



Bioactive Metal Complexes of Schiff Base Derived from 2,3-Dioxobutane, Ethane-1,2-diamine and 4-Chloro-2-formylphenol: Spectral Studies and *in vitro* Antimicrobial Activity

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A novel series of trivalent coordination complexes was synthesized by the reaction between a chloride/acetate salt of iron, chromium, cobalt or manganese ions and NNNNOO type persuasive Schiff base ligand synthesized from 2,3-dioxobutane, ethane-1,2-diamine and 4-chloro-2-formylphenol. Synthesized compounds were characterized by using elemental analysis, molar conductance, magnetic moment, IR, UV-visible, ¹H NMR, ¹³C NMR and ESI-MS spectral analyses. IR and NMR spectra favoured hexadentate coordination behaviour of ligand. Electronic spectra and magnetic moment data reveal *O_h* geometry with distortion around the metal ion in complexes. The molar conductance values show 1:1 electrolytic nature of complexes. Biological potentiality of the ligand and its metal complexes were tested *in vitro* against two bacterial and two fungal strains; *Bacillus subtilis*, *Escherichia coli* and *Aspirgillus niger*, *Aspirgillus flavus*, respectively.

Keywords: Schiff base, Bioactive moieties, Mononuclear complexes, Antimicrobial potency.

INTRODUCTION

Schiff base, a class of potent lone pair donor moiety shows better response among other species of donors owing to easier designing and structural suppleness to bind with metal ions [1,2]. Schiff base ligands synthesized with diketones/hydroxy aldehydes and amines have the unique potential to behave as a drug from antimicrobial to anticancer and their metal complexes have always shown improved potency than free ligand [3-5]. Recent developments in Schiff bases and their metal complexes and their applications in various field of pharmacology as antibacterial, antifungal, anti-inflammatory, anti-oxidant, anticancer agent, MRI contrasting agent, *etc.*, clearly gives an indication of success opportunities in the field of medicinal inorganic chemistry, especially in coordination chemistry [6-9]. Metal complexes of several transition and some rare earth metal ions in their existing oxidation states with Schiff base moieties as well as with other lone pair donor moieties have/had been developed and then applied for their

therapeutic explorations in diabetes, tuberculosis, HIV, *etc.* [10-16]. Schiff base metal complexes are also the molecule of interest for those researchers who are searching potent material for catalysis, photovoltaic activity, chemosensor activity, nano-material syntheses and other emerging field of human wellness research [17-24].

In present period of COVID-19 pandemic, when co-infections of bacterial and fungal pathogens are seen in patients during viral infection, the researchers are seeking for novel and potent antimicrobial agents to treat these co-infections and thus to control COVID-19 mortality rate also [25-28]. In such type of condition, development of new antibacterial and antifungal agents is definitely a great support in the field of drug discovery. Other than traditional organic synthons, pharmacologists may also look towards metal based drugs like coordination molecules because previous studies indicate that complexation may enhance the potential of many commercially available antibiotic drugs against many pathogens and even also break the resistance nature of many drug resistance bacteria/fungi [29-32].

Keeping in view the up-and-coming requirements of anti-bacterial and antifungal moieties, herein, a series of structurally elucidated metal complexes with trivalent iron, chromium, cobalt and manganese metal ions in coordination with a novel Schiff base ligand of 2,3-dioxobutane, ethane-1,2-diamine and 4-chloro-2-formylphenol is synthesized, characterized and also evaluated the biological potency against the specific bacteria and fungi.

