

Metal Complexes of quinolin-8-yl (1, 3-benzoxazol-2-ylsulfanyl) acetate: Spectral, XRD, thermal, molecular docking and biological evaluation

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Abstract: The series of Co (II), Ni (II) and Cu(II) metal complexes quinolin-8-yl (1,3-benzoxazol-2-ylsulfanyl)acetate (BZ) have been synthesized. All the complexes thoroughly characterized by different physico-chemical and spectroscopic techniques (UV-Vis, IR, NMR and ESI-Mass). The powder XRD indicates the crystalline state and morphology of Ni (II) and Cu (II) metal complexes, the thermal stability of the metal complexes as been performed. In the current study, the synthesized compounds were evaluated for their antioxidant activity by using DPPH assay, Cu (II) metal complex exhibited higher antioxidant activity almost close to the standard BHT. In addition, antioxidant activity is correlated with docking interactions of human antioxidant enzyme receptor with the competitive inhibitor DTT (PDB: 3MNG), which showed greater binding interactions with metal complexes. The antimicrobial studies has been carried out against different bacterial and fungal strains and the results showed that metal complexes be more active than the ligand BZ.

Keywords; Benzoxazole, metal complex, XRD, Antioxidant, molecular docking.

I. Introduction

The benzoxazole and its derivatives are known to play exceptionally vital roles in medicinal chemistry which finds use as a preliminary material for the synthesis of larger nucleus. a range of benzoxazole derivatives were extensively considered for their biological and pharmacological activities concerning antibiotic [1,2] antimicrobial [3-5] antifungal [6-8] and antitumor activities [9-11]. In addition, benzoxazole analogous and their metallic complexes have been widely applied for use in chemistry and medicine with various transition metal ions via nitrogen donor atoms [12-14]. Better antimicrobial and antitumor activities have been reported for a few metal-benzoxazole complexes [15-17] in comparison with isolated benzoxazole ligands.

Keeping in view of this we hereby report the synthesis of ligand quinolin-8-yl (1,3-benzoxazol-2-ylsulfanyl)acetate (BZ) and their characterization by elemental, spectral and XRD analysis were performed. We aimed to evaluate the antioxidant features of metal complexes, In-vivo and docking interactions. In-vitro and Antimicrobial activity of ligand (BZ) and metal complexes were also performed against bacterial and fungal strains.

II. Experimental Section

2.1 Materials

The chemicals 5-chloro-2-mercapto-benzoxazole and 8-Quinolinol were Sigma-Aldrich Co. The chlorides of Co(II), Ni(II) and Cu(II) were of S.R.L. grade. All other reagents and solvents were purchased from commercial sources and were of analytical grade

2.2 Physical measurements

Melting points had been recorded on an electro-thermal melting factor apparatus and are uncorrected. ¹H NMR spectra were recorded on Bruker 400 MHz spectrometer at IISc, Bangalore, Karnataka, India. The chemical shifts have been proven in δ values (ppm) with tetramethylsilane(TMS) as an internal standard. LC-MS changed into acquired the usage of a C-18 column on Shimadzu, LCMS 2010A, Japan. The FT-IR spectra of the compounds were taken as KBr pellet (a 100 mg) the usage of Shimadzu Fourier Transform Infrared (FTIR) spectrometer. Magnetic susceptibility have been measured at 35 °C through the Gouy technique, Silica gel GF254 thin plates from Merck were used for TLC and spots were positioned either by UV or dipping in potassium permanganate solution. The powder X-ray studies was carried out by using Rigaku MiniFlex

instrument with Cu-K α radiation (wavelength 0.154nm) and The thermal gravimetric analysis of all metal complexes were taken by the Diamond TG/DT Analyzer (TG/DTA) at room temperature of 700°C below heating pace of 20°C min⁻¹.

