



Cobalt(II) and Nickel(II) Metal Complexes of Glycine-Benzimidazole Conjugate Based Ligands: Synthesis, Characterization and Biological Activities

Sabithakala Thatituri*, Pushpanjali Kale

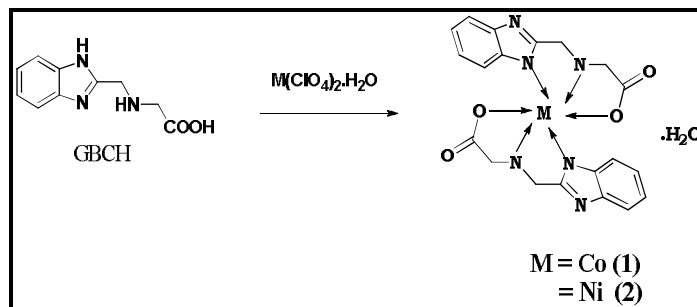
Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad-UCEST,
Hyderabad, 500085, **INDIA**
E-mail: sabithakalatituri@jntuh.ac.in

Accepted on 26th October, 2024

ABSTRACT

Benzimidazole derivatives are prominent ligands in coordination chemistry, known for their ability to form stable complexes with transition metals. This study focuses on the synthesis, characterization, and biological activity of cobalt(II) and nickel(II) complexes of glycine, benzimidazole conjugate ligand, 2-((1H-benzimidazol-2-yl)methylamino) acetic acid (**GBCH**). The results demonstrate that ligand acts as an effective tridentate ligand, and complex structure have been determined by electronic, IR, UV, powder XRD, TGA and DTA. An in vitro antibacterial activity study of Ligand and its complexes showed activity against *Bacillus subtilis* and *Staphylococcus aureus*.

Graphical abstract:



Schematic representation of the synthesis of metal complexes of GBCH.

Keywords: Benzimidazole, cobalt(II) complex, nickel (II) complex, Antibacterial activity, molecular docking.

INTRODUCTION

Benzimidazole derivatives have garnered significant attention in the field of coordination chemistry due to their versatile binding properties and biological activities [1, 2]. The benzimidazole moiety, characterized by a fused benzene and imidazole ring, exhibits a unique ability to coordinate with various metal ions, forming stable complexes with diverse applications [3-5]. Cobalt and nickel, as

transition metals, are known for their rich coordination chemistry, biological and catalytic properties [6]. Complexes of these metals with benzimidazole ligands have shown promising results in various fields, including medicinal chemistry, catalysis, and material science. The ability of benzimidazole to act as a bidentate or tridentate ligand enhances the stability and reactivity of these metal complexes.

Recent studies have highlighted the potential of cobalt(II) and nickel(II) complexes with benzimidazole derivatives in exhibiting significant antimicrobial, anticancer, and catalytic activities [7, 8]. These complexes have been synthesized and characterized using various spectroscopic techniques, revealing insights into their structural and electronic properties. This manuscript aims to explore the synthesis, characterization, and biological activity of benzimidazole-based cobalt and nickel complexes. By delving into their coordination behavior, spectral properties, and biological activities, we seek to provide a comprehensive understanding of these complexes and their relevance in contemporary research.

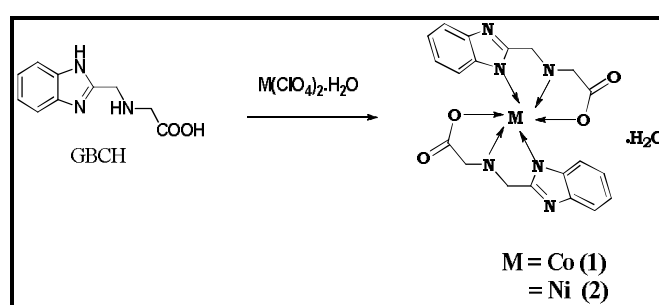
MATERIALS AND METHODS

Materials: All the chemicals such as iminodiacetic acid, *o*-phenylenediamine, Cobalt(II) perchlorate hexahydrate and nickel(II) perchlorate hexahydrate were used as obtained from Aldrich. All other chemicals and solvents used for the synthesis were of reagent grade.

Instruments and Analytical methods: IR spectra were recorded on a JASCO FT-IR 5300 spectrometer. Elemental analysis for C, H and N was done using a FLASH Ea 1112 SERIES CHNS analyzer. Magnetic moments were recorded on Lakeshore VSM 7410. Diffusion reflectance spectra were obtained using a Shimadzu UV-3100 PC Spectrophotometer, thermo gravimetric analysis was made using Exstar TG DTA 6300.

