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Synthesis, characterization, spectral, thermal, molecular docking and biological studies of benzimidazol-2-ylmethyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide and their Co(II), Ni(II) and Cu(II) complexes

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Abstract: *The new series of Co(II), Ni(II) and Cu(II)metal complexes of N-(1H-benzimidazol-2-ylmethyl)-2-(pyridin-4-ylcarbonyl)hydrazinecarbothioamide(L)ligand was synthesized and characterized by [1]H-NMR, LC-mass, IR, UV–Visible and thermal studies. The metal/ligands ratio of 1:2 was proposed to afford square pyramidal geometry; octahedral geometry and tetragonal geometry for the complexes, the measured molar conductance values in DMF indicate that the complexes are non-electrolytic in nature. The ligand and complexes have been screened for their antioxidant activity on in vitro DPPH free radical scavenger method show promising results, and it is correlated with computational in silico molecular docking using tyrosinase enzyme structure (PDB ID: 3NM8) from Bacillus megaterium. Further the studies on antibacterial strains (Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Salmonella typhi) and antifungal strains (Aspergillusniger, Aspergillusflavus and Cladosporium)exhibits promising activity.*

Keywords: *2-chloro methyl benzimidazole, isonicotinic hydrazide, metal complexes, molecular docking and antioxidant studies.*

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I. Introduction

The benzimidazole moiety is part of the chemical structure of vitamin B_{12}which is one of the biologically significant natural compounds [1]. Benzimidazole and its derivatives have involved continuing interest over the years because of their varied biological activities viz. anticancer [2], antihypertensive [3], antiviral [4], anti-inflammatory [5], vasodilator [6] and antimicrobial [7-9]. Moreover, as a typical heterocyclic ligand, the large benzimidazole rings not only can afford potential supramolecular recognition sites for π–π stacking interactions, but also act as hydrogen bond acceptors and donors to accumulate multiple coordination geometry[10].Transition metal complexes containing benzimidazole-based ligand are a subject of intensive researches not only owing to their rich coordination chemistry but also due to a number of established and prospective application areas [11-14],which gives the possibility for further research, such as design of structural probes and the development of novel therapeutics. The aim of present work deals specifically the coordination properties of N-(1H-benzimidazol-2-ylmethyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide (L) concerning its interactions with Co(II), Ni(II), and Cu(II) complexes, spectral characterization and thermal decomposition studies serve as important tools for the interpretation of structures of molecules and also biological and analytical importance. molecular docking study have been performed to investigate the interaction and binding energies of the complexes with tyrosinase enzyme *by using HEX 8.0 for* antioxidant activity, the compounds were also performed to investigate against the growth of *in vitro* bacteria and pathogenic fungi.

II. Experimental

2.1 Material and methods

Melting points were recorded on electro-thermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer at IISc, Bangalore, Karnataka, India. The chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as an internal standard. LC-MS was obtained using C 18 column on Shimadzu, LCMS 2010A, Japan. The FTIR spectra of the compounds were taken as KBr pellet (100 mg) using Shimadzu Fourier Transformed Infrared (FTIR) Spectrophotometer. Silica gel GF254

plates from Merck were used for TLC and spots were located either by UV or dipping in potassium permanganate solution. The chemicals were purchased from Sigma-Aldrich Co and from spectrochem chemicals. The TGA graphs of all metal complexes were taken by the Diamond Thermogravimetric/Differential Thermal Analyzer (TG/DTA) at room temperature of 900^0C under heating rate of 20^0C min^{-1}.

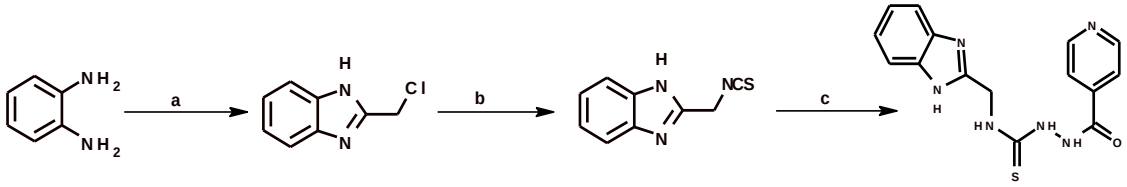
2.2 Synthesis

The key intermediate2-(chloromethyl)-1H-benzimidazole was synthesized from commercially available benzene-1,2-diamine as reported previously[15-16].