2.3 Synthesis of Ligand and Complexes

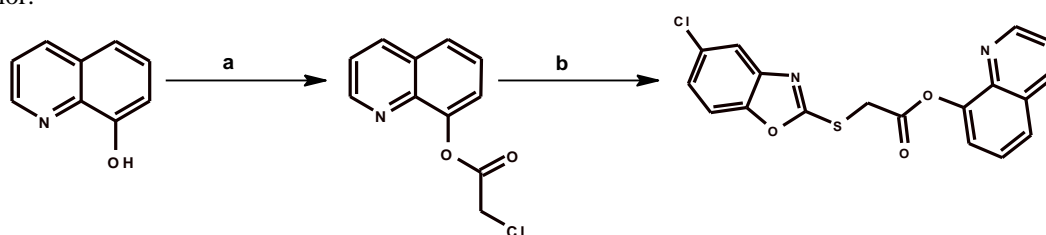
Synthesis of quinolin-8-yl (1,3-benzoxazol-2-ylsulfanyl)acetate (BZ)

Step-1

The 8-hydroxyquinoline (5.0 mmol) is dissolved in the mixture of Tetra hydrfuran and Try ethylamine, stirred at room temperature by adding chloroacetyl chloride drop wise and the reaction mixture stirred for 8 h the product formed was filtrated. The solvent was removed under vacuum and washed with Hot ethanol and dried over anhydrous Na₂SO₄ and the product was obtained as cream solid. Yield: 75%. m.p. 160–162 °C.

Step-2

A mixture 2-mercaptobenzoxazole (4.2 mmol) and quinolin-8-yl chloroacetate (4.2 mmol) dissolved in anhydrous ethanol (30 mL) The mixture was heated under reflux for 12 h, the reaction mixture poured into cursed ice and the precipitate was collected by filtration and washed with ethanol, the product was obtained as cream color.



Scheme 1 [a] THF, TEA RT, 8h [b] 2-mercaptobenzoxazole, Dry C₂H₅OH

2.4. Synthesis of metal complexes

The Ethanolic solution of metal (II) chlorides (0.02mol) was added in drops of ethanolic of ligand BZ (0.04mol) and the mixture was refluxed on water bath at 70 °C for 4-5h. The solid complex obtained was filtered, washed with hot ethanol and dried in vacuum over anhydrous calcium chloride.

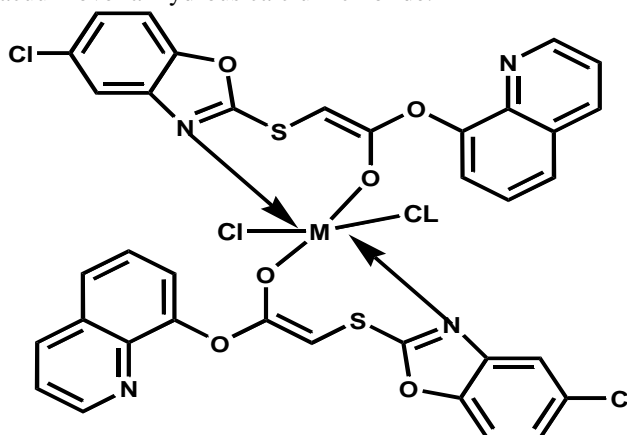


Figure 1 Proposed structures of Metal complexes (M=Co, Ni, & Cu)

III. Biological activity

3.1. Antioxidant activity

The free radical scavenging activity of the ligand BI and complexes was measured In vitro by 2, 20-diphenyl-1-picrylhydrazyl (DPPH) assay. 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 All the tested samples in various concentrations (50, 75 and 100 µg/mL) were prepared in methanol and the homogeneous solutions were achieved by stirring. A liquot of test sample (1 mL) was added to 4 mL of 0.004% (w/v) methanol solution of DPPH and then reaction mixture was vortexed for 1 min and kept at room temperature for 30 min in the dark to complete the reaction. The absorbance was read against blank at 517 nm. The synthetic antioxidant BHT was used as positive control [18, 19]. The ability of the tested samples at tested concentration to scavenge DPPH radicals was calculated using equation.

$$\text{Scavenging ratio (\%)} = [(A_T - A_0) / (A_C - A_0)] \times 100\%$$

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.

3.2. Molecular docking

Molecular modeling studies were performed by using *Hex* 8.0.0 protein-ligand docking in PDB formats. The parameters used for docking include: correlation type-shape only, FFT mode -3D, grid dimension -0.6, receptor range -180, ligand range -180, twist range -360, distance range -40. The starting coordinates of the human antioxidant enzyme in complexes with the competitive inhibitor *DTT* (PDB: 3MNG) were taken from the Protein Data Bank (<http://www.rcsb.org/pdb>) [18, 20]. The selected ligands were docked against the lead competitive inhibitor ligand DTT at the crystal enzyme structure of the target protein and the best energy conformations of receptor ligand were studied, and the energy of binding was calculated as the difference between the energy of the complex and the individual energies of enzyme and ligand.

