=N, C=S). The lower HOMO energy values show that molecule donating electron ability is the weaker. On contrary, the higher HOMO energy implies that the molecule is a good electron donor. LUMO energy presents the ability of a molecule receiving electron [22,71].

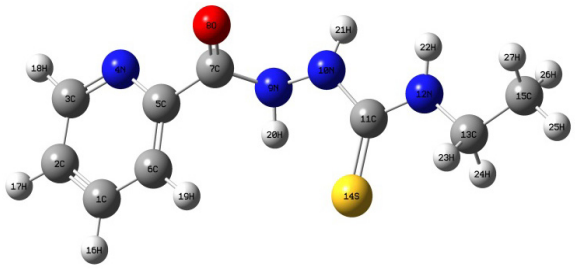


Figure 3. The optimized structural geometry of EPHC along with the atom numbering scheme.

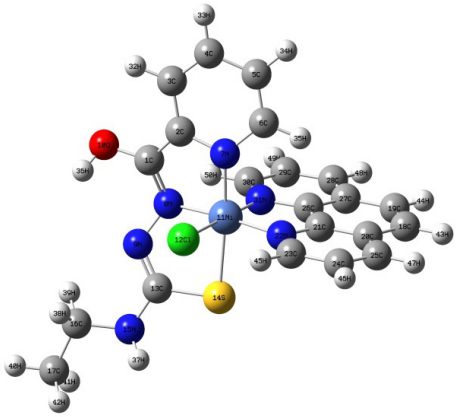


Figure 4. The optimized structural geometry of [Ni(EPHC)(1,10-phen)Cl] (**2**) along with the atom numbering scheme.

The bond lengths and bond angles of EPHC-thiosemicarbazone ligand and [Mn(EPHC)(1,10-phen)Cl] complex as a representative example of M(II) compounds are given in Table 7 and 8, respectively. A drawing of EPHC-thiosemicarbazone ligand is shown in Figure 3 while Ni(II) and Co(II) complexes with the atomic numbering scheme is shown in Figure 4 and 5, respectively. The coordination results in the changes of bond lengths and angles of the thiosemicarbazone moiety, as expected, thus when the bond lengths in the coordinated thiosemicarbazone ligand are compared with those in the free thiosemicarbazone ligand, it is seen that coordination elongates the thiosemicarbazone moiety's C–S bond from 1.660 Å to 1.729-1.811 Å and contracts adjacent N–C(S) bond from 1.426 Å to 1.313-1.361 Å in , which is consistent with the C–S acquiring a partial single bond and N–C(S) a partial double bond character. These changes in bond lengths are attributable to stabilization of the iminothiolate form of the thiosemicarbazone ligand upon complexation via loss of the hydrazinic proton [72].

Table 8. Bond distances (Å) and angles (°) for [Mn(EPHC)(phen)Cl] complex.