2.3 Preparation of N-(1H-benzimidazol-2-ylmethyl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide (L)

A mixture of 2-(chloromethyl)-1H-benzimidazole(0.5mmol) in 30ml of dry ethanol was added to a solution of potassiumthiocyanate (0.6mmol) in 10 ml dry ethanol the reaction mixture was refluxed for 6h forming isocyanate derivative as an intermediate. After cooling, the white precipitate of potassium chloride was filtered off, to the filtrate solutions of isonicotinic hydrazide (0.5mmol) was added and allowed to reflux with continuous stirring for 8h. The reaction was monitored by TLC (chloroform: methanol, 0.9:0.2).After completion of the reaction, the solution was poured into crushed ice; the solid so obtained was collected by filtration to afford L.

Yellow solid, Yield 72%; mp 181^{o}C; Anal.Calcd for$_1C_5H_{14}N_6OS$ (%): C, 56.83; H, 5.30; N, 29.46. Found: C, 55.75; H, 5.19; N, 28.65. IR (KBr): m (cm^-1):(-NH) 3380, (-C=N)1668, (-*C=S)*1557, (-C=O) 1520,(-*C=C*) 1441.^{1}H NMR (DMSO-d_6) d (ppm): 7.96-7.25δ (ppm)(m,Ar1H), 8.82 - 8.53δ ppm(s -NH 1H), 4.17 - 4.07δ ppm (dd–CH_2^{1}H). MS: m/z 328.96.



Scheme 1. (a) Chloroacetyl Chloride, 5 N HCl, reflux, 4 h; (b) KSCN , EtOH reflux, 6 h; (c) isonicotinic hydrazidereflux, 8h.

2.4 Preparation of Metal Complexes [M $(L)_2Cl_2$].nH_2O

Hot solution of hydrated metal chlorides (0.1 mmol, Co, Ni and Cu) in absolute ethanol was added to the hot solution of the ligand (L) (0.2 mmol) ethanol (25 mL). The resulting mixture was stirred under reflux for 5-6h.The complex precipitated was then collected by filtration and washed with distilled water and cold ethanol. The physical properties and analytical data of the ligand and its metal complexes are given the Figure 1 and Table 1.

Table 1. Physical Properties of the Metal Complexes

Compound	*Mol.Wt*	*Colour*	*M.p (^{o}C)*	**Molar conductance (ohm^{-1} cm^2mol^{-1})**	*Yield (%)*
[Co $(L)_2$]	713.70	Brown	295-300 ^{o}C	62.4	68%
[Ni $(L)_2$]	713.45	Dark green	300-305 ^{o}C	41.6	65%
[Cu $(L)_2$]	718.31	Light green	315-320 ^{o}C	31.4	70%

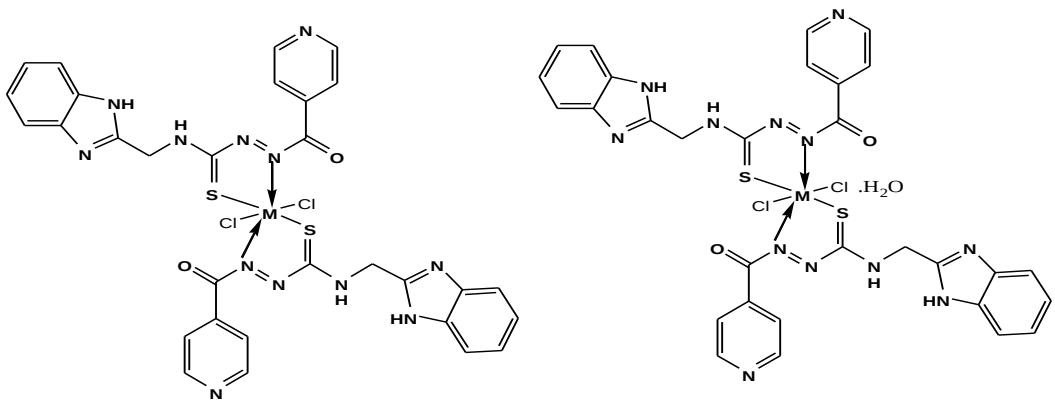


Fig.1. Proposed structure of metal complexes (M=Co, Ni, and Cu)