IV. Results and Discussion

The analytical data of the metal complexes reveals that while reactions with metal (II) chlorides and ligand performed in 1:2 (M:L) molar ratio, the BZ behaves as a bidentate ligand and coordinate through metal oxazole nitrogen and metal oxygen of carbonyl group giving octahedral geometry for Co(II), Ni(II) and Cu(II) complexes. The observed molar conductance of the complexes in DMSO (10^{-2} M solution) are consistent with Co(II), Ni(II) and Cu(II) complexes are non electrolytic in nature [21].

Table 1 Analytical data and molar conductance data BZ and metal complexes

Compounds	Colour	Mol.Wt	Yield (%)	Calcd. (found) (%)			Molar conductance ($\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$)	Melting point $^{\circ} \text{C}$
				C	H	N		
BZ	Pale Yellow	739.60	79	58.46(58.04)	2.73(2.14)	7.58(6.95)	-	180
[Co(BZ) ₂ Cl ₂].2H ₂ O	Light blue	866.89	65	49.73(48.93)	2.32(2.01)	6.78(6.14)	38.12	>250
[Ni(BZ) ₂ Cl ₂]. H ₂ O	Pale green	865.89	69	49.75(49.12)	2.32(2.01)	6.45(6.09)	35.2	>250
[Cu(BZ) ₂ Cl ₂].2H ₂ O	dark blue	870.89	74	49.47(49.14)	2.31(2.01)	7.27(6.98)	27.5	>250

4.1. ¹H NMR and Mass spectra

NMR spectra of ligand BZ showed singlet peak appears at 4.94 ppm attributed to $-\text{CH}_2$ protons, The multiple signals at 7.88 to 7.06 ppm attributed to aromatic protons of 8-hydroxyquinoline and 2-mercaptobenzoxazole rings respectively which reveals the structural evidences for BZ (Figure 2). In the mass spectra pattern (Figure 3) showed molecular ion peak [M^+] at m/z 336.1 (335.4), that concurrence with the molecular weight of BZ ligand respectively.