Synthesis: The ligand, glycine benzimidazole conjugate ligand (GBCH) was synthesized by a known procedure [9].

Synthesis of [Co(GBCH)₂]. H₂O (1): The ligand d(GBCH) (0.250g, 1.12 mmol) was dissolved in 25 mL water, to which 5 mL aqueous solution of Co(ClO₄)₂.6H₂O (0.450 g, 1.12 mmol) was added slowly and stirred for 5 min. The resultant pink solution was filtered and kept for crystallization in a desiccator over H₂SO₄. Good quality pale pink crystals obtained were collected after 10 days. Yield: 0.36 g. HRMS: *m/z* = 467.9992 [M-ClO₄]⁺ (Figure 1).



Scheme 1. Schematic representation of the synthesis of metal complexes of GBCH.

Synthesis of [Ni(GBCH)₂]. H₂O (2): The ligand(GBCH) (0.250g, 1.12 mmol) was dissolved in 25 mL water, to which 5mL aqueous solution of Ni(ClO₄)₂.6H₂O (0.440 g, 1.12 mmol) was added slowly and for stirred 5 min. The green coloured solution obtained was filtered and kept for crystallization in desiccator over H₂SO₄. Light green colour powder formed was separated after ten days. Yield: 0.39 g (75%). HRMS: *m/z* = 464.0754 [M-ClO₄]⁺ (Figure 2).

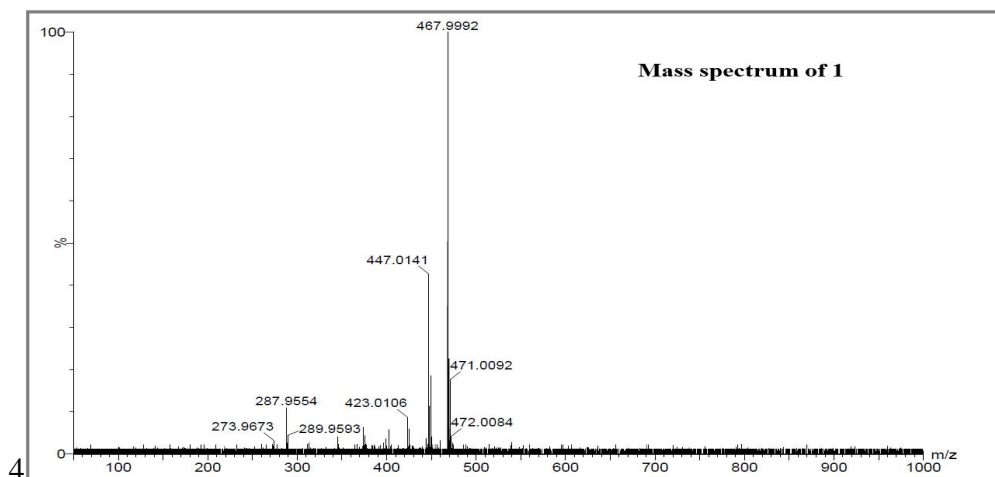


Figure 1. Mass Spectrum of 1.

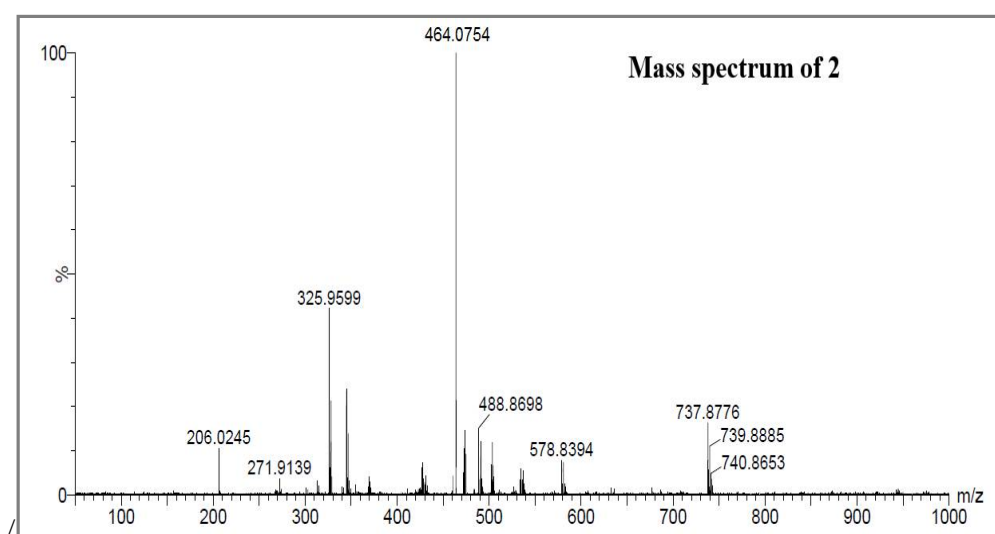


Figure 2 Mass Spectrum of 2.