III. Biological Studies

3.1 Molecular Docking Studies

The docking is a method which involves the prediction of ligand conformation and orientation in the binding receptacle of the receptor. All the synthesized compounds were screened for docking analysis carried out with antioxidant strain tyrosinase enzyme (PDB ID: 3NM8) from *Bacillus megaterium* by HEX 8.0 and compared with uncoordinated ligand. The receptor was downloaded from RCSB protein data bank. A rigid body docking was performed with HEX 8.0 [17-20], by SP Fourier Transform, FFT steric scan, FFT final search and MM refinement. More negative E-total energy value implies that a strong binding interaction exists between drug and receptor which leads to the inhibition of receptor activity. The enzyme structure containing hetero molecules were removed before docking was carried out. The corresponding CIF files of derivatives were converted into PDB file using Argus lab. The ligands were converted to 2D and 3D energy-minimized conformations using Hex 3D Ultra 8.0.

3.2 Antioxidant Activity studies

The free radical scavenging activity of the fractions was measured *in vitro* by 2, 20- diphenyl-1-picrylhydrazyl (DPPH) assay according to the method described in the reports [21].The stock solution was prepared by dissolving 24 mg DPPH with 100 ml methanol and stored at 20°C until required. The working solution was obtained by diluting DPPH solution with methanol to attain an absorbance of about 0.98±0.02 at 517 nm using the spectrophotometer. A 3 ml aliquot of this solution was mixed with 100 µl of the sample at various concentrations (10 - 500 µg/ml). The reaction mixture was shaken well and incubated in the dark for 15 min. at room temperature. Then the absorbance was measured at 517 nm. The control was prepared as above without the sample.

Scavenging ratio (%) = $[(A_i–A_o)/(A_c–A_o)] \times 100\%$

Where A_i is the absorbance in the presence of the test compound; A_0 is absorbance of the blank in the absence of the test compound; A_c is the absorbance in the absence of the test compound.

3.3 Antimicrobial Activity

In vitro antibacterial and antifungal studies

The *in-vitro* antibacterial and antifungal activity of ligand and the metal complexes was determined by well plate method [22-23].The following Gram positive and negative bacteria were used as test organism *Escherichia coli, Bacillus subtilis and Salmonella typhi and* fungal strains are *Candida albicans, Aspergillusflavus and cladosporium* to investigate the activity. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 25, 50 and 100µ/mL and incubated at 37 $^{\circ}$C for 24 h for bacteria and 38 h for fungi, the diameter of the zone of inhibition around each well plate was measured after the incubation period.

IV. Results And Discussion

The newly synthesized synthetic route of the ligand (L) is shown in Scheme 1. The complexes were prepared by reaction of ligand with metal halides in the ratio of 1:2using absolute ethanol. The molar conductance values of the complexes in DMF at a concentration of 10^{-3} M at room temperature are in the range of 31-70 $ohm^{-1}cm^2\ mol^{-1}$.Thelow molar conductivities of the complexes in DMF solution indicates that partial dissociation of Ni(II) and Cu(II) complexes in DMF, signifying the non-electrolytic nature. In the case of Co(II) complex, high molar conductance value imply that the complex is electrolytic in nature, and the values were presented in Table 1.

4.1 ^{1}H NMR Spectra and Mass Spectra

^{1}H NMR spectrum of the ligand is shown in Fig 2, in DMSO-d_6 conform its structure by displaying a singlet in the range in between 8.82 and 8.53ppm for secondary amine hydrogen of imidazole ring, The multiplets observed in the range of 7.96–7.25ppm is assigned to aromatic protons of both imidazole and isonicotinic hydrazide ring, the two double doublet at 4.17–4.07ppm for $–CH_2$ protons respectively. The mass spectrum of ligand is depicted in Fig. 3. The spectrum showed a molecular ion peak at m/z 328.96, which is almost equivalent to expected molecular weight.