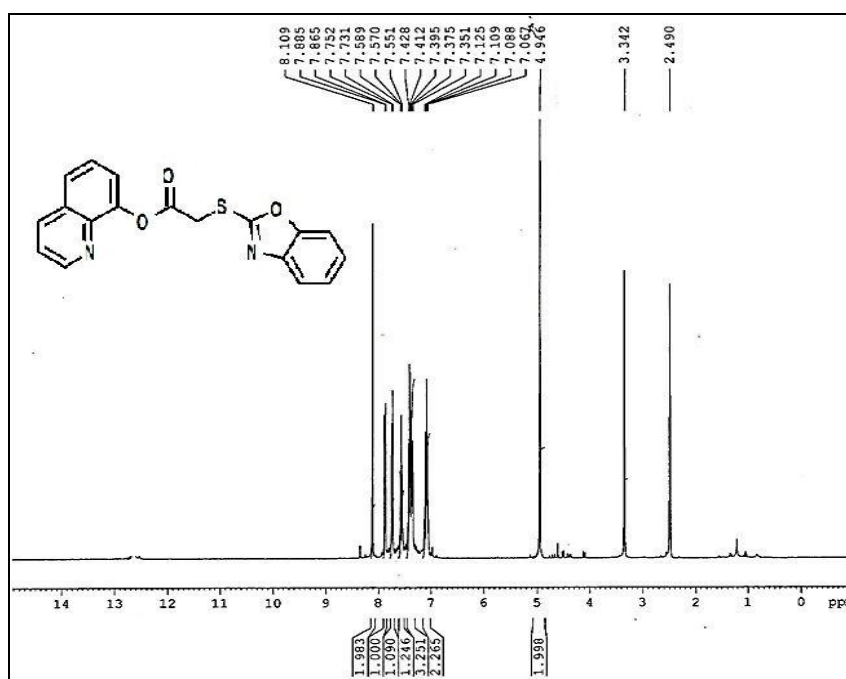


Fig.2 ¹H NMR spectrum of the ligand BZ

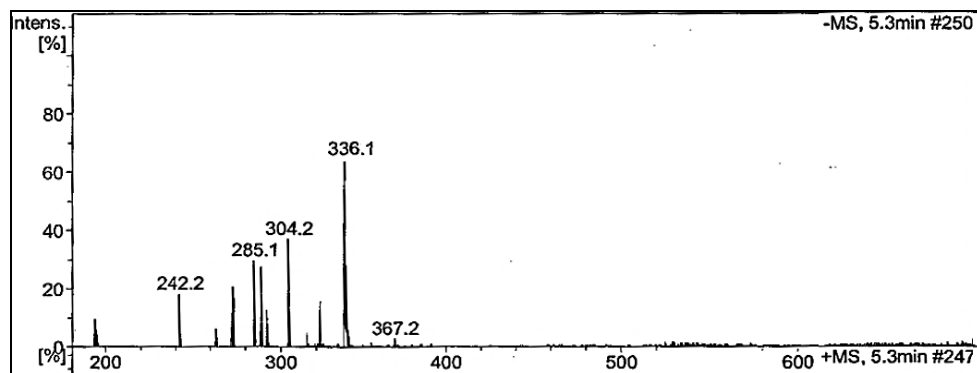


Fig.3 Mass spectrum of the ligand BZ

4.2. IR spectra

The IR spectra of the ligand shows the sharp peak at 1696cm^{-1} for C=O group, while in the Coordinated metal complexes the C=O group is shifted to a lower frequency of 1605cm^{-1} , 1604cm^{-1} and 1612cm^{-1} in its Co(II), Ni(II) and Cu(II) complexes indicating coordination of the C=O group to the metal ion [22]. Followed by -C=N group shows band at 1604cm^{-1} for ligand and it was shifted to lower frequency of $40\text{--}50\text{cm}^{-1}$ in the metal complexes suggesting that coordination through -C=N group. The medium band appears at 1103cm^{-1} for C-O stretching, and 704cm^{-1} for C-Cl group in free ligand. Coordination properties of the ligand and suggesting the association of oxygen atoms in the bonding with the metal ions observed at the range of 520cm^{-1} , 528cm^{-1} and 530cm^{-1} , for $\nu(\text{M-O})$ bonding and followed 467cm^{-1} , 465cm^{-1} and 470cm^{-1} are assigned as $\nu(\text{M-N})$ bonding [23,24].

4.3. Electronic spectra and magnetic moments

The electronic spectral data of ligand shows two strong peaks at $44,843$ and $38,023\text{cm}^{-1}$ attributed to the presence of $\pi\text{--}\pi^*$ and $n\text{--}\pi^*$ transitions [25]. The $\pi\text{--}\pi^*$ transition in the complexes (Co^{II}, Ni^{II}, Cu^{II} & Zn^{II}) is shifted to a longer wavelength as a consequence of coordination to the metal-ligand. The Co(II) complex exhibits three spin allowed transitions at 19555 , 14728 and 9546cm^{-1} assignable to ${}^4\text{T}_{1g}(\text{F})\rightarrow{}^4\text{T}_{1g}(\text{P})$, ${}^4\text{T}_{1g}(\text{F})\rightarrow{}^4\text{A}_{2g}(\text{F})$ and ${}^4\text{T}_{1g}(\text{F})\rightarrow{}^4\text{T}_{2g}(\text{F})$ transitions respectively, It has a magnetic susceptibility value of 5.02 BM suggest an octahedral geometry for Co^{II} complex [26], Ni(II) complex exhibits two absorptions bands at $24,507$ and $18,182\text{cm}^{-1}$ assignable to ${}^3\text{A}_{2g}(\text{F})\rightarrow{}^3\text{T}_{1g}(\text{P})$ and ${}^3\text{A}_{2g}(\text{F})\rightarrow{}^3\text{T}_{1g}(\text{F})$ transitions respectively, exhibiting the magnetic moment of 3.12 BM , representing octahedral geometry. The absorption spectrum of Cu (II) complex has one broad band at $26,876\text{cm}^{-1}$, assigned to ${}^2\text{B}_{1g}\rightarrow{}^2\text{E}_{1g}$ transition, The observed magnetic moment of the Cu(II) complex is 2.17 B.M. , which confirms the octahedral structure of this complex [27].

4.4 XRD analysis

The powder XRD diffraction is carried out for Ni(II) and Cu(II) complexes which shows prominent sharp peaks while no peaks for the rest of the complexes indicating that their amorphous in nature, by evaluating the diffraction patterns of complexes given in figure 2 which reveals Crystalline nature of the complexes [28 29].

