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Spectral, DFT Calculations, Biological and Molecular Docking Studies of 2-[(Thiophen-2-*Yl*sulfanyl)Methyl]-1H-Benzimidazole Based Metal (II) Complexes

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ABSTRACT

The metal complexes of Co(II), Ni(II), Cu(II) and Zn(II) derived from 2-[(thiophen-2-*yl*sulfanyl)methyl]-1H-benzimidazole (BT) were synthesized. The bonding mode and geometrical structures of the BT and its metal complexes were attained by different analytical and spectral methods. All the complexes adopt the bide date mode of coordination and displays the octahedral geometry, except Cu(II) complex exhibits distorted octahedral geometry, X-ray diffraction (powder pattern) data suggest that nano-crystalline phase for BT, Co(II) and Cu(II) metal complexes. The DFT calculation was applied to optimize geometric structures of the ligand BT, Co(II), Ni(II) and Cu(II) complexes. Using DFT-based optimization of structures, bond length, bond angle, HOMO-LUMO, energy gaps were theoretically calculated at the B3LYP/LANL2DZ level of theory. The anti-lipase activity has been carried out, in which Ni(II) and Zn(II) exhibits potent enzyme inhibition against chicken pancreatic lipase enzyme. Moreover, the BT and all complexes were studied with respect to their DPPH antioxidant activity, showed excellent activity and it is correlated with in-silico docking studies by using antioxidant inhibitor 1,2-dithiane-4,5-diol (DTT) with human antioxidant enzyme (PDB code : 3MNG).

KEYWORDS: 2-mercaptobenzimidazole, metal complexes, DFT, XRD, In-silico docking

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INTRODUCTION

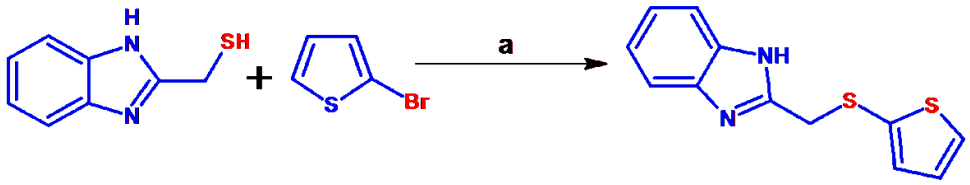
The benzimidazole scaffold of both natural and synthetic are the key components and useful structural motif for the development of therapeutic /pharmaceutical agents[1, 2]. The broad spectrum of biological activities exhibited by benzimidazole and their derivatives viz. antimicrobial, H_2 receptor, antioxidant[3-5] anti-allergic antihistamine and antitumor[6-8] they are highly in demand for use as precursors in metal-based drug regime. Transition metal ions enhance the biological activity of the different ligands, and in some cases the activity has been solely attributed to metal ions only [9-11]. The coordination mode of benzimidazole derived ligands with the Ni, Cu, Ir, Re, Pd, Ti, Zn and Ru complexes having much attention in the high thermal stability, good catalytic performance and optical properties[12]. In this context, we have synthesized and spectrally characterized the metal complexes [Co(II), Ni(II), Cu(II) and Zn(II)] derived from 2-[(thiophen-2-*yl*sulfanyl)methyl]-1H-benzimidazole,The density functional theory (DFT) were studied for both ligand and complexes, *In-vitro* biological activity assay was carried out to study the anti-lipase and antioxidant activities of the ligand and the metal complexes. *In-silico* docking studies have been performed in co-relation with antioxidant assay using PDB code: 3MNG.

EXPERIMENTAL

Synthesis of 2-[(thiophen-2-ylsulfanyl)methyl]-1H-benzimidazole [BT]

1H-benzimidazol-2-*yl*methanethiol (0.1 mmol) was dissolved in DMF, to this solution 2-bromothiophene (0.1 mmol) was added drop wise and a catalytic amount of KI was added. The reaction mixture refluxed with stirring under a N_2 atmosphere at 80 °C for 5h. Then the excess solvent was removed under vacuum, cooled at room temperature, poured into ice, filtered, and washed with warm water. The light brown product of BT was obtained after recrystallization from hot ethanol.