4.2 IR Spectra and Mode of Bonding

The prominent IR frequencies of the ligand and metal complexes are presented in Table2.The most characteristic bands of the ligand are at 3380 cm^{-1}υ(–NH) of benzimidazole ring , 1668 cm^{-1} υ(–C=N)1557 cm^{-1} υ(–C=O) of isonicotinic hydrazide, 1520 cm^{-1} υ(–C=S), and 1441cm^{-1}υ(C=C) of ligand indicates that isocyanate intermediate compound was formed by condensation from Isoniazid as expected. The IR spectrum of the metal complexes showed that the band at 1668 cm^{-1}assigned to the υ(–C=N) vibration of the ligand was shifted to lower frequency after complexation, to 1611, 1617, and 1604 cm^{-1} for the Co (II), Ni (II), and Cu (II) complexes, respectively. This shift indicates coordination of the ligand to the metal ions through nitrogen of isonicotinic hydrazide. At the similar to this υ(–C=S) band at 1520 $cm^{-1}$is shifted to lower frequency suggest a

weakening of the (–C=S) vibration therefore, This confirms that the coordination of the metal complexes has takes place through M-N and M-S atoms of the ligand [24-25].

Table 2. Characteristic IR bands of the ligand and its complexes

Compound	*ν(NH)*	*ν(C=N)*	*ν(C=O)*	*ν(C=S)*	*ν(C=C)*	*ν(M-N)*	*ν(M-S)*
Ligand (L)	3380	1668	1557	1520	1441	740	687
[Co (L)$_2$]	3267	1611	1555	1450	1381	742	691
[Ni (L)$_2$]	3393	1617	1618	1468	1353	743	698
[Cu (L)$_2$]	3265	1604	1608	1372	1320	742	697

4.3 Electronic Spectral Studies

The UV-visible spectral data of ligand and their Co(II), Ni(II) and Cu(II) complexes are given in the Figure2.The electronic spectra of the free ligands showed two adsorption bands in the region of 280 to 310 nm due to π→π* transition. The visible spectra of all complexes in DMF displayed clear bands in the range of 535 to 785nm and the broad low laying shoulder at 380 to 420 nm due to the red shift shows π→ d_x^2 - $_y^2$LMCT transition in all complexes [26] The UV-visible spectrum of Co(II) showed electronic transition at 24390 cm^{-1} (410nm) and another at 18518cm^{-1}(540nm) may be assigned to $^4A_2$+^4E→$^4A_2$(P) and $^4A_2$+4_E→4E(P) respectively [27]. The molar conductance also shows that uni electrolytic behavior in DMF hence the complex is expected to have square pyramidal geometry, for Ni (II) complex the bands appear at 16393 cm^{-1}(610nm) and 25000 cm^{-1} (400nm) due to $^3A_{2g}$(F) → $^3T_{1g}$(F) (γ_2) and $^3A_{2g}$(F) → $^3T_{1g}$(P) (γ_3) respectively. The conductance measurement value indicate that the complex is non electrolytic behavior therefore the complex is tentatively proposed to have octahedral geometry [28]the electronic spectra of Cu(II) complex showed a low intensity broad band around 24390 cm^{-1}(410nm) and 13517cm^{-1} (760nm) nm assignable to ^{2}Eg → $^2T_2$g transition (d^9), which is due to tetragonal geometry.

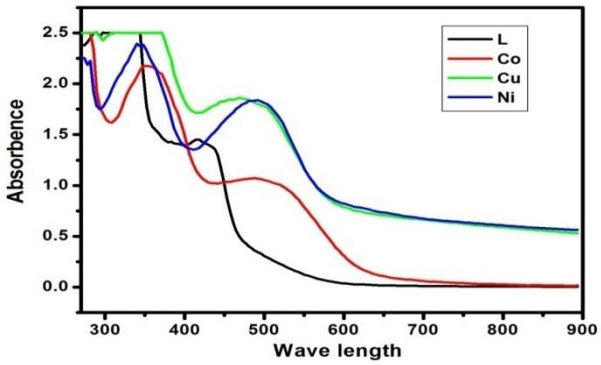


Fig 2 Electronic spectras of metal complexes

4.4 Thermal Studies of Metal Complexes

The thermal behavior of Co (II), Ni (II) and Cu (II) complexes has been studied in thetemperature range 50-800°C as represented in fig 3 and table 3.