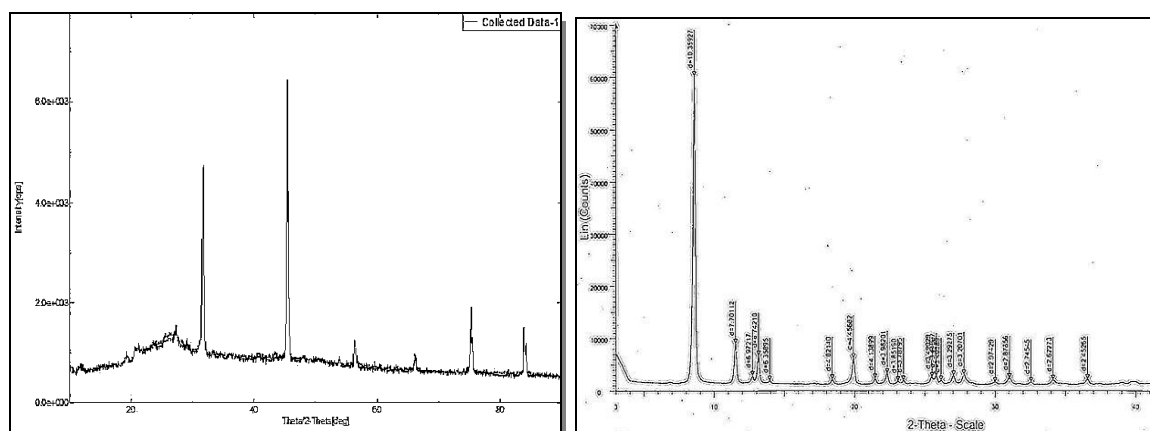


Fig 4. XRD Patterns of (a) Ni(II) and (b) Cu(II) complexes

The Miller indices (hkl) along with observed and calculated d angles, 2θ values, and relative intensities are given in Tables 2 and 3. The average crystallite sizes of the complexes d_{xrd} were calculated using Debye Scherrer equation ($D = K\lambda/\beta\cos\theta$) Where D = Particle size, K = Dimensionless shape factor, λ = Xray

wavelength (0.15406Å) β = Line broadening at half the maximum intensity, θ = Diffraction angle. Complexes 1 and 3 have a crystallite size of 30.45 and 35.21 nm respectively suggesting that the complexes are in a nanocrystalline phase.

Table 2. XRD data of [Ni (II)] complex

Peak No	2 θ	θ	Sin θ	h k l	D		Intensity	a in Å
					Cal	obs		
1	8.529	4.264	0.0743	110	10.36	10.359	100	5.65
2	11.481	5.740	0.1000	445	7.70	7.701	14.8	5.65
4	12.686	6.343	0.1104	396	6.97	6.972	4.5	5.65
5	13.915	6.95	0.1210	414	6.36	6.742	3.0	5.65
6	18.387	9.193	0.1597	461	4.82	4.821	3.4	5.65
7	19.09	9.545	0.1658	566	4.64	4.456	10.2	5.65
8	21.452	10.726	0.1861	635	4.13	4.38	5.4	5.65
9	22.308	11.25	0.1951	630	3.94	3.982	2.9	5.65
10	23.071	11.535	0.1999	670	3.85	3.878	3.1	5.65
11	25.500	12.75	0.2206	832	3.49	3.409	4.2	5.65

Table 3 XRD data of [Cu (II)] complex

Peak No	2 θ	θ	Sin θ	h k l	D		Intensity	a in Å
					Cal	obs		
1	20.7275	10.36375	0.1798	635	4.2818	4.2825	13.3103	3.62
2	27.2962	13.6481	0.2359	829	3.2645	3.264	15.7031	3.62
4	31.6896	15.8448	0.2730	926	2.8212	2.820	67.3941	3.62
5	31.8186	15.9093	0.2741	837	2.8101	2.8091	33.7029	3.62
6	45.4042	22.7021	0.3859	428	1.9950	1.9953	84.6667	3.62
7	45.6651	22.83255	0.3880	435	1.9851	1.9845	34.6159	3.62
8	56.344	28.172	0.4721	454	1.6315	1.6310	27.3827	3.62
9	66.1056	33.0528	0.5453	365	1.4123	1.4128	23.7947	3.62
10	75.3033	37.65165	0.6108	398	1.2612	1.2606	43.1507	3.62
11	83.9143	41.95715	0.6685	352	1.1521	1.1518	39.954	3.62