Atoms	Bond distances (Å)	Atoms	Angle (°)	Atoms	Angle (°)
C(30)-N(31)	1.4013	C(30)-N(31)-C(26)	115.3974	C(16)-N(15)-C(13)	122.7854
C(29)-C(30)	1.3793	C(30)-N(31)-Mn(11)	129.9560	C(13)-S(14)-Mn(11)	93.9839
C(28)-C(29)	1.4036	C(26)-N(31)-Mn(11)	114.4310	N(15)-C(13)-S(14)	119.6797
C(27)-C(28)	1.4005	N(31)-C(30)-C(29)	121.5916	N(15)-C(13)-N(9)	116.4556
C(26)-N(31)	1.4166	C(30)-C(29)-C(28)	122.0829	S(14)-C(13)-N(9)	123.8348
C(26)-C(27)	1.4076	C(29)-C(28)-C(27)	118.8145	N(31)-Mn(11)-N(22)	85.1370
C(24)-C(25)	1.3735	C(28)-C(27)-C(26)	117.8240	N(31)-Mn(11)-S(14)	103.5590
C(23)-C(24)	1.4222	C(28)-C(27)-C(19)	124.6801	N(31)-Mn(11)-Cl(12)	156.8913
N(22)-C(23)	1.3367	C(26)-C(27)-C(19)	117.4928	N(31)-Mn(11)-N(8)	101.1144
C(21)-N(22)	1.4030	N(31)-C(26)-C(27)	124.2319	N(31)-Mn(11)-N(7)	85.2175
C(21)-C(26)	1.4135	N(31)-C(26)-C(21)	115.1995	N(22)-Mn(11)-S(14)	90.8034
C(20)-C(25)	1.4159	C(27)-C(26)-C(21)	120.5656	N(22)-Mn(11)-Cl(12)	85.0861
C(20)-C(21)	1.4060	C(24)-C(25)-C(20)	119.1748	N(22)-Mn(11)-N(8)	173.7317
C(19)-C(27)	1.4349	C(25)-C(24)-C(23)	121.2291	N(22)-Mn(11)-N(7)	99.6526
C(18)-C(20)	1.4266	C(24)-C(23)-N(22)	121.4085	S(14)-Mn(11)-Cl(12)	97.4653
C(18)-C(19)	1.3662	C(23)-N(22)-C(21)	117.3742	S(14)-Mn(11)-N(8)	87.2966
C(16)-C(17)	1.5154	C(23)-N(22)-Mn(11)	132.2493	S(14)-Mn(11)-N(7)	166.9528
N(15)-C(16)	1.4831	C(21)-N(22)-Mn(11)	110.3765	Cl(12)-Mn(11)-N(8)	89.2363
C(13)-N(15)	1.3786	C(26)-C(21)-N(22)	114.8215	Cl(12)-Mn(11)-N(7)	75.8655
C(13)-S(14)	1.7919	C(26)-C(21)-C(20)	121.3150	N(8)-Mn(11)-N(7)	81.4774
Mn(11)-N(31)	1.8500	N(22)-C(21)-C(20)	123.8621	C(13)-N(9)-N(8)	113.3163
Mn(11)-N(22)	1.9985	C(25)-C(20)-C(21)	116.9490	Mn(11)-N(8)-N(9)	121.5031
Mn(11)-S(14)	2.2451	C(25)-C(20)-C(18)	125.3884	Mn(11)-N(8)-C(1)	116.6753
Mn(11)-Cl(12)	2.3074	C(21)-C(20)-C(18)	117.6625	N(9)-N(8)-C(1)	121.3887
N(9)-C(13)	1.3510	C(27)-C(19)-C(18)	121.6815	Mn(11)-N(7)-C(6)	128.1585
N(8)-Mn(11)	1.9519	C(20)-C(18)-C(19)	121.2692	Mn(11)-N(7)-C(2)	113.2535
N(8)-N(9)	1.3831	C(17)-C(16)-N(15)	111.0054	C(6)-N(7)-C(2)	118.5623
N(7)-Mn(11)	2.0087			N(7)-C(6)-C(5)	121.5164
C(6)-N(7)	1.3620			C(6)-C(5)-C(4)	119.7913
C(5)-C(6)	1.3935			C(5)-C(4)-C(3)	119.5456
C(4)-C(5)	1.3923			C(4)-C(3)-C(2)	118.9493
C(3)-C(4)	1.3903			N(7)-C(2)-C(3)	121.6342
C(2)-C(3)	1.3974			N(7)-C(2)-C(1)	113.6817
C(2)-N(7)	1.3861			C(3)-C(2)-C(1)	124.6731
C(1)-O(10)	1.3655			O(10)-C(1)-N(8)	127.3163
C(1)-N(8)	1.3318			O(10)-C(1)-C(2)	117.8329
C(1)-C(2)	1.4682			N(8)-C(1)-C(2)	114.8259

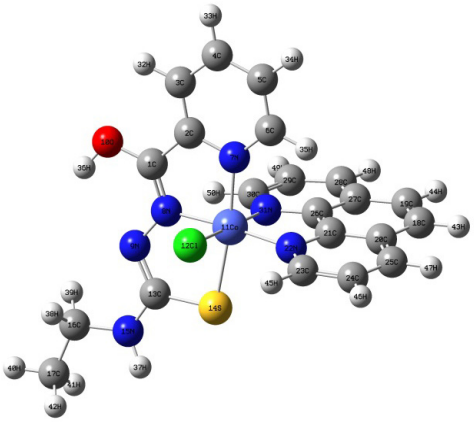


Figure 5. The optimized structural geometry of [Co(EPHC)(1,10-phen)Cl] (3) along with the atom numbering scheme.