Ligand BT: Yield: 72%, Mp: 210 °C, Anal, Cald, for C(58.51%) H(4.09%) N(11.37%), Found: C(58.23%) H(4.31%) N(11.10%). MS(LC): 247.12 (248.34).



Scheme 1. a) DMF, KI, 80°C, N_2 reflux 12-14h

Synthesis of the metal complexes

The ethanolic solution (25mL) of ligand BT (0.1moL) was mixed with Co(II), Ni(II) and Cu(II) metal chlorides (0.2mol) in ethanol (25mL) solution with 1:2 metal–ligand ratio. The mixture was refluxed for 4 h. The solid product was precipitated on cooling and collected by filtration and washed with hot ethanol until the washing becomes colorless. The product was dried in vacuum over $CaCl_2$.

BIOLOGICAL ACTIVITY

Antioxidant activity

The 2, 20- diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay method using the procedure described previously reported [12, 13].

Lipase Inhibition Test

The anti-lipase inhibition activity was evaluated by different concentrations (1 mg, 2 mg) of methanol extracts of samples 100µl each, to this 8 ml of oil emulsion and 1 ml of chicken pancreatic lipase has been mixed and incubated for 60 minutes. 1:1 of 1.5 ml of acetone and 95% ethanol has been added to stop the reaction. The liberated fatty acid were determined by titrating method (0.02M NaOH (Standardization 0.01 M oxalic acid).

Lipase inhibition = A − B/A × 100, where A is lipase activity, B is activity of lipase when incubated with the sample.

Molecular docking analysis

The docking study was performed by HEX 8.0 in correlation with anti-oxidative activity, the antioxidant inhibitor 1,2-dithiane-4,5-diol (DTT) with human antioxidant enzyme (PDB code: 3MNG), and the method has been previously reported by our group [14,15].

RESULTS AND DISCUSSION

All the metal complexes are colored, stable and having high melting points above 300 ℃. The molar conductance values of Co(II), Ni(II), Cu(II) and Zn(II) metal complexes are in the range of 30 to 35 $\Omega^{-1}cm^3$ in DMF solution at concentration 10^{-3} M and are non-electrolytes [16] and having the molar ratio of metal:ligand as 1:2, as represented in Table 1.

Table 1: Physical properties and analytical data of the metal complexes

Compounds	colour	Mol. Wt	Yield (%)	Calcd. (found) (%)				Molar conductance ($ohm^{-1} cm^2 mol^{-1}$)
				C	H	N	M	
$[CoCl_2(BT)_2].H_2O$	Dark brown	620.93	54	46.30 (46.17)	3.24 (2.99)	9.00 (8.94)	9.47 (8.53)	30
$[NiCl_2(BT)_2].H_2O$	Light maroon	619.93	50	46.32 (46.78)	3.24 (3.05)	9.02 (8.82)	9.43 (9.12)	33
$[CuCl_2(BT)_2]$	Dark green	624.92	52	41.73 (41.52)	2.92 (2.71)	8.11 (8.01)	9.20 (8.93)	35
$[ZnCl_2(BT)_2]$	Light cream	625.11	53	45.83 (45.94)	3.20 (3.08)	8.91 (9.03)	10.40 (10.56)	31

IR spectral studies

IR spectrum of the ligand and their complexes were recorded as KBr pellets, it provides the information regarding the coordination of the metal ions with BT. The IR spectrum of BT showed a band at 3185 cm^{-1} is due to (-NH) stretching, and band at 1606 cm^{-1} is due to (C=N) at 1606 cm^{-1} stretching and the 986 cm^{-1} is presence of (C-S-C) stretching at 986 cm^{-1} which supports the formation of coordination band. In their complexes, the band due to C=N group is appeared at 1596-1599 cm^{-1} signifying the coordination of azomethine nitrogen with metal ions. Moreover, it is further supported by M-N characteristic bands at 445-456 cm^{-1}. In additional to this, the band of (C-S-C) also shifted to 965 cm^{-1} indicating that the coordination of metal ions and the appearance of new bands in the range 590-596 cm^{-1} also supports this and represented in supplementary file S1 to S4 [17-19].