EXPERIMENTAL

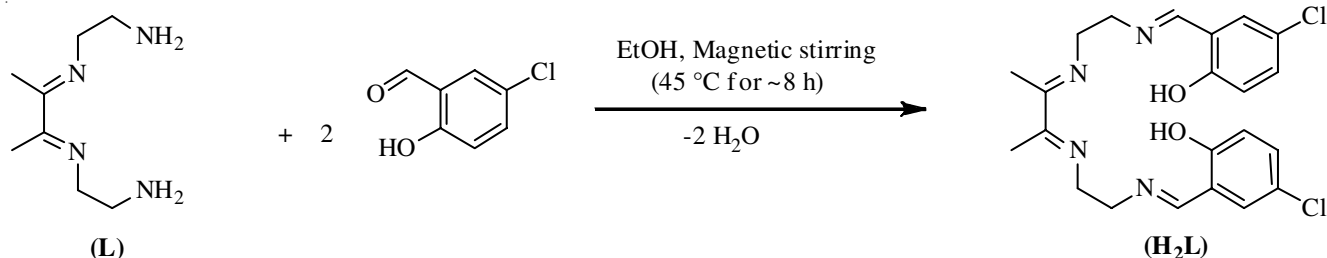
AnalR grade reagents and solvents were purchased from Qualigens (MeOH, EtOH, *n*-BuOH, diethyl ether and metal salts), Aldrich (2,3-dioxobutane) and Fisher (ethane-1,2-diamine and 4-chloro-2-formylphenol). Chemicals were dried and purified before their utilization in reactions as per requirements. Carbon, hydrogen and nitrogen element percentage were analyzed by a VarioEL elementary analysis system instrument. Metals and chlorides were determined by volumetric titration and gravimetric analysis methods adopted for the determination of metal and chloride content in complexes, respectively [33]. Temperature of melting/decomposition for each compound was measured on electrothermal melting point apparatus at °C scale. Structural representations of chemicals were drawn with ChemDraw Ultra 7.0 computer machine based software. Infrared spectrum of compounds, in the frequency range of 4000-200 cm^{-1} was recorded as KBr discs on Shimadzu 8300 infrared spectrophotometer. Covering the wavelength range from 200-900 nm, electronic absorption spectra of complexes were investigated in DMF solvent ($\sim 1 \times 10^{-4}$ M) using Systronic UV-visible spectrophotometer instrument. A Jenway Model-4070 conductivity meter apparatus was used to determine molar conductance value of complexes in DMSO solvent ($\sim 1 \times 10^{-3}$ M) at room temperature. Gouy method with $\text{Hg}[\text{Co}(\text{SCN})_4]$ as calibrant was applied to find out magnetic

moment measurement values. Chemical shift values (δ scale) related to ^1H and ^{13}C NMR spectra of compounds were observed on Bruker-Avance-II-400 NMR spectrometer at room temperature with deuterated dimethyl sulfoxide as a solvent. AB-Sciex-Q-Star-LCMS-MS spectrometer instrument was used for Electrospray ionization mass analysis of the complexes.

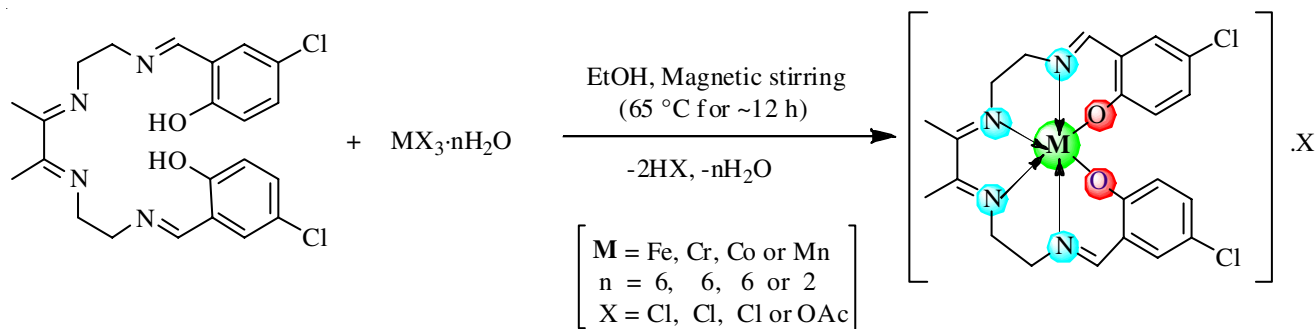
Synthesis of Schiff base ligand (H_2L): 2,3-Dioxobutane (0.44 mL, 5 mmol) solution in 20 mL of *n*-butanol was added to ethane-1,2-diamine (0.67 mL, 10 mmol) and stirred for ~ 2.5 h which yielded white solid of (L) [N^1 -[2-(2-amino-ethylimino)-1-methylpropylidene]-ethane-1,2-diamine]. The product was filtered off, washed with cold water and diethyl ether and then dried in vacuum desiccators CaCl_2 moisture absorbent. In the second step, a solution of (L) (0.85 g, 5 mmol) was prepared in 30 mL of $\text{C}_2\text{H}_5\text{OH}$ and then added to 4-chloro-2-formylphenol (0.156 g, 10 mmol) solution in 20 mL of $\text{C}_2\text{H}_5\text{OH}$. The reaction mixture was stirred well at 45 °C for ~ 8 h on hotplate magnetic stirrer and cooled at room temperature. A yellowish precipitate of Schiff base ligand (H_2L) was filtered off, washed with diethyl ether and dried in vacuum desiccator loaded with anhydrous CaCl_2 as moisture absorbent (**Scheme-I**).