This means that, C–S distances which are in the range of single bond character being some of the largest found for M(II) complexes (typical bond lengths being C(sp^2)–S 1.706 Å in $(MeS)_2C=C(SMe)_2$ and C=S 1.630 Å in naphthylphenyl thioketone) [73,74]. This also confirms the IR and spectral data which assumed that the C=S on coordination gains C–S character. Similar structural features are known for other metal complexes of such ligands that have the same coordination sites [75,76]. The other bond lengths and angles also suffer some changes, but not significantly. In general, the M–S bond length is longer than that of M–Cl for the all M(II) complexes and the M–N bond length is shorter than M–Cl bond length showing that the bond length obeyed this order M–S > M–Cl > M–N. In all complexes, $C=N_{py}$ bond distance of the pyridine ring is elongated. Owing to the formation of the M-N bond which makes the C=N bond weaker as a result of coordination. The bond angles of the thiosemicarbazone moiety of EPHC are altered somewhat upon coordination and may be reduced or increased on complex formation as a consequence of bonding. The bond angles around the M(II) center (≃90) prove that the geometric is octahedral as proposed by the different tools of analysis mentioned previously. Finally, from the interpretation of elemental analysis, spectral data (infrared, electronic and ESR) as well as magnetic susceptibility measurements at room temperature, conductivity measurements and QM calculations, it is possible to draw up the tentative octahedral structures of the metal complexes.

4. Conclusions

The reaction of 2-picolinic acid hydrazide with ethyl isothiocyanate afforded the corresponding *N*-ethyl-2-picolinoyl hydrazinecarbothioamide thiosemicarbazone compound. The bonding of ligands to the metal ion is confirmed by analytical, spectral and magnetic measurements. The IR spectra showed that, thiosemicarbazone compound present in the thione form in the solid state. In the absence of X-ray single crystal data of the current synthesized complexes and based on the physicochemical studies and geometrical optimization, a tentative structure could be proposed as shown in Figures 3-5. M(II)-complexes are formulated as $[M(EPHC)(1,10\text{-}phen)Cl].nH_2O$ where EPHC is the deprotonated thiosemicarbazone ligand. In these complexes the thiosemicarbazone ligand is coordinated to the metal (II) ion as a tridentate anion, coordinating via the azomethine nitrogen, pyridine nitrogen atoms and the thiolate sulfur atom after deprotonation. From elemental analysis, IR, spectral, thermal analysis, magnetic and conductance measurements, all M(II)-complexes are nonelectrolytes with octahedral structure. In this work, it was

found that the M(II) compounds show significantly different levels of biological activity. The antibacterial, antifungal, screening data revealed that newly generated compounds are potential antimicrobial agents.