Uv-Visible spectroscopy and magnetic moment studies

The BT exhibits the absorption band around 262 nm and 324 nm which are assigned to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and on complexation the $n \rightarrow \pi^*$ transitions and are shifted to lower frequencies suggest the coordination of imine nitrogen atom with the metal ions [20]. The Co(II) complex exhibits bands at 21,302 and 20,408 cm^{-1} assigned to as $^4T_1(F) \rightarrow {}^4A_2(F)$ and $^4T_1(F) \rightarrow {}^4T_1(P)$ transitions respectively and the magnetic moment at 4.0 BM that supports the octahedral geometry. The electronic spectra of Ni(II) complex showed two bands 24,154 and 19,379 cm^{-1} corresponds to $^3A_{2g} \rightarrow {}^3T_{2g}$ (F) (ν_1) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) (ν_2) transitions, and the magnetic moment of 2.7 BM suggest an octahedral

geometry. The Cu(II) complex showed a board band at 18,832 cm^{-1} assigned to the transition ^2B_1g (F) → $^2A_{1g}$ and the obtained magnetic moment of 1.8 BM confirms the octahedral geometry [21-23].

^{1}H NMR and Mass studies

The ^{1}H NMR spectrum of BT in DMSO showed a singlet at 12.40 ppm assigned for (-NH) proton and the peaks in the region 7.33 to 7.54 ppm were assigned for chemical shift for hydrogen of symmetrical aromatic rings and the two moieties which bridges by $–CH_2$ protons at 4.43 ppm appear as a singlet. The Zn(II) complex also showed a signal due to proton of (-NH) group but shifted to down field and appeared at 11.42 ppm compared to the position of the ligand. The multiplet protons of imidazole and thiophene moiety also shifted to 7.11 to 7.89 ppm respectively and also the signal due to $–CH_2$ group proton shifted to down filed and appeared at 3.91 ppm which indicates the formation complex and the spectra are represented in Supplementary file S5 and S6.

The mass spectrum of the ligand observed that m/z = 247.3 (248.3) corresponds to the molecular ion peak due to (M+1). The Zn(II) complex exhibits the molecular ion peak at m/z = 625.11 (626.21) which is represented in supplementary file S7 and S8.

X-ray Diffraction studies

The XRD patterns of ligand BT, Co(II) and Cu(II) complexes were recorded between 2θ values ranging from 10° to 80° as shown in Fig. 1. The degree of crystallinity nature is high in both BT and the metal complexes, upon complexation the intensity of diffraction pattern enhances, the changes in the intensity of patterns indicates that complexation has occurred with change in strain. The average crystalline size were calculated Scherrer equation ($D = K\lambda/\beta Cos\ \theta$), and it was found by 14.12 nm, 23.44 nm and 33.41 nm for ligand BT, Co(II) and Cu(II) complexes respectively, suggesting that the nanocrystalline phase.