Synthesis of metal complexes (1-4): A 1.0 mmol of hydrated metal chloride salt [$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.27 g), $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.26 g), $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.24 g) or $\text{Mn}(\text{CH}_3\text{CO}_2)_3 \cdot 2\text{H}_2\text{O}$ (0.27 g)] dissolved in 15 mL $\text{C}_2\text{H}_5\text{OH}$ was added to 1.0 mmol solution of H_2L (0.45 g) in 20 mL $\text{C}_2\text{H}_5\text{OH}$ and then reaction mixtures were stirred well on hotplate magnetic stirrer at 65 °C for ~ 12 h and cooled in refrigerator for overnight. In $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ reaction mixture, 5.0 mL of 30% H_2O_2 solution was added. Coloured products of metal complexes were obtained which were filtered off, washed with cold water, methanol, ethanol and diethyl ether and dried in vacuum desiccator loaded with anhydrous CaCl_2 as moisture absorbent (**Scheme-II**).

***in vitro* antimicrobial studies:** Synthesized ligand (H_2L) and its metal complexes (1-4) were evaluated for their *in vitro*



Scheme-I: Synthesis of ligand (H_2L)



Scheme-II: Synthesis of metal complexes (1-4)

antibacterial properties against *Bacillus subtilis* MTCC 2423 (Gram-positive) and *Escherichia coli* MTCC 739 (Gram-negative) bacterial strains and the antifungal properties against *Aspergillus niger* MTCC 1344 and *Aspergillus flavus* MTCC 2509 fungal strains by agar-well diffusion procedure [34]. Streptomycin and fulconazole were used as reference antibacterial and antifungal drugs, respectively. Each compound and reference drugs (1.0 mg) were dissolved separately in 10 mL DMSO solvent yielding stock solution of 1.0 mg/mL which was further diluted in two concentrations of 500 µg/mL and 100 µg/mL by adding double distilled water. A 10 mL solvent was diluted separately with sterilized distilled water to prepare control plate. Sterilized petri plates loaded with 0.01 mL culture of bacterial strains prepared in 20 mL Mueller Hinton Agar (Oxoid) were allowed to solidify. Like the same way, petri plates loaded with 0.01 mL culture of fungal strains prepared in 20 mL malt extract broth (Difco) were also allowed to solidify. The enumeration of microorganism within 24 h was observed as 10^5 per mL and 10^3 - 10^4 per mL for bacteria and fungi, respectively with the help of dilution plate method. A 7 mm diameter wells were created on culture plates with a sterilize cork borer of same diameter and simultaneously wells were filled with 0.2 µL solution of test compounds dissolved in DMSO. Fully loaded petri plates were refrigerated up to 4 °C for *ca.* 2 h and were incubated at room temperature for *ca.* 28 h and *ca.* 78 h to check the bacterial inhibition zone and fungal inhibition zone, respectively. Inhibition zone on petri-plates was measured at millimeter (mm) scale and percentage of zone inhibition was calculated by using following expression:

$$\text{Inhibition level (\%)} = \frac{(C-T)}{C} \times 100$$

where C is the diameter of colony in control plate and T is the diameter of colony in the tested plate after same incubation period.