References

[1]. Lakshmi, B.; Avaji, P. G.; Shivananda, K. N.; Nagella, P.; Manohar, S. H.; Mahendra, K. N. *Polyhedron* **2011**, *30*, 1507-1515.
[2]. Chan, J.; Huang, Y.; Liu, G.; Afrasiabi, Z.; Sinn, E.; Padhye, S.; Ma, Y. *Toxicol. Appl. Pharm*. **2004**, *197*, 40-48.
[3]. Rosen, J.; Smith, H.; Wiggall, K. J.; Zhang, L.; Luengo, J. I. *J. Med. Chem*. **2002**, *45*, 3573-3575.
[4]. Du, X.; Guo, C.; Hansel, E.; Doyle, P. S.; Caffrey, C. R.; Holler, T. P.; McKerrow, J. H.; Cohen, F. E. *J. Med. Chem*. **2002**, *45*, 2695-2707.
[5]. Kovala-Demertzi, D.; Demertzis, M. A.; Filiou, E.; Pantazaki, A. A.; Yadav, P. N.; Miller, J. R.; Zheng, Y.; Kyriakidis, D. A. *Biometals* **2003**, *16*, 411-419.
[6]. Scovill, J. P.; Klayman, D. L.; Franchino, D. G. *J. Med. Chem.* **1982**, *25*, 1261-1264.
[7]. Klayman, L.; Scovill, J. P.; Bartosevich, J. F.; Bruce, J. *J. Med. Chem*. **1983**, *26*, 35-39.
[8]. Demertzi, D. K.; Demertzis, M. A.; Miller, J. R.; Papadopoulou, C.; Dodorou, C.; Filousis, G. *J. Inorg. Biochem*. **2001**, *86*, 555-563.
[9]. Shongwe, M. S.; Al-Kharousi, H. N. R.; Adams, H.; Morris, M. J.; Bill, E. *Inorg. Chem.* **2006**, *45*, 1103-1107.
[10]. Saha, N. C.; Saha, A.; Butcher, R. J.; Chaudhari, S.; Saha, N. *Inorg. Chim. Acta* **2002**, *339*, 348-352.
[11]. Gupta, P.; Basuli, F.; Peng, S. M.; Lee, G. H.; Bhattacharya, S. *Inorg. Chem*. **2003**, *42*, 2069-2074.
[12]. Singh, N. K.; Srivastava, A. *Trans. Met. Chem*. **2000**, *25*, 133-140.
[13]. Li, J.; Zheng, L. M.; King, I.; Doyle, T. W.; Chen, S. H. *Curr. Med. Chem*. **2001**, *8*, 121-133.
[14]. Chandra, S.; Kumar, U.; Verma, H. S. *J. Saudi Chem. Soc*. **2003**, *7(3)*, 337-346.
[15]. Chandra, S.; Kumar, U.; Verma, H. S. *Oriental J. Chem*. **2003**, *19(2)*, 355-359.
[16]. Saha, N. C.; Butcher, R. J.; Chaudhuri, S.; Saha, N. *Polyhedron* **2003**, *22*, 383-390.
[17]. Chandra, S.; Singh, G.; Tyagi, V. P.; Raizada, S. *Synth. React. Inorg. Met. Org. Chem*. **2001**, *31(10)*, 1759-1770.
[18]. Malon, M.; Travnicek, Z.; Marysko, M.; Zboril, R.; Maslan, M.; Marek, J.; Dolezal, K.; Rolcik, J.; Krystof, V.; Strnad, M.; *Inorg. Chim. Acta* **2001**, *323*, 119-129.
[19]. Saha, D. K.; Padhye, S.; Sinn, E.; Newton, C. *Indian J. Chem. A* **2002**, *41A*, 279-283.
[20]. Booth, B. A.; Moore, E. C.; Sartorelli, A. C. *Cancer Res*. **1971**, *31*, 228-234.
[21]. Tojal, J. G.; Orad, A. G.; Serra, J. L.; Pizarro, J. L.; Lezama, L.; Arriortua, M. I.; Rojo, T. *J. Inorg. Biochem*. **1999**, *75*, 45-54.
[22]. El-Sherif, A. A.; Aljahdali, M. S. *Inorg. Chim. Acta* **2013**, *407*, 58-68.
[23]. Sammes, P. G.; Yahioglu, G. *Chem. Soc. Rev.* **1994**, *23*, 327-334.