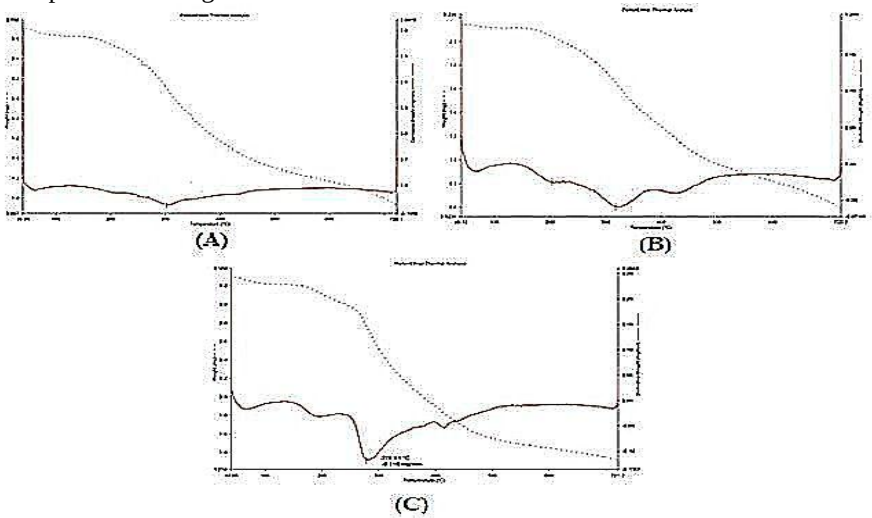


Fig3 TG-DTA of (A) Co(II), (B) Ni(II) and (C) Cu(II).

The $[CoCl_2(L)(H_2O)].H_2O$ complex exhibits three decomposition steps. The first step in the range of 30-90 °C by mass loss of 4.81 % (Calcd. mass loss 4.01 %) of water molecule of hydration. The second and third steps found within the range 250-310 °C and 420-850 °C with an estimated mass loss 81.92 % (Calcd. Mass loss 81.00 %) which are responsible for decomposition of the rest organic part ($C_5H_{14}N_6OS$) leaving CoO as a residue.$[NiCl_2(L)(H_2O)].H_2O$ complex exhibits thermally decomposition at two steps. The first step estimated mass loss of 8.63 % (Calcd. mass loss 8.90 %) in the temperature range of 30-150 °C of coordinated water molecules. The second step found within the range 290-900 °C with an estimated overall mass loss 73.99 % (Calcd. Mass loss 72.27 %) which are responsible for decomposition of the rest organic part of the ligand ($C_5H_{14}N_6OS$) leaving NiO as a residue. The TGA for $[CuCl_2(L)(H_2O)].4H_2O$ chelate represent three steps. The first step of decomposition within the temperature range 30–140 ◦C corresponds to the loss of four hydrated water molecules with a mass loss of 14.91% (calcd. mass loss 14.30%). The left over steps of decomposition takes place at 270-850 °C corresponds to the removal of organic part associated with ligand ($C_5H_{14}N_6OS$) leaving CuO as a residue.

Table 3 Thermogravimetric data of Co(II), Ni(II) and Cu(II) complexes

Complexes	TG range (°C)	Estimated (calcd.) %	Total mass loss	Metallic Residue (n*)
$[CoCl_2(L)(H_2O)]\cdot H_2O$	30-90 280-850	4.81 (4.05) 81.92 (81.00)	86.73 (85.11)	CoO (3)
$[NiCl_2(L)(H_2O)]\cdot H_2O$	30-150 290-900	8.63 (8.09) 73.99 (72.27)	82.62 (80.36)	NiO (2)
$[CuCl_2(L)(H_2O)]\cdot 4H_2O$	30-140 270-850	14.91 (14.30) 70.31 (68.11)	85.22 (83.21)	CuO (3)

n* = number of decomposition steps

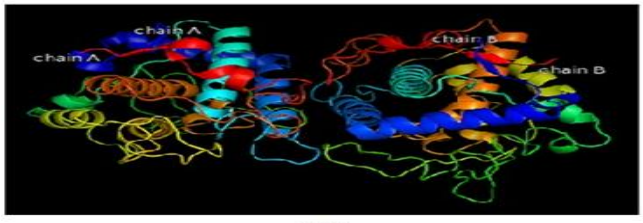
4.5 Molecular Docking Studies

Molecular docking analysis of all the compounds have been carried out against protein receptor tyrosinase enzyme (PDB ID: 3NM8) from *Bacillus megaterium, in* order to rationalize the obtained biological data and explain the possible interactions that might take place with the amino acid residue.