RESULTS AND DISCUSSION

Metal complexes (**1-4**) of chromium, cobalt, manganese and iron metal ions were synthesized with a potent ligand (H_2L) having six coordination sites, derived from the condensation reaction between N^1 -[2-(2-aminoethylimino)-1-methylpropyl]-

dene]ethane-1,2-diamine (L) and 4-chloro-2-formylphenol. Stability of H_2L and its metal complexes (**1-4**) at room temperature for long months in solid state without any discernible change in physical state. The synthesized ligand is soluble in non-polar organic solvents like MeOH, EtOH, *etc.* while polar solvents like DMF, DMSO are found suitable for complexes solubility.

Physico-analytical statics along with spectral studies are in good agreement of proposed molecular/chemical formulae (Table-1). Molar conductance values fall in the range of 81.40-98.80 $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ recorded in DMSO solvent clearly suggest the 1:1 electrolytic nature of complexes [35]. Deprotonated hexadentate nature of ligand, confirmed by IR and NMR data, produce an octahedral environment with distortion around the metal ion of complexes (**1-4**) (Figs. 1 and 2) has been favoured by magnetic moment values and electronic spectral data.

IR spectra: Infrared spectral vibration data of bands informative for synthesis of targeted ligand (H_2L) as well as its coordination nature with metal ions are summarized in Table-2. Bands corresponding to free amine, aldehyde and

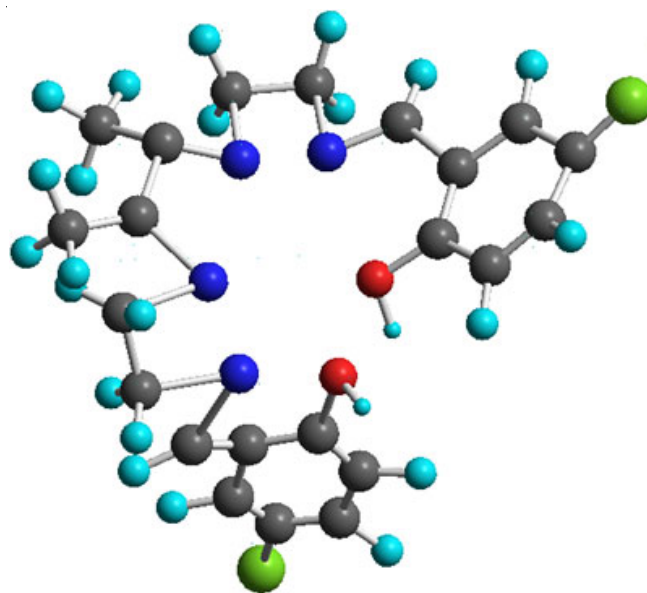


Fig. 1. Three dimensional structural representation of ligand [H_2L]

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF LIGAND (H_2L) AND METAL COMPLEXES (**1-4**)

Compound (m.f)	Colour	m.w.	Yield (%)	m.p. (dec.) (°C)	Elemental analysis (%): Calcd. (found)					Molar conductance (Λ_M) [#]
					C	H	N	Cl	M ⁺	
H_2L ($C_{22}H_{24}N_4O_2Cl_2$)	Yellowish	447.36	70	138	59.07 (58.99)	5.41 (5.12)	12.52 (12.26)	15.85 (15.22)	-	-
[FeL].Cl (1) ($C_{22}H_{22}N_4O_2FeCl_3$)	Brown	536.64	72	247	49.24 (49.02)	4.13 (4.01)	10.44 (10.18)	19.82 (19.52)	10.41 (10.34)	98.80
[CrL].Cl (2) ($C_{22}H_{22}N_4O_2CrCl_3$)	Greenish	532.79	64	243	49.59 (49.12)	4.16 (4.05)	10.52 (10.14)	19.96 (19.42)	9.76 (9.39)	86.60
[CoL].Cl (3) ($C_{22}H_{22}N_4O_2CoCl_3$)	Brown	539.73	65	239	48.96 (48.56)	4.11 (4.03)	10.38 (10.27)	19.71 (19.52)	10.92 (10.66)	81.40
[MnL].(CH ₃ CO ₂) (4) ($C_{24}H_{26}N_4O_4MnCl_2$)	Deep brown	559.32	68	225	51.54 (51.37)	4.51 (4.28)	10.02 (9.88)	12.68 (12.35)	9.82 (9.52)	93.20