[24]. Farrell, N. Transition Metal Complexes as Drugs and Chemotherapeutic Agents, Kluwer Academic, Dordrecht, 1989.
[25]. Hyper Chem. version 7. 5 Hypercube, Inc., 2003.
[26]. Bauer, A. W.; Kirby, W. M.; Sherris, C.; Turck, M. *Am. J. Clin. Pathol*. **1966**, *45*, 493-496.
[27]. Liebowitz, L. D.; Ashbee, H. R.; Evans, E. G. V.; Chong, Y.; Mallatova, N.; Zaidi, M.; Gibbs, D. *Microbiol. Infet. Dis*. **2001**, *24*, 27-33.
[28]. Pfaller, M. A.; Burmeister, L.; Bartlett, M. A.; Rinaldi, M. G. *J. Clin. Microbiol*. **1988**, *26*, 1437-1441.
[29]. National Committee for Clinical Laboratory Standards, Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi: Proposed standard M38-A, NCCLS, Wayne, PA, USA, 2002.
[30]. Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst*. **1990**, *82*, 1107-1112.
[31]. Aljahdali, M. S. *Eur. J. Chem*. **2013**, *4(4)*, 434-443.
[32]. Li, Z.; Zhang, Y.; Wang, Y. *Phosphor., Sulfur Silicon Relat. Elem*. **2003**, *178*, 293-297.
[33]. Braibanti, A.; Dallavalle, F.; Pellinghelli, M. A.; Leporati, E. *Inorg. Chem*. **1968**, *7*, 1430-1433.
[34]. Maurya, R. C.; Mishra, D. D.; Jaiswal, S. K.; Dubey, J. *Synth. React. Inorg. Met. Org. Chem*. **1995**, *25*, 521-535.
[35]. John, R. P.; Sreekanth, A.; Rajakannan, V.; Ajith, T. A.; Kurup, M. R. P. *Polyhedron* **2004**, *23*, 2549-2559.
[36]. Sreekanth, A.; Joseph, M.; Fun, H. K.; Kurup, M. R. P. *Polyhedron* **2006**, *25*, 1408-1411.
[37]. Philip, V.; Suni, V.; Kurup, M. R. P.; Nethaji, M. *Polyhedron* **2004**, *23*, 1225-1233.
[38]. Lever, A. B. P. Inorganic Electronic Spectroscopy, 2nd Edition, Elsevier, Amsterdam, 1984.
[39]. El-Sherif, A. A.; Shoukry, M. M.; Abd-Elgawad, M. M. A. *Spectrochim. Acta A* **2012**, *98*, 307-321.
[40]. Nakamoto, K. Infrared and Raman Spectra of Inorganic and Coordination Compounds, Wiley-Interscience, New York, 1986.
[41]. Philip, V.; Suni, V.; Kurup, M. R. P. *Polyhedron* **2006**, *25*, 1931-1938.
[42]. Sankaraperumal, A.; Karthikeyan, J.; Shetty, A. N.; Lakshmisundaram, R. *Polyhedron* **2013**, *50*, 264-269.
[43]. Suzuki, M.; Kanatomi, H.; Koyama, H.; Murase, I. *Bull. Chem. Soc. Japan* **1980**, *53*, 1961-1970.
[44]. Li, Q.; Tang, H.; Li, Y.; Wang, M.; Wang, L.; Xia, C. J. *Inorg. Biochem*. **2000**, *78*, 167-178.
[45]. Mohan, M.; Kumar, M. *Transit. Met. Chem.* **1985**, *10*, 255-258.
[46]. Singh, V. P.; Katiyar, A. J. *Pestic. Biochem. Phys.* **2008**, *92*, 8-14.
[47]. El-Sherif, A. A.; Eldebss, T. M. *Spectrochim. Acta A* **2011**, *79*, 1803-1814.
[48]. Niswander, R. H.; St Clair A. K.; Edmondson, S. R.; Taylor, L. T. *Inorg. Chem.* **1975**, *14*, 478-482.
[49]. Lever, A. B. P.; Lewis, J.; Nyholm, R. S. *J. Chem. Soc.* **1963**, 2552-2556.