4.5. Thermal Analysis

The TGA curves of the metal complexes are presented in figure. The Co (II) complexes were having three stages of decomposition, in which first stage involves in the Co (II) complex shows a mass loss of 7.5 % (calcd.8.2 %) in the temperature range 80-95 °C indicates the loss of two lattice water molecules. The second step of the decomposition from 210–320 °C, with a mass loss of 38.0 % (calcd. 40.58%) corresponds to the decomposition of the coordinated part of the oxazole moiety in the ligand, the third step involves in the dissociation at the temperature of 340-550 °C with weight loss of 42.0 % (calcd. 44.18%) corresponds to the decomposition of quinoline group. Leaving the residue corresponded to stable CoO 8.15 % (calcd. 9.17 %). The TG curve of the Ni(II) complex shows a three-steps of decomposition. The first step at 35–90 °C with weight loss of 11.10 (Calcd.12.01%) is attributed to the loss of the two water molecules, the second step with weight loss of 25.62 (Calcd. 26.29%) at 180– 265° C is corresponding to the removal of corresponding oxazole with carbonyl group from the coordinated ligand. The third step at 280–618° C with weight loss of 32.00 (Calcd. 34.81%) is referring to the removal of quinoline moiety, and giving the residual part is NiO 13.85 % (calcd. 15.37 %). In the TG curve of Cu(II) complex, the first step of decomposition from 28 to 75 °C, with a mass loss 11.75 % (calcd. 12.83 %), ascribed to the removal of the non-coordinated part of the oxazole group. The second step starts from 155 to 340 °C with mass loss 49.30 % (calcd. 49. 10 %) corresponds the loss of one more part of ligand quinoline moiety, the mass of the final residue corresponded to stable CuO, 20.85 % (calcd. 18.37 %). The results well established with the composition of the metal complexes.

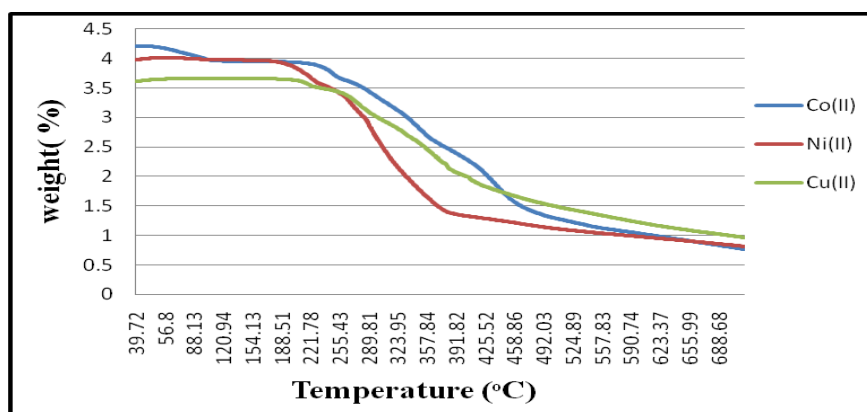


Fig 5. TGA and DTA curves Co (II), Ni(II) and Cu(II) complexes.

2.5. Antimicrobial activity

All the synthesized complexes and ligand (BZ) have been examined towards three bacterial and fungal strains the use of agar well diffusion method [30]. All bacterial traces were maintained on nutrient agar medium at $\pm 37^\circ\text{C}$, and fungal strains were maintained on potato dextrose agar (PDA) at $\pm 25^\circ\text{C}$. The test compounds had been dissolved in DMSO. Sample-loaded plates were inoculated with the micro organism incubated at 37°C for 24 h, and culture was incubated at 25°C for 60 h. DMSO as control and chloramphenicol and fluconazole is used as standards for bactericide and fungicide. (Table 6) All the synthesized complexes and ligand (BZ) showed inhibition property, among them Ni(II) and Cu(II) complexes shows excellent when compared to standards. The compounds were also tested for minimal inhibitory concentration (MIC) values [19]. MIC values of less than $25\mu\text{g/mL}$ are shown in table 7, it observed that ligand (BI) and Co(II) complex showed least activity, Ni(II) and Cu(II) complexes showed promising activity.