[#]Fe, Cr, Co or Mn; [#] $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$

TABLE-2
SIGNIFICANT IR SPECTRAL DATA (ν , cm^{-1}) OF THE LIGAND (H_2L) AND METAL COMPLEXES (**1-4**)

Compound	$\nu(\text{C}=\text{N})$	$\nu(\text{OH-Ph})$	$\nu(\text{C-O})_{\text{Ar}}$	$\nu(\text{M-N})$	$\nu(\text{M-O})$
H_2L	1636	3431	1278	–	–
[FeL].Cl (1)	1588	–	1259	476	518
[CrL].Cl (2)	1592	–	1252	484	530
[CoL].Cl (3)	1584	–	1263	480	520
[MnL].(OAc) (4)	1572	–	1255	476	524

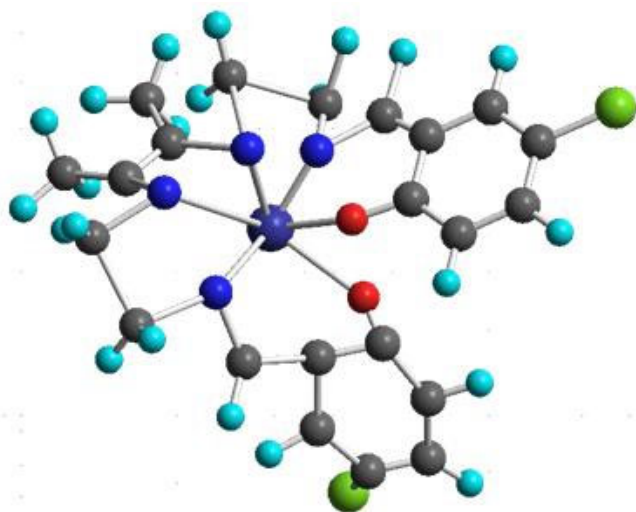


Fig. 2. Three dimensional structural representation of [ML].X (counter ion is omitted)

ketone functional groups are absent in the spectrum of H_2L , which confirms the condensation among carbonyl groups and amine groups [36]. Instead of these all, a fresh sharp band appeared at 1636 cm^{-1} , which may be corresponding to $\nu(\text{C}=\text{N})$ vibration of azomethine group [36,37]. Presence of phenolic group was indicated by a broad band at 3431 cm^{-1} correspondent to $\nu(\text{OH-Ph})$ vibrations and the absorption bands at 1278 cm^{-1} was assignable to $\nu(\text{C-O})_{\text{Ar}}$ vibration [38]. Other bands for $-\text{CH}_3$, $-\text{CH}_2$, $-\text{CH}_{(\text{Ar})}$, $-\text{C-Cl}_{(\text{Ar})}$ were also present with specific vibrations like 3078 – 3018 cm^{-1} , 730 cm^{-1} , *etc.* in the spectrum of H_2L .

