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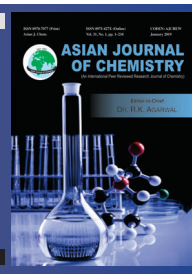

Synthesis, Spectral, Antibacterial, Antifungal and Antipyretic Activities of Co(II) and Ni(II) Complexes with Bioactive Benzimidazole and Benzoate Ion

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The Co(II) and Ni(II) transition metal complexes with benzimidazole and benzoate ion was synthesized using microwave heating. The synthesized complexes were characterized by elemental analysis, metal estimation, molar conductance, cyclic voltammetry, magnetic moment and electronic spectra, IR, Far-IR spectral data. The structure and metal ligand stoichiometry of the synthesized complexes were confirmed by using elemental analysis and metal estimation. Molar conductance of 10^{-3} M complex solution confirming their non-electrolyte nature. The Redox behaviour of metal ions in the synthesized complexes was confirmed by cyclic voltammogram. Six coordinated geometry of complexes were concluded from magnetic moment and electronic spectra. The *in vitro* antibacterial activities of the ligand and its Co(II) and Ni(II) complexes were screened against Gram +ve bacteria, *Bacillus*, Gram-ve bacteria, *Pseudomonas*, *Klebsiella pneumonia* and *Proteus* and *in vitro* antifungal activities were screened against pathogenic yeast, *C. albicans* by agar well diffusion method. The antipyretic activities of ligand and its Ni(II) complex were evaluated by yeast- induced fever test. The percentage reduction of the sample at yeast induced temperature was deduced.

Keywords: Benzimidazole, Benzoate, Cobalt(II) complex, Nickel(II) complex, Biological activities.

INTRODUCTION

Nitrogen donor ligands are used to the effective formation of coordination complexes with metal ions due to the presence of lone pair of electrons and variety of oxidation states. Benzimidazole is one of 'N' donor heterocycles used as ligands for coordination complexes. It acts as a neutral monodentate ligands which is coordinated with the metal ions through N atom [1,2].

Benzimidazole derivatives are important class of heterocyclic compounds due to their pharmaceutical activities such as antibacterial, antifungal, antihelmintic, antiallergic, local analgesic, antihistaminic, hypertensive and spalmolytic activities [3]. Due to its nitrogen donor atom site, this is sterically hindered after it forms bulky benzimidazole groups and therefore the irregular geometry was obtained around the metal ions after complexation [4,5]. Benzimidazole derivative are important in pharmacokinetic and pharmacodynamics properties. The medicinal activities of benzimidazole containing moiety have been well predictable albendazole and mebendazole [6,7]. The present investigation focused on the synthesis of transition metal complexes with benzimidazole, benzoate ion and characterized by various physico-chemical, spectral and biological activities.

EXPERIMENTAL

The elemental analyses of complexes were carried out using (Thermo Finnegan make, Flash EA1112 series) CHNS(O) analyzer instrument. The molar conductance of complexes of 10^{-3} M in acetonitrile was conducted using Systronic Conductivity Bridge at 30 ºC. The solid state UV-visible spectra of the complexes were measured by using Varian carry-5000 model UV-visible spectrophotometer. IR spectra of free INH (ligand) and its complexes were carried out using Schimadzu FT-IR 8400s spectroscopy at 4000-400 cm^{-1} wave number with KBr pellet technique. The antibacterial and antifungal activities of INH and its complexes were done by *in vitro* agar well diffusion method using amikacin and ketoconazole as a standard for bacterial and fungal strain, respectively. All the chemicals were purchased and used as it is without further purification. Benzimidazole: Alfa Aesar, cobalt nitrate, nickel nitrate, sodium benzoate,

DMSO, methanol, ethanol and CH_3CN were used of AnalaR grade.

Animals study: Male albino rats of Wistar strain approximately weighing 180-220 g were used in this study. They were healthy animals procured from Sri Venkateswara enterprises, Bangalore, India. The animals were housed in spacious polypropylene cages bedded with rice husk. The animal room was well ventilated and maintained under standard experimental conditions (temperature 27 ± 2 ºC and 12 h light/dark cycle) throughout the experimental period. All the animals were fed with standard pellet diet (Gold Mohur, Mumbai, India) and water *ad libitum*. They were acclimatization to the environment for one week prior to experimental use. The experiment was carried out according to the guidelines of the Committee (Ethical No: MC/1416/a/11/CPCSEA) for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

Synthesis of complex: The Co(II) complex was synthesized by mixing 3.24 g of benzimidazole (13.74 mmol) in 10 mL methanol with 2 g of cobalt nitrate (3.24 mmol) in 10 mL methanol and then 1.98 g of sodium benzoate (6.87 mmol) in ethanol was mixed and the whole mixture was heated on a microwave oven for about 10 s. Similarly, Ni(II) complexes were synthesized by mixing 3.24 g of benzimidazole (13.75 mmol) in 10 mL methanol with 2 g of nickel nitrate (3.24 mmol) in 10 mL methanol and then 1.98 g of sodium benzoate (6.87 mmol) in ethanol, respectively and the whole mixture was irradiated on a microwave oven for 10 s. The precipitated coloured complexes were filtered, washed with ethanol and dried. The complexes are stable under ordinary condition.