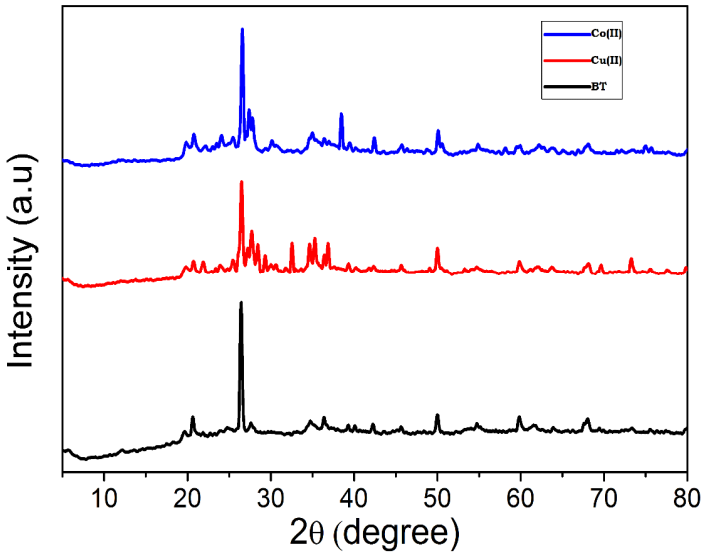


Fig. 1. P-XRD pattrens of BT, Co(II) and Cu(II) complexes

Computational studies

The Calculations, optimized geometry of BT, Co(II) and Ni(II) complexes are carried out with Gaussian 09 software [24] using B3LYP/6-311++G(d,p)(5D, 7F) basic set in gas phase.

Frontier molecular orbital analysis (FMOs) and Molecular electrostatic potential (MEP)

Frontier molecular orbital analysis are very helpful to calculate electric and optical parameters, HOMO act as donor, and LUMO as electron acceptor, that is energy gap between occupied and unoccupied orbitals are shown in Fig. 2 and 3. The energy gap ΔE of HOMO-LUMO for ligand is 0.917 eV, in which HOMO orbital are delocalized on nitrogen atom and CH_3 group while the LUMO orbital are occupied on phenyl and thiophene rings [25].

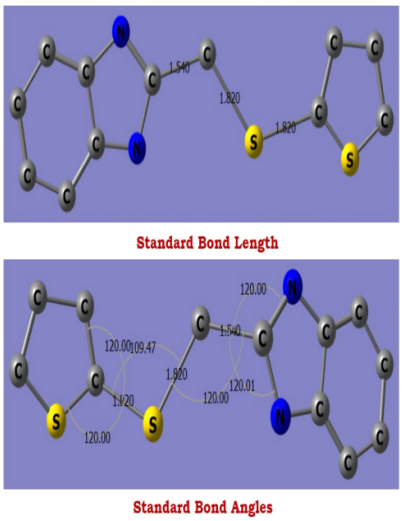


Fig. 2. Standard bond length and bond angles of BT

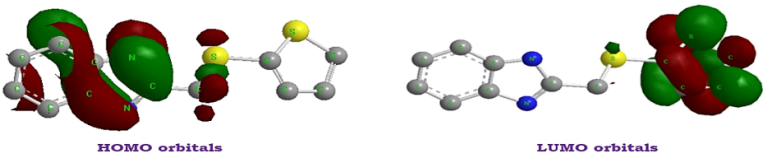


Fig. 3. HOMO-LUMO orbitals of BT

The energy gaps ΔE of Co(II), Ni(II) and Cu(II) complexes are 0.999, 5.504 and 2.110 eV. In HOMO orbitals for Co(II), Ni(II) and Cu(II) complexes are mainly delocalized on corresponding metal ions and thiophene and phenyl rings. Where as in LUMO electrons are concentrated on nitrogen, methyl group and some part of metal ions. These tell us the chemical reactivity and stability of the ligand and their corresponding metal (II) complexes and these are represented in Fig. 4 and Table 2 [26].

Table 2: Calculated quantum parameters of metal complexes

Compounds	HOMO (eV)	LUMO (eV)	ΔE Gap	X	η in eV	σ	μ	S	ω eV
BT-Co(II)	-11.828	-12.817	0.999	-12.32	0.492	2.032	12.32	1.016	3.56
BT-Ni(II)	-14.658	-20.162	5.504	-17.41	2.752	0.363	17.41	1.376	22.94
BT-Cu(II)	-19.521	-21.631	2.110	-20.57	1.061	0.942	20.57	0.471	18.40

MEP is an electrostatic effect of electron and proton in molecule which relate with chemical reactivity and electronegativity of compounds (Fig. 5). Red colour shows the negative electrostatic potential and mostly contains on the nitrogen and methyl moiety, whereas the blue colour represents the positive electrostatic potential contains on the phenyl and OH group of the molecule. The potential shows the oxygen is nucleophilic center nitrogen acts as electrophilic center and gives molecular interactions in a compounds [27, 28].