IR spectra of metal complexes (**1-4**) were observed with apposite transformations compared to free ligand H_2L . Vibrations due to azomethine group of Schiff base were shifted by 1592 – 1572 cm^{-1} indicating coordination through nitrogen atoms of ($-\text{C}=\text{N}$) groups [37-39]. Involvement of azomethine nitrogen atoms in coordination was additionally suggested by the appearance of new bands in the range of 484 – 476 cm^{-1} correspond to $\nu(\text{M-N})$ vibrations [37-40]. Disappearance of phenolic group vibrations and assessable shift in $\nu(\text{C-O})_{\text{Ar}}$ band in the range of 1263 – 1252 cm^{-1} clearly indicate the deprotonation of (OH-Ph) group during coordination with metal ions [41,42], which was further revealed by presence of new-fangled bands in the range of 530 – 518 cm^{-1} consistent with $\nu(\text{M-O})$ vibrations [36-38].

^1H & ^{13}C NMR spectra: The ^1H NMR spectra of ligand and Co(III) metal complex (**3**) were recorded in $\text{DMSO-}d_6$. The ^1H NMR spectra of ligand, shows the following signals with chemical shift values (δ ppm): 1.24 (6H, s, $-\text{CH}_3$), 3.20

(4H, t, $=\text{N-CH}_2$), 3.82 (4H, m, $-\text{CH}_2-\text{N}=\text{}$), 7.10 – 7.54 (6H, m, Ar), 9.10 (2 H, m, $=\text{CH}$), 11.26 (2H, s, br, $-\text{OH}$). These values are in favour of synthesis of ligand (H_2L) as the spectrum data is free from the δ -values correspondent to free amine and aldehyde protons of reactant species [36]. The ^1H NMR spectrum of Co(III) complex shows following signals with chemical shift values (δ ppm): 0.96 (6H, s, $-\text{CH}_3$), 2.90 (4H, t, $=\text{N-CH}_2$), 3.28 (4H, m, $-\text{CH}_2-\text{N}=\text{}$), 6.76 – 7.38 (6H, m, Ar), 8.82 (2H, m, $=\text{CH}$). The signal of azomethine protons and $-\text{CH}=\text{N}$ protons shifted compared to the free ligand, suggesting coordination through azomethine and ($-\text{CH}=\text{N}$) nitrogen atoms [12,37,38, 43]. Absence of signals corresponding to phenolic proton suggests the participation of phenolic $-\text{OH}$ in the formation of metal complex by deprotonation of ligand [37,38].

The ^{13}C NMR spectrum of H_2L and [CoL].Cl recorded in $\text{DMSO-}d_6$ solvent produced chemical shift values (δ ppm) as shown in Fig. 3. The δ values (per ppm) presented in Fig. 3a are in conformity of desired Schiff base ligand synthesis by the condensation reaction among carbonyl groups ($-\text{C}=\text{O}$) and primary amine groups ($-\text{NH}_2$) available in starting materials [44]. Coordination between Co(III) ion and donor sites of ligand is clearly supported by good shift Fig. 3b in δ ppm values of carbon atoms associated to azomethine groups ($-\text{C}=\text{N}$), methylene groups ($-\text{CH}_2$) and aromatic ring along with somehow influenced δ values of other carbon atoms as compared to free ligand [36-38,44].

ESI-mass spectra: Electro-spray ionization method was applied to record the mass spectral data of ligand (H_2L) and its metal complexes (**1-4**). Comparison of formulae mass and observed mass to charge (m/z) data of compounds illustrate their proposed molecular formulation. Predictable peaks of fragmented ions (m/z) are at: 447.24 [$\text{M}]^+$ (H_2L), 537.28 [$\text{M} + 1]^+$ (**1**), 533.62 [$\text{M} + 1]^+$ (**2**), 540.58 [$\text{M} + 1]^+$ (**3**), 560.18 [$\text{M} + 1]^+$ (**4**). Other peaks associated to the thermal cracking of compounds in various fragments were also available in spectral data.