[50]. Ballhausen, C. J. An Introduction to Ligand Field; 3rd Edn., McGraw Hill: Newyork, 1962.
[51]. Hathaway, B. J.; Tomlinson, A. A. G. *Coord. Chem. Rev*. **1970**, *5*, 143-207.
[52]. Balasubramanian, B.; Krishnan, C. N. *Polyhedron* **1986**, *5*, 669-675.
[53]. Dudley, R. J.; Hathaway, B. J. *J. Chem. Soc. A* **1970**, 1725-1728.
[54]. Ferrari, M. B.; Capacchi, S.; Pelosi, G.; Reffo, G.; Tarasconi, P.; Al-bertini, R.; Pinelli, S.; Helicin, P. L. *Inorg. Chim. Acta* **1999**, *286*, 134-141.
[55]. Jayabalakrishnan, C.; Natarjan, K. *Synth. React. Inorg. Met. Org. Chem.* **2001**, *31*, 983-988.
[56]. Jeeworth, T.; Wah, H. L. K.; Bhowon, M. G.; Ghoorhoo, D.; Babooram, K. *Synth. React. Inorg. Met. Org. Chem.* **2002**, *30*, 1023-1038.
[57]. Dharmaraj, N.; Viswanathamurthi, P.; Natarajan, K. *Transit. Met. Chem.* **2001**, *26*, 105-112.
[58]. El-Sherif, A. A. *Inorg. Chim. Acta* **2009**, *362*, 4991-5000.
[59]. El-Sherif, A. A.; Shoukry, M. M.; Abobakr, L. O. *Spectrochim. Acta A* **2013**, *112*, 290-300.
[60]. El-Sherif, A. A. *J. Coord. Chem*. **2011**, *64(12)*, 2035-2055.
[61]. Pal, I.; Basuli, F.; Bhattacharya, S. *Chem. Sci*. **2002**, *114(4)*, 255-268.
[62]. Anjaneyula, Y.; Rao, R. P. *Synth. React. Inorg. Met. Org. Chem.* **1986**, *16*, 257-272.
[63]. Aljahdali, M. S. *Spectrochim. Acta A* **2013**, *112*, 364-376.
[64]. Chohan, Z. H.; Arif, M.; Akhtar, M. A.; Supuran, C. T. *Bioinorg. Chem. Appl.* **2006**, Vol. 2006, Article ID 83131.
[65]. Chohan, Z. H.; Scozzafava, A.; Supuran, C. T. *J. Enzym. Inhib. Med. Ch*. **2003**, *18(3)*, 259-263.
[66]. Prasad, K. S.; Kumar, L. S.; Shekar, S. C.; Prasad, M.; Revanasiddappa, H. D. *J. Chem. Sci.* **2011**, *12*, 1-10.
[67]. Thangadurai, T. D.; Natarajan, K. *Transit. Metal Chem.* **2001**, *26(4-5)*, 500-504.
[68]. Dharmaraj, N.; Viswanathamurthi, P.; Natarajan, K. *Transit. Metal Chem*. **2001**, *26(1-2)*, 105-109.
[69]. Joseyphus, R.; Nair, M. *Mycobiology* **2008**, *36*, 93-98.
[70]. Malhota, L.; Kumar, S.; Dhindsa, K. S. *Indian J. Chem. A* **1993**, *32*, 457-459.
[71]. Koch, A. L. *Clin, Microbiol. Rev*. **2003**, *16*, 673-678.
[72]. Collins, R. C.; Davis, R. E. *Acta Crystallogr. B* **1978**, *34*, 283-285.
[73]. Sagdinc, S.; Kpksoy, B.; Kandemirli, F.; Bayari, S. H. *J. Mol. Struct*. **2009**, *917*, 63-70.
[74]. Dutta, S.; Basuli, F.; Peng, S. M.; Lee, G. H.; Bhattacharya, S. *New J. Chem*. **2002**, *26*, 1607-1613.
[75]. Arjunan, P.; Ramamurthy, V.; Ventakesan, K. *Acta Crystallogr. C* **1984**, *40*, 556-558.
[76]. Kraker, A.; Krezoski, S.; Schneider, J.; Minkel, D.; Petering, D. H. *J. Biol. Chem.* **1985**, *260*, 13710-13718.