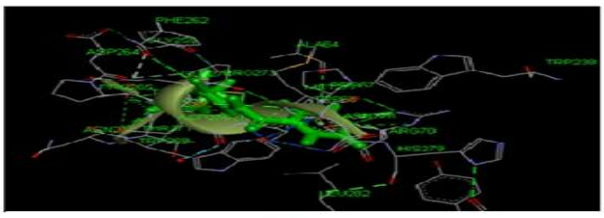
Table 4 Docking study results of screened antioxidant compounds

Compounds	Total energy value (E-total)
Ligand(L)	-221.80
Co–L	-287.27
Ni–L	-281.88
Cu–L	-286.24

It can be concluded that the receptor with metal complexes fits best with the highest binding energy for the compounds *Co–L complex* (energy value -287.27), followed by *Ni–L complex* (energy value -281.88), and Cu–*L complex* (energy value -286.24).The compound ligand showed least binding energy with energy value of -221.80. Docking studies showed that Tyr267A, Pro268A, Ala44A, Leu282, Tyr267B His60, and Pro268B amino acids in the tyrosinase enzyme (PDB ID: 3NM8) may play major role in substrate binding or catalysis and given Figure4 and Table 4.



(A)



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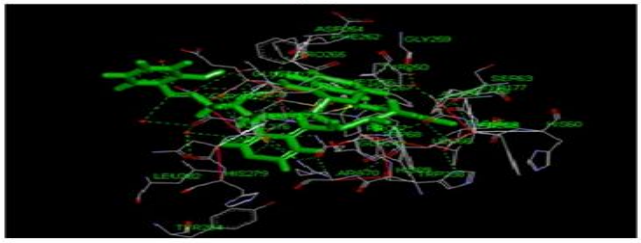

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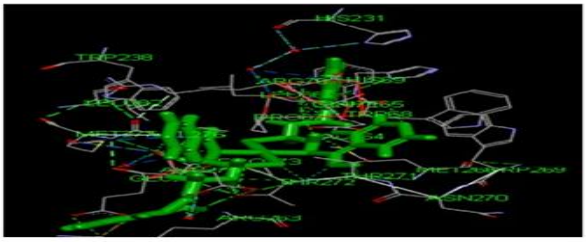
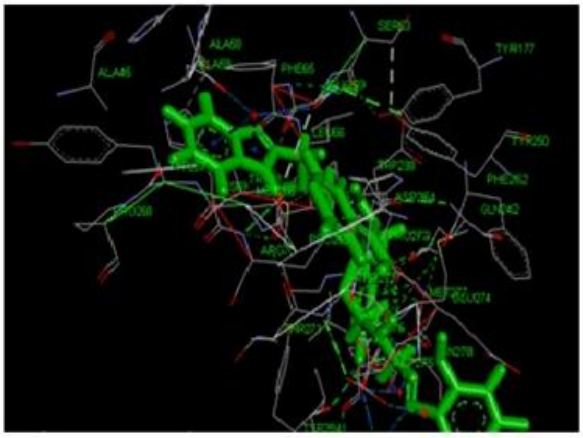


(D)



(E)

Fig 4. 3-Dimensional (3D) interactions of ligand and complexes (A) Tyrosinase enzyme (PDB ID: 3NM8) from Bacillus megaterium. (B) Co (II) complex. (C) Ni (II) complex. (D) Cu (II) complex.

4.6 Antioxidant Activity

According to relevant reports in the literature [29], some transition metal complexes exhibit potential antioxidant activity**.** The free radical scavenging activity of all compounds was measured using the DPPH method. The ascorbic acid was used as the standard. Among the tested compounds shows significant DPPH scavenging activity (>60%) at 100 mg concentration (Figure5). All complexes exhibited potent scavenging activity, among them Cu(II) and Ni(II) shown highest scavenging activity compared with the standard expecting the ligand shows slightly lower activity than that of complexes.