Table 4 Antimicrobial datas – Zone inhibition

Compounds	Antibacterial zone inhibition in mm (mean \pm SD)			Antifungal zone inhibition in mm (mean \pm SD)		
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. coccus</i>	<i>C. albicans</i>	<i>A. niger</i>
Ligand (BZ)	03 \pm 0.3	05 \pm 0.2	05 \pm 0.7	04 \pm 0.4	03 \pm 0.1	-
Co(II)	06 \pm 0.3	-	07 \pm 0.3	08 \pm 0.2	-	06 \pm 0.3
Ni(II)	14 \pm 0.2	12 \pm 0.4	10 \pm 0.2	10 \pm 0.6	09 \pm 0.2	11 \pm 0.3
Cu(II)	13 \pm 0.1	15 \pm 0.1	12 \pm 0.3	08 \pm 0.4	10 \pm 0.1	10 \pm 0.3
Chloramphenicol	15 \pm 0.2	16 \pm 0.3	13 \pm 0.3	12 \pm 0.2	11 \pm 0.4	13 \pm 0.3
Fluconazole	-	-	-	12 \pm 0.2	10 \pm 0.1	12 \pm 0.3
DMSO	0	0	0	0	0	0

Table 5. Antimicrobial datas Minimal inhibitory concentration

Compounds	MIC of the compounds in $25\mu\text{g/mL}$					
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. coccus</i>	<i>C. albicans</i>	<i>A. niger</i>
Ligand (BZ)	10	-	12	09	08	-
Co(II)	11	10	-	08	10	11
Ni(II)	18	21	17	19	21	15
Cu(II)	19	20	22	17	13	22

4.7. Antioxidant activity

DPPH radical scavenging activity data of the synthesized ligand BZ and their metal complexes exhibited that all the compounds having highly potency activity represented in figure 6. The metal complexes exhibited more radical scavenging activity than that of the ligand BZ. Cu(II) metal complex exhibited effective antioxidant activity almost close to the standard BHT and ligand BZ complex showed lower antioxidant activity and Co(II), Ni(II) complexes showed moderate activity when compared with BHT. The activity is due the presence imidazole and Isoniazid nucleus in the coordinated metal ion with ligand BZ [31].

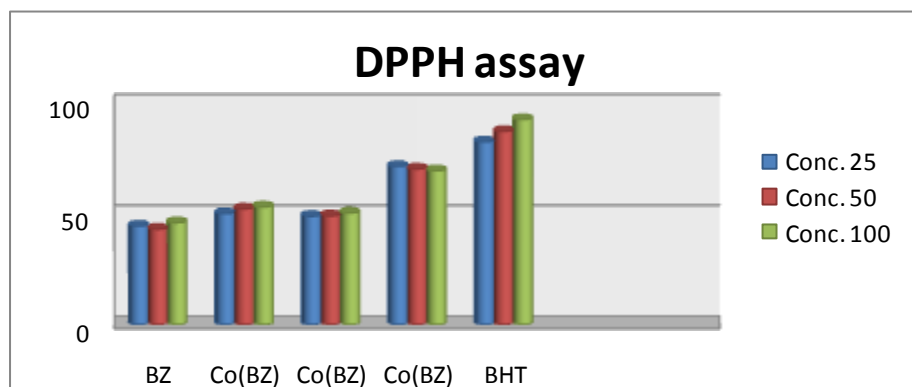


Fig 6. Antioxidant datas of BZ and metal complexes

4.8. Molecular docking studies

In order to interrupt the binding interactions modes In-vitro of BZ and metal complexes with human antioxidant enzyme in complexes with the competitive inhibitor DTT (PDB: 3MNG) [32]. The binding energy all the complexes showed prominent binding interactions, Co(II) exhibits the -330.54Kcal/mol , while Ni(II)

complexes shows -335.21Kcal/mol and Cu(II) complex gives highest binding energy of -354.58Kcal/mol with human antioxidant 3MNG protein receptor by the key of amino acids LEU-97, VAL-69, ALA-71, CYS-72, PHE-37. Hydrophobic and hydrophilic spheres are used to recognize the interactive positions which will be the potential ligand binding sites in each possible position. Finally, the molecular docking studies for the selected compounds revealed that the synthesized compounds are antioxidant competitive inhibitors in comparison to antioxidant inhibitor DTT at 3MNG binding receptor.