Table 1. Analytical and physical data of 1 and 2

Complex	Y (%)	M.P.	Colour	λ_m	Anal. Calcd % (found)		
					C	H	N
[Co(GBC) ₂]. H ₂ O 1	64.1	> 250	Light pink	24.28	46.43 (46.41)	4.28 (4.23)	16.24 (16.35)
[Ni(GBC) ₂]. H ₂ O 2	75.3	> 250	Light green	8.37	46.45 (46.47)	4.28 (4.31)	16.25 (16.20)

RESULTS AND DISCUSSION

Infrared spectral studies: The IR spectral data of the GBCH and its complexes are listed in table 2 and presented in figures 3 to 5. The IR spectra of complexes (1 and 2) are compared with the free ligand to observe the position and intensity changes in frequency bands which may confirm the metal chelation. The IR spectrum of the GBCH shows absorption frequencies appearing at 3460, 2781 and 1596 cm^{-1} due to O-H stretching of carboxylic acid, N-H stretching of aliphatic amine and C=N (azomethine) stretching in imidazole ring respectively, which are possible binding sites in the ligand. These frequencies are shifted or vanished in the IR spectrum of complexes and also the new band at 1114-1089 cm^{-1} in the IR spectrum confirms the presence of perchlorate in the complexes (1 and 2)

[10]. The C=N stretching frequencies slightly shifted to lower frequencies due to the decrease in the C=N bond strength which indicates coordination of the azomethine nitrogen lone pair to the metal ion. Thus, it confirms the involvement of nitrogen atoms and oxygen atom in chelation with the metal ion. Hence, a broad band at 3400-3450 cm^{-1} indicates the presence of a coordinated or lattice water molecule in the complex.

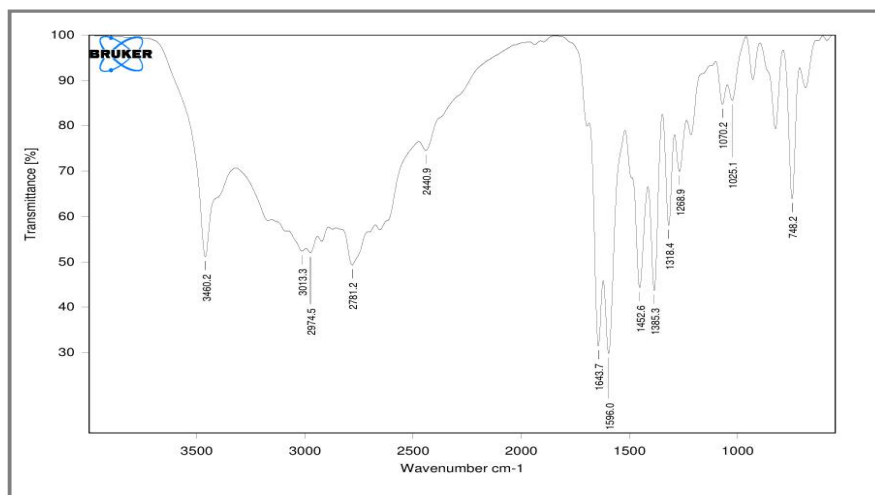


Figure 3. IR Spectrum of GBCH.