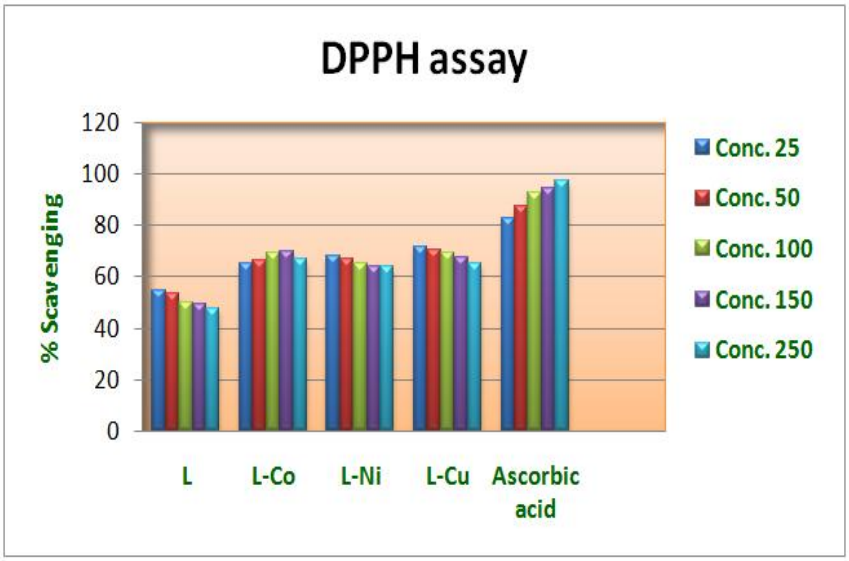


Fig 5 Radical scavenging activity of ligand and complexes.

4.7 Antimicrobial Activity

The results of tested compounds shown in Table5 and 6, indicates that all the complexes exhibit higher inhibition efficiency than the free ligand against various tested microbial strains. The chelation reduces the polarity of the ligand due to the overlap of the ligand orbitals and partial sharing of the positive charge of the metal ions with donor groups. Further, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lyophilic nature of the complexes [30].

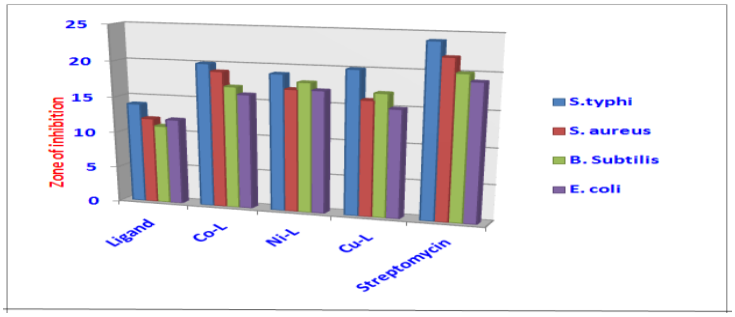


Fig6 Antimicrobial activity of ligand and the metal complexes

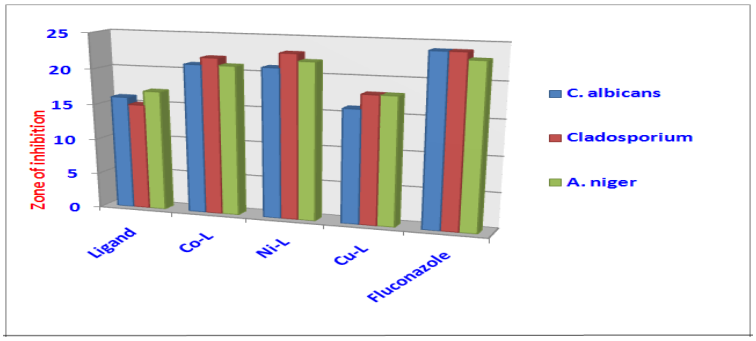


Fig7 Antimicrobial activity of ligand and the metal complexes

Thus chelating tends to make the benzimidazole derivatives act as more powerful and poten tbactereostatic agents, thus inhibiting the growth of bacteria and fungi. The Co(II), Ni(II) and Cu(II) complexes exhibit eminent efficiency then the free ligand compared to standard drug Streptomycin for bacterial activity. For fungal activity the Co(II) and Co(II) complexes shows good efficiency then that of Cu(II) complex and free ligand when compared to standard drug Fluconazole represented in figure 6 and 7.