Electronic absorption spectra and magnetic moment measurements: The electronic absorption data of all the metal complexes (**1-4**) were measured in DMF solvent. The UV-visible spectrum of Fe(III) complex shows absorption band at 718 and 565 nm , which is assigned to the ${}^6\text{A}_1 \rightarrow {}^4\text{T}_1$ and ${}^6\text{A}_1 \rightarrow {}^5\text{T}_1$ transitions, respectively and additional band at 458 and 362 nm may be recognized as ${}^6\text{A}_1 \rightarrow {}^5\text{T}_2$ and charge transfer ($\text{L} \rightarrow \text{M}$) transition, respectively for Fe(III) complex. These transitions are favourable to distorted octahedral Fe(III) complexes [17,45,46]. The Cr(III) complex shows three absorption bands at 638 , 450 and 324 nm which are assigned to ${}^4\text{T}_1 \rightarrow {}^4\text{T}_2$, ${}^4\text{T}_1 \rightarrow {}^4\text{A}_2$ and ${}^4\text{T}_1 \rightarrow {}^4\text{T}_2$ transitions, respectively, characteristics of octahedral Cr(III) complexes with distortion [36,45,47]. The

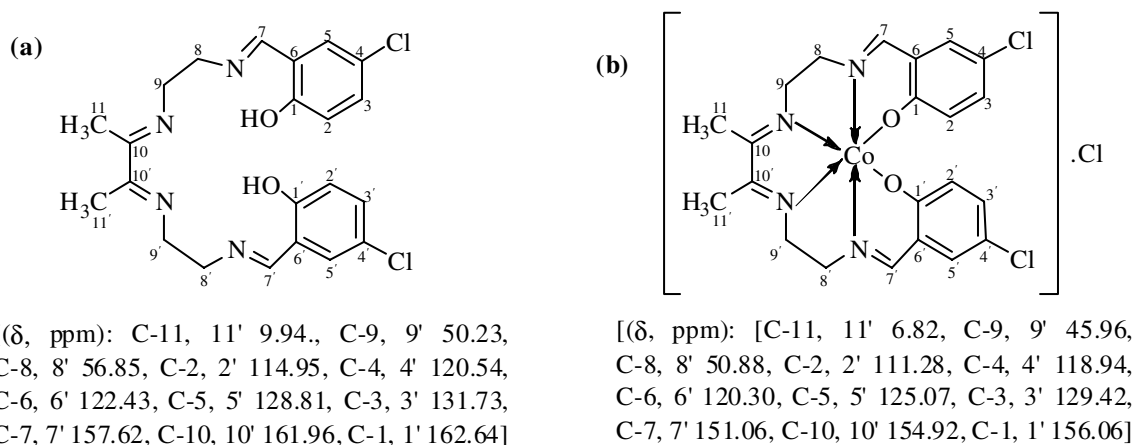


Fig. 3. Number assignment to carbon atoms and their ^{13}C NMR spectral data in $\text{DMSO-}d_6$ solvent: (a) (H_2L) ligand, (b) $[\text{CoL}]\cdot\text{Cl}$ complex (**3**)

spectral absorption band for Co(III) complex is observed at 653, 438 and 357 nm, which may be assigned to transitions $^1\text{A}_1 \rightarrow ^3\text{T}_2$, $^1\text{A}_1 \rightarrow ^1\text{T}_1$ and $^1\text{A}_1 \rightarrow ^1\text{T}_2$, respectively for octahedral environment with distortion around cobalt metal ion [48]. The Mn(III) complex shows absorption bands in the wave length range of 310-350, 300-470 and 320-665 nm to assignable to transitions $^5\text{B}_1 \rightarrow ^5\text{A}_1$, $^5\text{B}_1 \rightarrow ^5\text{B}_2$ and $^5\text{B}_1 \rightarrow ^5\text{E}$ transitions, respectively evocative to distorted octahedral Mn(III) complexes [24,49]. Magnetic moments of the metal complexes were measured at room temperature and the effective magnetic (μ_{eff}) values of the complexes (**1**, **2**, **4**) were found 5.82, 4.10 and 4.80 B.M., respectively which favours the geometry prediction of electronic spectral analysis around Fe(III), Cr(III) and Mn(III) metal ions, respectively [24,36,45,46]. Co(III) complex (**3**) showed a diamagnetic behaviour as expected for the system configuration in octahedral geometry [45,48].