RESULTS AND DISCUSSION

Micro-analytical data of complexes: The synthesized complexes are soluble in DMSO and DMF, stable under ordinary condition. Elemental analyses, C, H, N were found to be good agreement with the proposed molecular formulae (Table-1). In addition to that metal estimation is also confirmed by molecular formula of the complexes. The magnetic moment values of 10^{-3} M complex solution in acetonitrile shows non-elctrolyte type neutral nature of the complexes [8].

Cyclic voltammetry: The electrochemical studies of the complexes were studied by cyclic voltammetry in DMSO solvent with tetraethylammonium bromide as supporting electrolyte. The voltammogram of Co(II) complex was recorded in the potential range from -2.000 V to 1.5 V and shows the Ep_a = - 0.700 V, Ep_c = - 0.900 V and ΔE_p = - 0.200 V confirming by the quasi reversible one electron transfer reaction of Co(II)/Co(I) couple (Fig. 1), the ratio of peak anodic current and cathodic current (Ip_a/Ip_c) is 0.380 V also established by quasi-reversible reaction [9]. In Ni(II) complex, Ep_a = - 0.600 V, Ep_c = -1.000 V, ΔE_p = - 0.400 V and (Ip_a/Ip_c) is 0.211 V also confirmed by the one electron quasi reversible Ni(II)/Ni(I) couple [10].

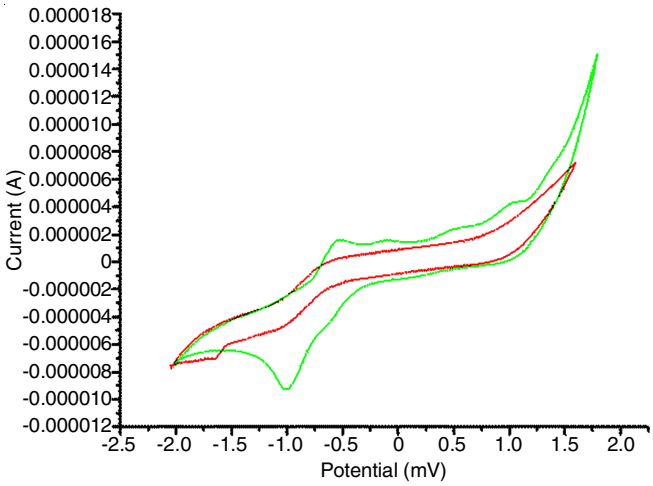

Fig. 1. Cyclic voltammogram of Co(II) and Ni(II) complexes

Electronic spectra and magnetic moment: The electronic spectra of benzimidazole and its Co(II) and Ni(II) complexes were recorded by diffused reflectance spectra method. The ligand shows band at 234 nm which is assignable to π-π^* transition which is present in all the complexes. Co(II) shows three prominent peaks at 570 nm, 330 nm and 272 nm are assignable three transitions which indicated their octahedral geometry. In Ni(II) complex three peaks at 579 nm, 332 nm & 270 nm are also assignable to three transitions, respectively are also confirming the octahedral environment around the Ni(II) complex. The magnetic moment of Co(II) complex is 2.90 BM and Ni(II) is 2.60 BM are also confirming the octahedral geometry [11,12].

IR and far-IR spectra: The IR and Far-IR spectra are the best tool to find out the complexation and metal coordinate site in metal complexes. The free nitrogen donor benzimidazole ligand exhibit ν(C=N) stretching frequency at 1650 cm^{-1}, ν(N-H) at 3200 cm^{-1} and ν(C-N) at 1290-1270 cm^{-1} after complexation these stretching frequencies in Co(II) complex shifted at 1600, 3138 and 1275 cm^{-1} whereas in Ni(II) these values shifted at 1606, 3115 and 1279 cm^{-1}, respectively confirming the complex formation. It is evident that ν(C=N) frequency shifted to lower value in complexes shows benzimidazole can coordinate to the metal ion through nitrogen atom (freely available lone pair electrons) [13]. The mixed anionic ligands benzoate ion in complex gives ν(C=C) at 1492 cm^{-1}, ν(C=O) at 1240 cm^{-1}, ν(C=H) at 2962 cm^{-1} and ν(C-O) at 1240 cm^{-1} in Co(II) complex whereas in Ni(II) complex these values shifted to ν(C=C) at 1468 cm^{-1}, ν(C=O) at 1676 cm^{-1}, ν(C=H) at 2924 cm^{-1} and ν (C-O) 1251 cm^{-1}, respectively indicating the coordination of benzoate ion through its oxygen to the metal ions [14]. The far-IR spectra shows ν(M-N) bond at 423 cm^{-1} in Co(II) complex whereas 430 cm^{-1} in Ni(II) complex indicated that benzimidazole can coordinate to the metal ion through its nitrogen atom (freely available lone pair electron). The ν(M-O) at 345 and 388 cm^{-1}