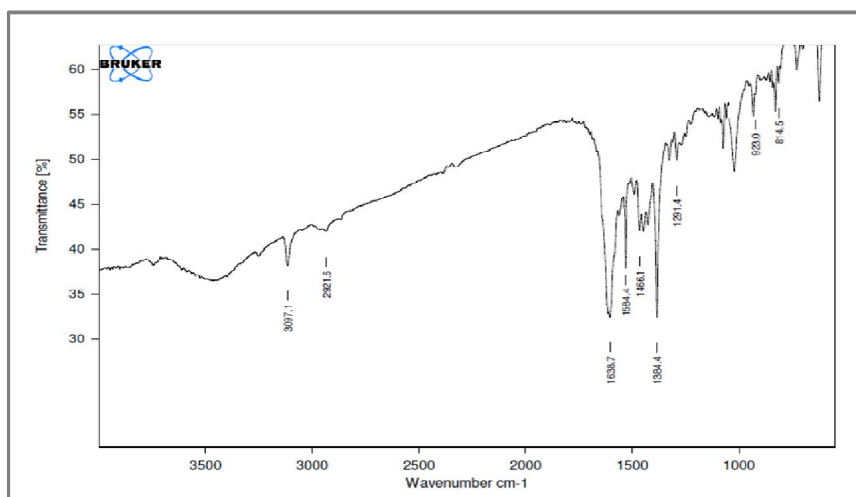


Figure 4. IR Spectrum of 1.

Table 2. IR spectra of the BIGH and its metal complexes 5(a-d) in cm^{-1}

Compound	$\nu(\text{OH})$	$\nu(\text{N-H})^a$	$\nu(\text{C=N})^b$	$\nu(\text{N-H})^c$	$\nu(\text{C=O})$
GBCH	3460	2781	1596	3013	1643
1	--	--	1584	3097	1638
2	--	--	1575	3149	1630

^aN-H aliphatic amine, ^bC=N of cyclic azomethine group;

^cN-H of benzimidazole ring.

Therefore, from the IR spectra, it is concluded that GBCH behaves as a mono basic tridentate ligand coordinating through cyclic azomethine nitrogen, aliphatic secondary amine nitrogen and deprotonated carboxylate oxygen. The absorption frequency bands due to M-O and M-N stretching occur at 495–560 cm^{-1} and 440-480 cm^{-1} respectively, in the spectra of all the complexes. These bands are not observed in the spectra of the free ligand.

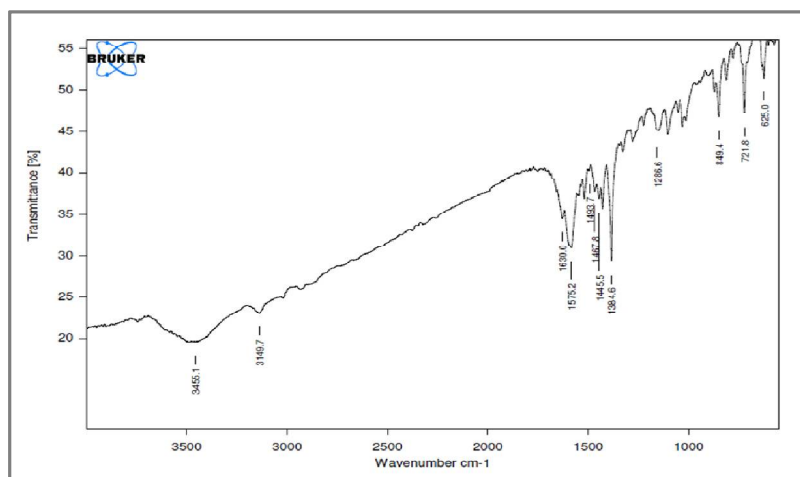


Figure 5. IR Spectrum of 2.

Electronic spectral and magnetic moments studies: The UV spectra of BIGH and its metal complexes were recorded in aqueous medium at room temperature. The absorption band in the region of 236-246 nm attributed to $\pi \rightarrow \pi^*$ transition correspond to aromatic nature of the ligand, while the absorption band at 268-274nm corresponds to intra-ligand charge transfer transitions. These bands were shifted to higher energy region due to complexation [11]. The absorption spectra of 1 and 2 are shown in figure 6.

The Cobalt(II) complex(1) show electronic absorption spectral bands at 363 and 339 nm which have been ascribed to the transitions, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and ${}^4T_{1g}(P) \rightarrow {}^4T_{1g}(F)$ respectively, these bands are characteristic bands of octahedral geometry of cobalt(II) complexes [12]. The cobalt(II) has magnetic moment of 4.88 B.M, which also suggest an octahedral geometry. The Ni(II) complex(2) exhibits three electronic spectral bands at 445, 330 and 304 nm which are attributed to ${}^3A_{2g} \rightarrow {}^3T_{2g}(F)$, ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and ${}^3T_{2g} \rightarrow {}^3T_{1g}(P)$ in an octahedral field. The magnetic moment of 3.29 BM for Ni(II) complex also suggest an octahedral geometry. The observed magnetic moments are near the upper limit value for nickel(II) octahedral complexes [12].