Table 5 & 6 Antimicrobial results of Ligand (L) and their metal complexes

Compounds	Conc(μgml^{-1})	*% inhibition against bacteria*			
		S.typhi	*S. aureus*	*B. Subtilis*	*E. coli*
Ligand (L)	25	*08 ± 0.3*	*05 ± 0.5*	*04 ± 0.3*	*06 ± 0.3*
	50	*06 ± 0.5*	*03 ± 0.2*	*02 ± 0.1*	*04 ± 0.5*
	100	*04 ± 0.5*	*04 ± 0.5*	*04 ± 0.5*	*04 ± 0.5*
Co-L	25	*11 ± 0.1*	*09 ± 0.2*	*13 ± 0.1*	*12 ± 0.2*
	50	*13 ± 0.4*	*12 ± 0.6*	*12 ± 0.3*	*13 ± 0.4*
	100	*20 ± 0.3*	*16 ± 0.4*	*17 ± 0.4*	*16 ± 0.4*
Ni-L	25	12 ± 0.5	11 ± 0.5	13 ± 0.1	12 ± 0.5
	50	14 ± 0.4	13 ± 0.4	14 ± 0.3	10 ± 0.4
	100	19 ± 0.4	17 ± 0.3	16 ± 0.2	10 ± 0.4
Cu-L	25	12 ± 0.5	11 ± 0.2	13 ± 0.3	12 ± 0.3
	50	13 ± 0.3	12 ± 0.1	14 ± 0.2	13 ± 0.4
	100	20 ± 0.4	16 ± 0.3	17 ± 0.4	15 ± 0.2
Streptomycin	25	12 ± 0.1	11 ± 0.2	13 ± 0.3	12 ± 0.5
	50	15 ± 0.4	14 ± 0.2	15 ± 0.3	14 ± 0.4
	100	24 ± 0.5	18 ± 0.5	18 ± 0.4	17 ± 0.2

Compounds	Conc(μgml^{-1})	% inhibition against fungi		
		C. albicans	Cladosporium	A. niger
	25	13 ± 0.3	12 ± 0.3	11 ± 0.3
	50	15 ± 0.4	13 ± 0.1	14 ± 0.4
Co-L	100	22 ± 0.5	23 ± 0.2	20 ± 0.2
	25	12 ± 0.3	11 ± 0.5	10 ± 0.3
	50	14 ± 0.2	14 ± 0.1	13 ± 0.4
Ni-L	100	21 ± 0.5	22 ± 0.6	21 ± 0.1
	25	10 ± 0.3	10 ± 0.5	10 ± 0.3
	50	12 ± 0.2	12 ± 0.2	11 ± 0.1
Cu-L	100	18 ± 0.4	19 ± 0.2	19 ± 0.2
	25	13 ± 0.3	12 ± 0.5	12 ± 0.3
Fluconazole	50	16 ± 0.5	15 ± 0.2	15 ± 0.1
	100	23 ± 0.5	24 ± 0.5	23 ± 0.5

V. Conclusions

A series of Co(II), Ni(II) and Cu(II) metal complexes with new benzimidzole ligand (L) have been successfully prepared and characterized by using various spectral & analytical techniques. The structure of ligand were established by ^{1}H NMR, LCMS followed by IR, UV-visible spectroscopy and thermal studies shows that the ligand are coordinated through the central metal ions through metal-N & metal-S bonding modes.The complexes and ligand were screened DPPH Free radical scavenger activity, the results revealed that, among complexes Cu(II) and Ni(II) exhibited good scavenging property followed by Co(II) and free ligand. Antibacterial and antifungal study reveals that, ligand and metal complexes were found to be highly active due to existence of imidazole moiety along with the metal ions. The comparative docking studies were carried out on synthesized ligand and its complexes compounds which exhibited higher binding energy for Co(II) followed by Ni(II) and Cu(II) complexes with the tyrosinase enzyme (PDB ID: 3NM8).

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