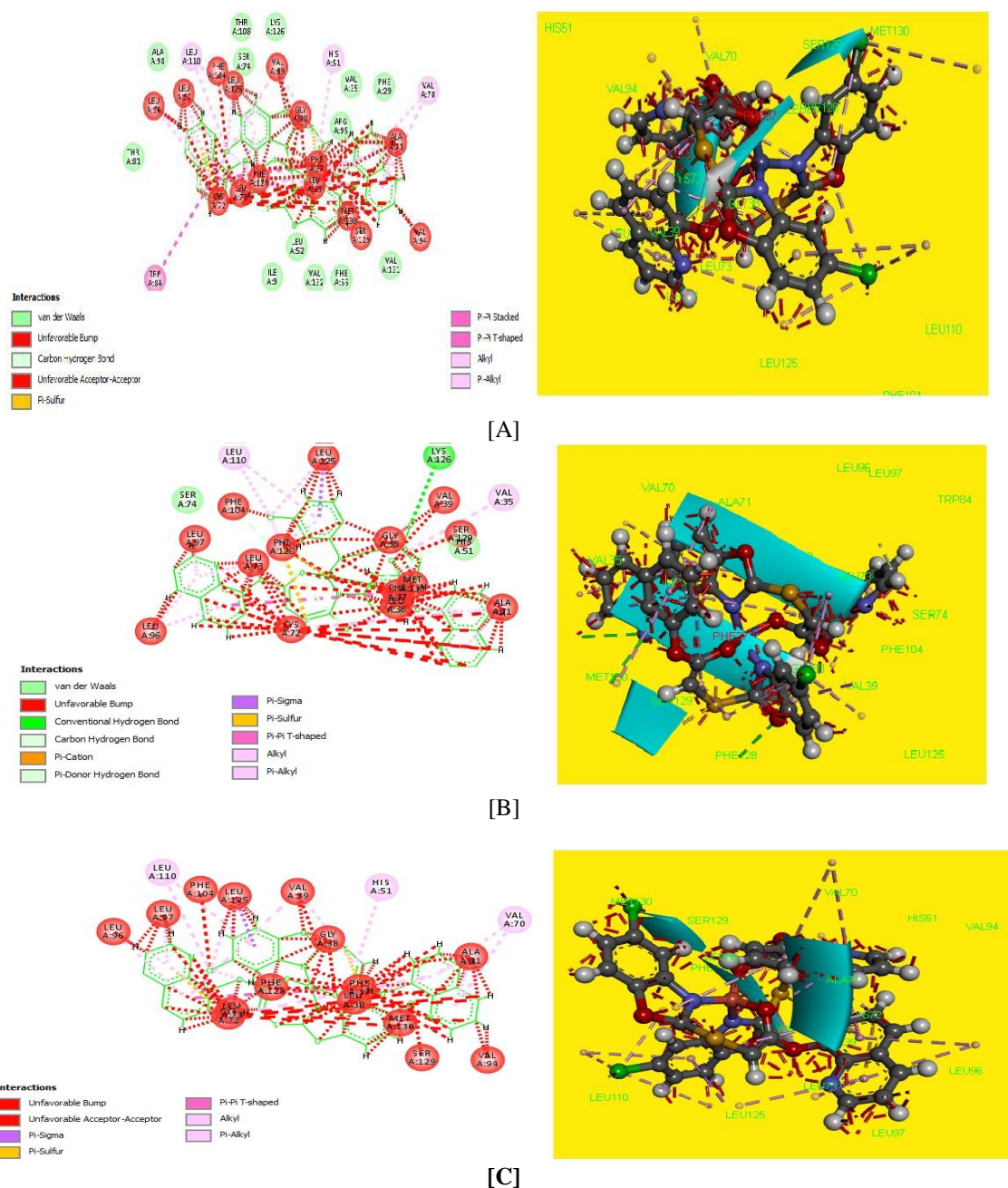


Fig 7. Binding interaction of [A] Co(II), [B] Ni(II) and [C] Cu(II) complexes with 3MNG receptor

V. Conclusion

The Co (II), Ni(II) and Cu(II) complexes with benzoxazole derived ligand quinolin-8-yl (1,3-benzoxazol-2-ylsulfanyl)acetate (BZ) were synthesized and characterized. The UV-visible and IR data showed that the complexes are tridentate in nature, by bonding with carbonyl oxygen and nitrogen of oxazoles group to the metal atom. The thermal stability of the complexes are performed and the powder XRD patterns of Ni(II) and Cu(II) complexes showed nanocrystalline in nature. The antioxidant activity of compounds showed that promising scavenging inhibition in DPPH and it is correlated with human antioxidant enzyme in complexes with the competitive inhibitor DTT (PDB: 3MNG), which gives good binding interactions between complexes and receptor. From antimicrobial results, all the complexes and uncoordinated ligand exhibits excellent zone inhibition towards bacterial and fungal strains.

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