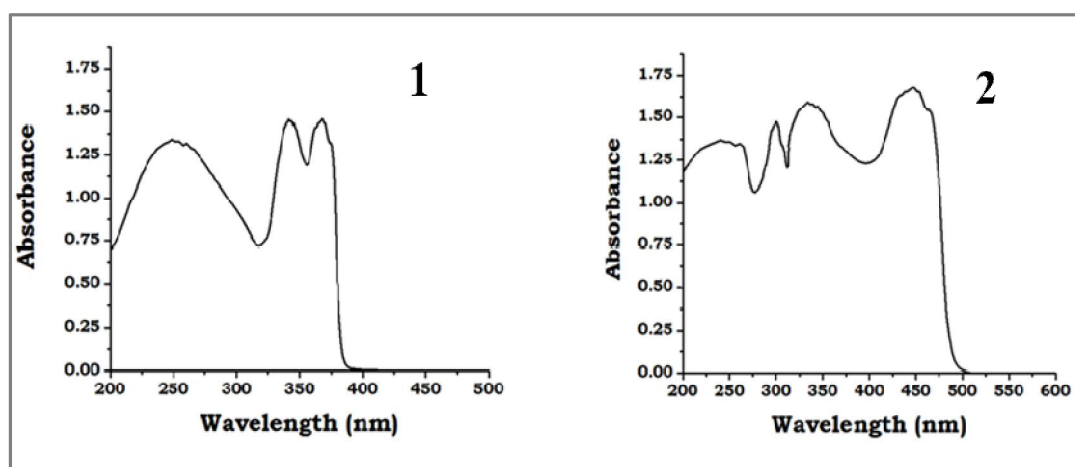


Figure 6. UV-Visible Spectra of 1 and 2.

Thermogravimetric study of the complexes: Thermal behavior of the complexes was studied by thermogravimetric analysis (TGA) recorded at 0 – 800°C as shown in figure 7. The TG data (Table 3) suggest that the complexes 1 and 2 contain lattice water molecules, which are lost below 120°C [13].

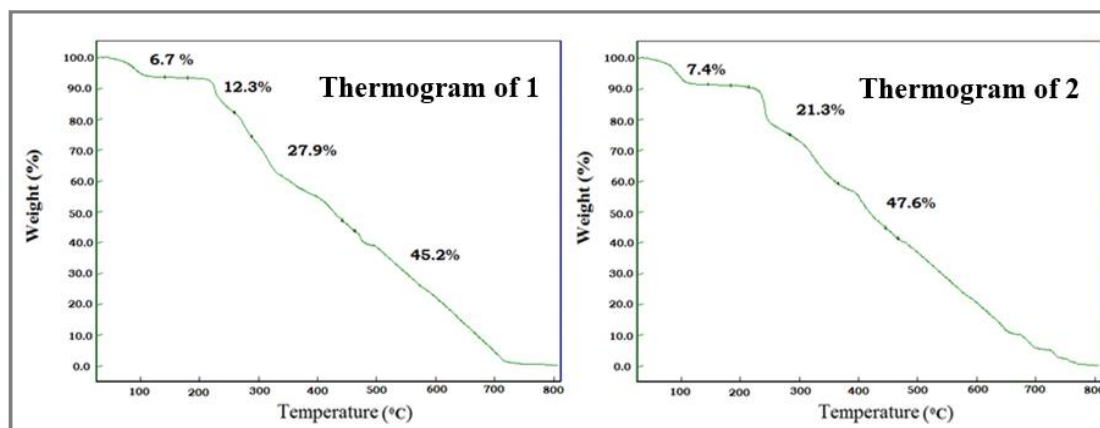


Figure 7. The TGA curves of 1 and 2.

Table 3. Thermal analysis (TGA) results of complexes 1 and 2

Complex	Temperature °C	Weight loss (%)*		Species loss
		Found	Calcd.	
1	< 100	6.7	6.8	H ₂ O (lattice)
2	< 100	7.4	7.9	H ₂ O (lattice)