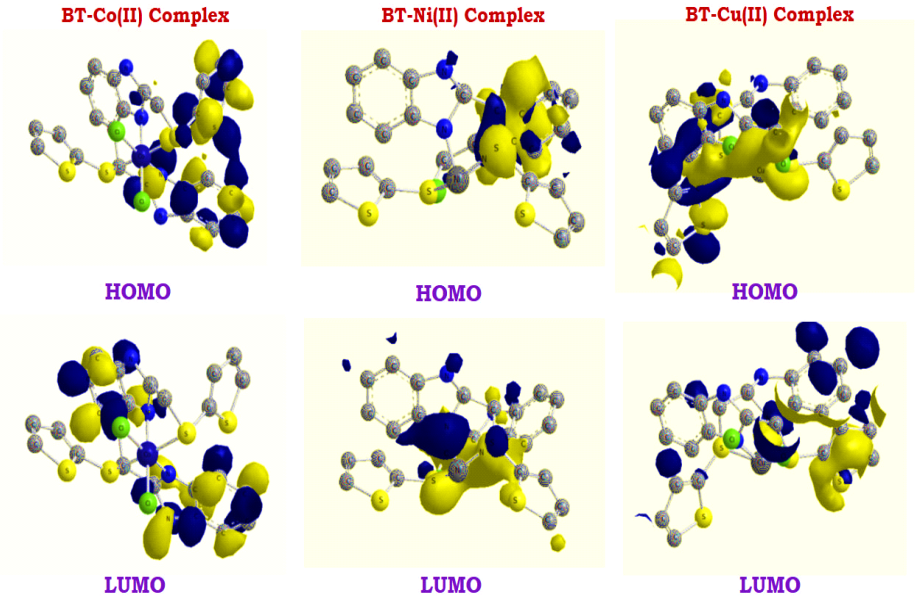


Fig. 4. HOMO-LUMO orbitals of metal complexes

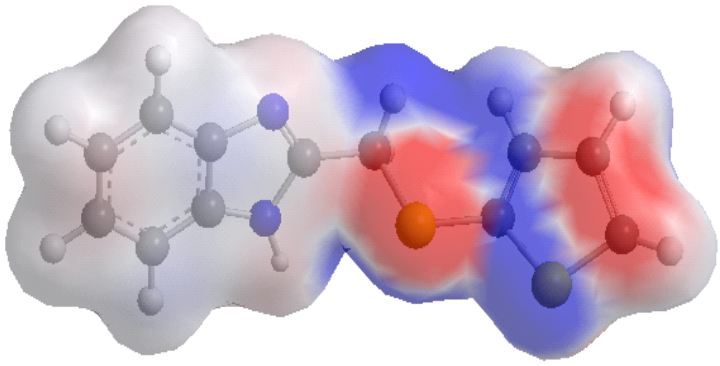


Fig. 5. Molecular electrostatic potential (MEP) of BT

BIOLOGICAL ACTIVITY

Anti-lipase inhibition assay

The ligand BT and their metal complexes with different concentrations (1 mg, 2mg) screened for anti-lipase activity, in which uncoordinated ligand showed lesser activity. The Ni(II) and Zn(II) complexes showed potential activity against chicken pancreatic lipase enzyme, this is due to π-π stacking interaction and σ-π interactions on imidazole and thiophene motifs [29]. While the Co(II) and Cu(II) complexes exhibits moderate activity and represented in Fig. 6 respectively.