***in vitro* antibacterial and antifungal activity:** *Bacillus subtilis*, *Escherichia coli* bacteria and *Aspurgillus niger*, *Aspurgillus flavus* fungi were targeted *in vitro* to assess the antimicrobial efficacy of H_2L and its metal complexes (**1-4**). Data summarized in Table-3 gives a clear indication that coordination may enhance the antibacterial and antifungal potential

of compounds as metal complexes showed greater potential than free ligand. Among all tested compounds, Cr(III) metal complex (**2**) elucidated highest biological activity against all microbes (Fig. 4). Among all tested compounds, the inhibition potential order is $[\text{CrL}]\cdot\text{Cl} > [\text{CoL}]\cdot\text{Cl} > [\text{FeL}]\cdot\text{Cl} > [\text{MnL}]\cdot(\text{OAc}) > \text{H}_2\text{L}$ and have more patency towards fungal strains. Against targeted microbes, all the compounds are more effective on Gram-negative bacteria (*Escherichia coli*) and fungi *Aspurgillus flavus*. Based on chelation theory, overlapping of ligand orbital and partial sharing of positive charge of metal ion with donor atoms may reduce the metal ion at a greater extent. As well as, it may boost up the incursion of the complexes into lipid membranes and may perturb enzyme activity inside the microbial cell due to increase in the delocalization of π -electrons over the whole chelate ring [6,32,50].

Conclusion

Hexadentate N,O occupied ligand employed to design mononuclear metal complexes of Fe(III), Cr(III), Co(III) and Mn(III) ions. Proposed octahedral geometry with distortion, 1:1 electrolytic behaviour and composition of synthesized complexes were confirmed on characterization by using various

TABLE-3
in vitro ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY DATA OF LIGAND (H_2L) AND METAL COMPLEXES (**1-4**)

Compound	Conc. ($\mu\text{g mL}^{-1}$)	Inhibition (%)			
		<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Aspurgillus niger</i>	<i>Aspurgillus flavus</i>
H_2L	100	43	54	65	68
	500	51	58	77	81
$[\text{FeL}]\cdot\text{Cl}$ (1)	100	54	65	72	74
	500	58	69	82	83
$[\text{CrL}]\cdot\text{Cl}$ (2)	100	57	76	85	85
	500	65	85	88	90
$[\text{CoL}]\cdot\text{Cl}$ (3)	100	55	66	77	77
	500	63	72	87	87
$[\text{MnL}]\cdot(\text{OAc})$ (4)	100	51	59	70	71
	500	56	60	81	82
Streptomycin	100	72	86	—	—
	500	80	90	—	—
Fluconazole	100	—	—	88	92
	500	—	—	91	93

Streptomycin = standard antibacterial drug, Fluconazole = standard antifungal drug

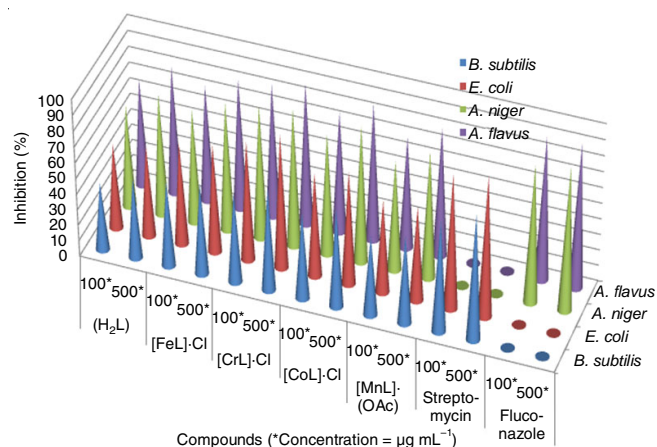


Fig. 4. Graphical representation of antibacterial and antifungal potential of compounds

physico-chemical methods. Biological potential testing of compounds by *in vitro* means clearly pointed toward enhanced antibacterial and antifungal potential of metal complexes with highest activity of [CrL]·Cl complex compared to free ligand.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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