*Calculated values are given in parentheses

APPLICATION

Biological activity

Antibacterial activity: In vitro antibacterial activity of the complexes 1 and 2 were studied by well-diffusion method under standard conditions [14]. The bacterial strains chosen were G(+)Staphylococcus aureus, Bacillus subtilis and G(-)Escherichia coli and Pseudomonas aeruginosa. Bacterial subculture medium was autoclaved for 20 min before inoculation. Later, the bacteria were cultured for 24 h in an incubator at 37°C. Nutrient agar media plates were prepared and each plate was seeded with pure test culture by spread plate technique. Wells were bored into the media using a sterile tip and 20 µL of the test compound (concentration = 1 mg mL⁻¹) was inoculated into the well by micropipette. Then the plates were incubated at 37°C. The width of the growth inhibition zone was measured after 24 h of incubation. The results, table 4 show that the complexes were active against *Bacillus subtilis* and *Staphylococcus aureus* and inactive against the other species. Further, the study evidently indicates that the antibacterial activity of the GBCH increase when coordinated to the metal ions. This may be due to the greater lipophilic nature of the metal complexes than the free ligand (GBCH) [15].

The antibacterial study show that the activity of the ligand(GBCH) increases when coordinated to the metal ions and forms chelates. Chelation increases the delocalization of π -electrons in the chelate ring and enhances the lipophilicity of the complex. Increased lipophilicity enhances the penetration of the metal complexes into bacterial lipid membrane and deactivates the enzymes of micro-organisms.

Table 4. In vitro antimicrobial activity of GBCH,1 and 2.

Microorganism	Zone of inhibition(mm)			
	GBCH	1	2	Furaciline (Reference)
<i>Bacillus subtilis</i>	20	35	32	45
<i>Staphylococcus aureus</i>	19	27	29	36

Docking studies: Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software[16] which is based on genetic algorithm (GA). This method allows partial flexibility of protein and full flexibility of ligand. The compounds are docked to the active site of the COX-2 (figure 8). The interaction of these compounds with the active site residues are thoroughly studied using molecular mechanics calculations listed in table 5.

Table 5. Gold scores for **1** and **2** in COX-2 model

Compound	Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)
1	3.35	2.00	22.82	0.00	-30.03
2	4.38	6.00	19.66	0.00	-28.66
Ibuprofen (Reference)	25.46	5.36	22.51	0.00	-8.27

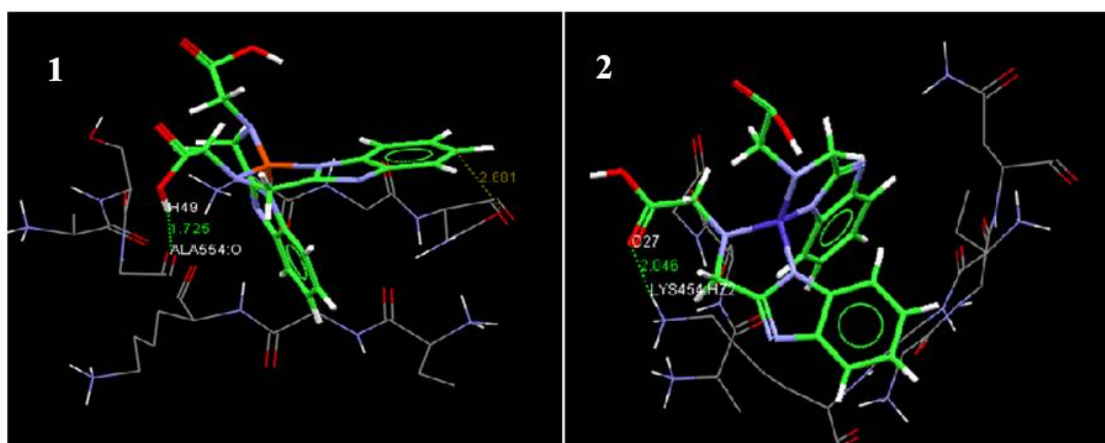


Figure 8. H-bond interactions of **1** and **2** with COX-2

CONCLUSION

In this chapter we have synthesized Co(II) and Ni(II) metal complexes of 2-((1H-benzimidazol-2-yl)methylamino)acetic acid, GBCH. These were found to be in octahedral geometry. The antibacterial study shows that the metal-complexes exhibit good activity against *Bacillus subtilis* and *Staphylococcus aureus*. Finally the molecular docking studies of the synthesized compounds were carried out and the results of *in silico* studies revealed that the compounds **1** and **2** have moderate binding energy with standard drug (**Ibuprofen**) we can conclude that complexes **1** and **2** are good inhibitors of COX-2.

ACKNOWLEDGMENT

Authors are thankful to Jawaharlal Nehru Technological University Hyderabad, Telangana, India for providing necessary facilities to carry out this work.

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