a

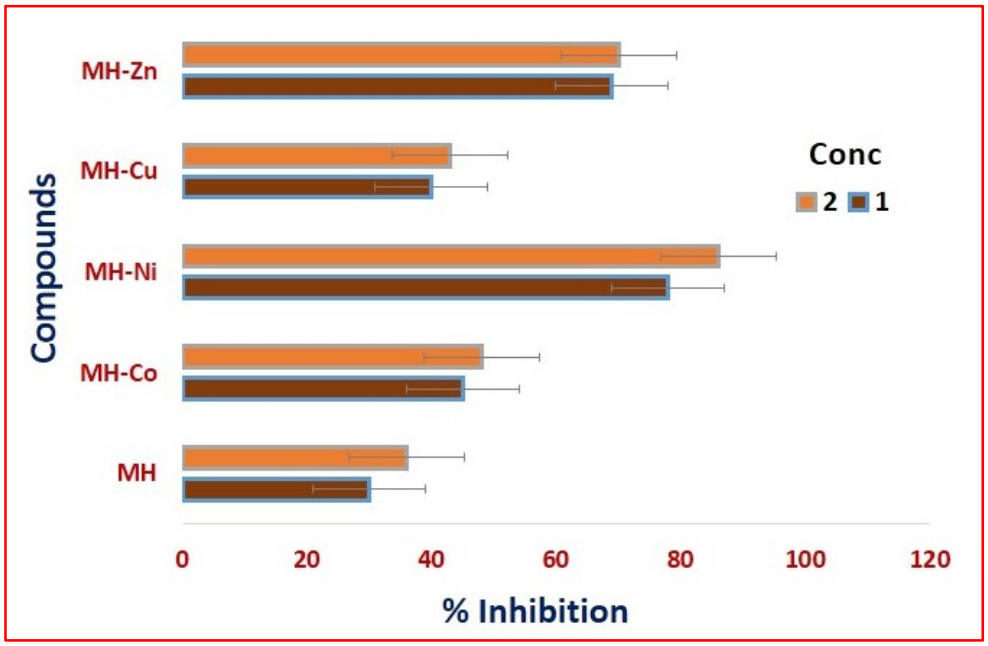


Fig. 6. Graphical representation of anti-lipase assay

Antioxidant activity

2, 20- diphenyl-1-picrylhydrazyl (DPPH) represented in Fig. 7. The generation of DPPH radical showed absorption maximum at 517 nm [30]. The complexes showed promising activity than that of uncoordinated BT. The Co(II) and Cu(II) complexes showed highest scavenging activity, almost similar to standard (vitamin C), this is due to thiophene and imidazole moiety with metal ions. The Ni(II) and Zn(II) complexes exhibits moderate activity. While the uncoordinated ligand BT showed least activity.

B

Molecular docking

In accordance with antioxidant activity, it is significant to carry out *in silico* docking studies. The human antioxidant enzyme receptor in complex with the competitive inhibitor DTT (PDB ID: 3NMG) revealed that the good docking interactions with different amino acids and E-total score [31]. The Ni(II) complex showed excellent binding affinity towards enzyme receptor 3NMG of -287.16 kcal/mol, while Co(II) and Cu(II) complexes also exhibit good binding interactions docking score of -257.11 and -222.99 kcal/mol. But the ligand, BT showed a least binding interactions of -197.73 kcal/mol and represented in Fig. 8-10. The ligand and the receptor interactions involves binding with different amino acids like His6, Phe20, Thr136, Ser165, Phe167, Glu198, Phe200, Val236, Thr237, Leu250 and Leu253.

Fig. 7. Antioxidant activity of BT and its metal complexes

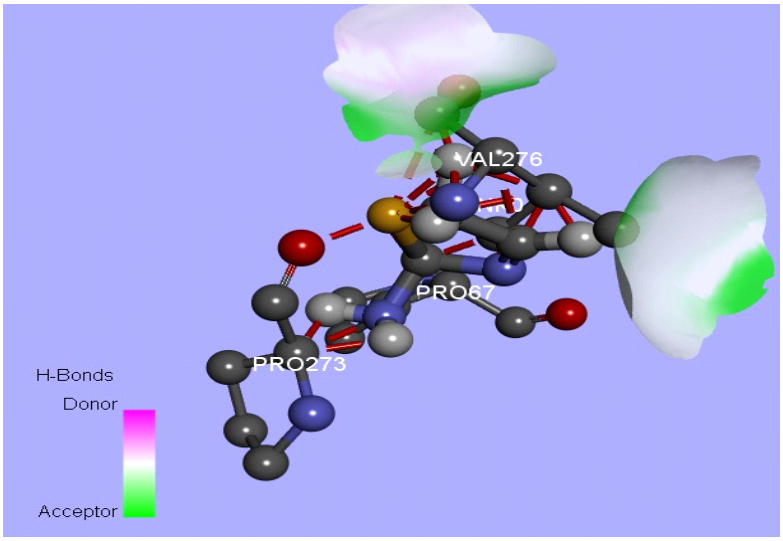


Fig. 8. 3D interactions of BT with PDB: 3NMG

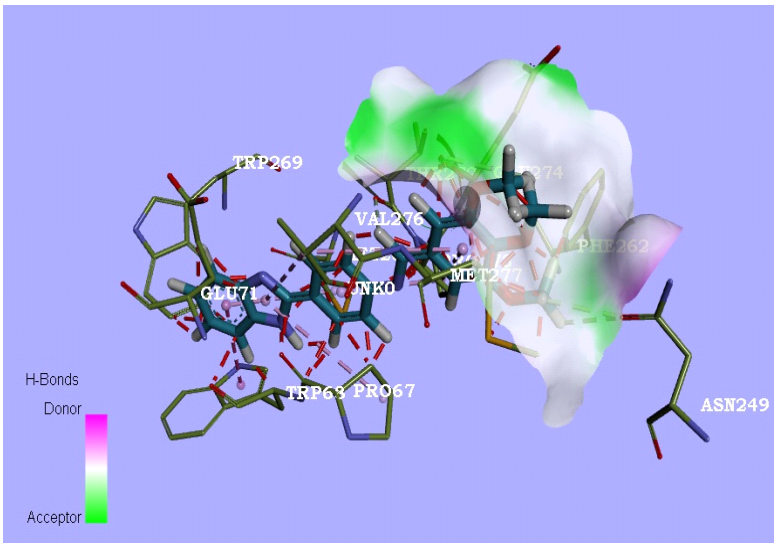


Fig. 9. 3D interactions of $[CoCl_2(BT)_2].H_2O$ with PDB: 3NMG

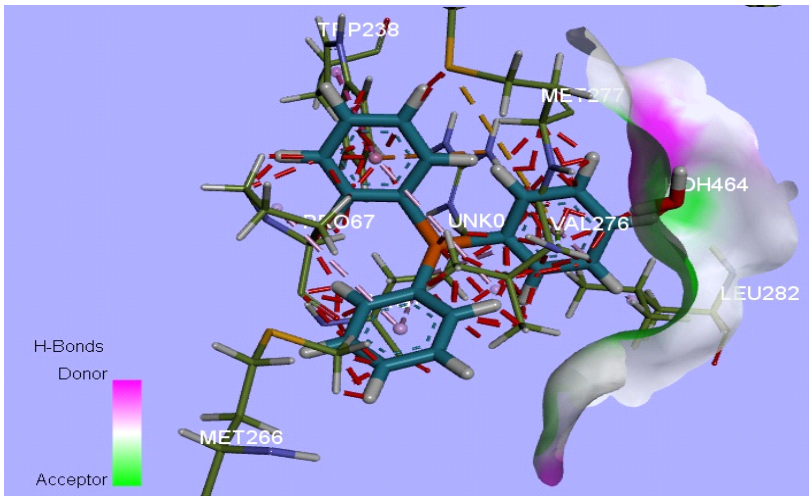


Fig. 10. 3D interactions of $[NiCl_2(BT)_2].H_2O$ with PDB: 3NMG

CONCLUSION

In outline, the ligand 2-[(thiophen-2-ylsulfanyl)methyl]-1H-benzimidazole [BT] and their metal complexes were synthesized and structurally characterized by elemental analysis, molar conductance, Uv-Visible spectra, ^{1}H NMR, and IR spectral techniques, which suggest the bidentate nature of the ligand, which coordinate through tertiary nitrogen of imidazole and sulfur atoms to the metal ion. The antioxidant activity of metal complexes also showed prominent inhibition against DPPH radical than that of the ligand and it is compared with *In silico* docking with human antioxidant enzyme receptor DTT (PDB ID: 3NMG).

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