TABLE-1
ANALYTICAL DATA OF Co(II) AND Ni(II) COMPLEXES WITH BIOACTIVE BENZIMIDAZOLE AND BENZOATE ION

Complex	Colour	Yield (%)	Elemental analysis (%): Calcd. (Found)					Molar conductance (Ohm^{-1} cm^2 mol^{-1})
			C	H	N	O	M	
$[Co(BI)_4(Benz)_2]$	Dark violet	78	61.48 (61.20)	4.14 (4.00)	13.66 (13.40)	7.80 (7.79)	7.18 (6.95)	17.60
$[Ni(BI)_4(Benz)_2]$	Pale green	69	61.50 (60.58)	4.15 (3.98)	13.66 (13.00)	7.81 (7.90)	7.16 (7.10)	17.58

in both the complexes respectively indicating the mixed anionic ligand benzoate ion can coordinate through its oxygen atom [15].

Bio-potential activities: The *in vitro* antibacterial and antifungal activities of the ligand and its complexes were screened against Gram +ve bacteria, *Bacillus*, Gram-ve bacteria, *Pseudomonas*, *Klebsiella pneumonia* and *Proteus*, and pathogenic yeast, *C. albicans* by agar well diffusion method using DMSO solvent and amikacin and ketoconazole standards. The minimum inhibitory concentration (MIC) concentration of the complex compared with those for the ligand, the values indicated that the metal complexes are moderately active than the ligand due to chelation reduce the polarity of metal complexes and the nitrogen atom of ligand sharing its lone pair electrons to metal ions and gets delocalization of chelate rings in metal complexes shows enhanced activities of complexes [16].

Antipyretic activities

Effect on hyperexia induced in rat by brewer's yeast: Antipyretic activity was evaluated by the yeast-induced fever test according to Ashok *et al*. [17]. Hyperthermia was induced in rats by 1 mL/100 g body weight of 44 % brewer's yeast suspension in saline. The animals were then fasted for the duration of the study (about 18 h), but water was made available *ad libitum*. A thermister probe was inserted about 3 cm into the rectum of each rat and their basal rectal temperatures were recorded on a digital thermometer. Temperature was measured after 18 h from injection and considered as zero time. Control temperatures were taken 18 h after the yeast injection to determine the pyretic response to the yeast. Rat which showed a rise in temperature more than 0.5 ºC were excluded from the experiment.

The antipyretic activities of ligand and Ni(II) complexes were carried out and compared with standard. The experiments were done by animals study using rate. The rats are grouping into five as Group I serves as normal rat treated with distilled water (no treatment), Group II served as negative control with hyperexia rat. Groups III & IV are hyperexia rats were treated with benzimidazole and Ni(II) complex at a dose of 50 mg/kg and 100 mg/kg body weight, respectively. Group V served as positive control with hyperexia rat treated with standard as paracetamol (50 mg/kg body weight). The temperature was measured at 0, 1, 2 and 3 h after drug administration. The mean change from the sample/standard/vehicle value over 3 h period was calculated for each rat and expressed as percentage of the sample yeast-induced temperature recorded for same animals. The results indicated that the ligand benzimidazole and Ni(II) complex are equally reduce the temperature of hyperexia rats at 2-3 h comparing positive control paracetamol which concluded that benzimidazole and Ni(II) complex also act as the antipyretic agent [18] (Tables 2 and 3).

Conclusion

The present investigations focused on the synthesis, spectral characterization and bio-potential activities of Co(II) and Ni(II) complexes. From the results of magnetic moment and electronic spectra, IR & far-IR spectra concluded that both complexes have octahedral geometry and coordinated through nitrogen and oxygen atoms of ligand to the metal ions. The complexes showed well redox properties and exhibited antibacterial and antifungal activities. The results of antipyretic activities shows that ligand and Ni(II)complex are very good antipyretic agent equally compared with standard paracetamol.

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TABLE-2
EFFECT OF BENZIMIDAZOLE ON YEAST-INDUCED PYRETIC IN NORMAL AND EXPERIMENTAL RATS

Treatment groups	Doses (mg/kg body wt)	Before Yeast injection	After Yeast injection	Mean total temperature ± SD (°C)			
				Time after treatment (h)			
		0 h	24 h	0	1	2	3
I	Distilled water	36.90 ± 0.08	36.60 ± 0.06	36.70 ± 0.06	36.90 ± 0.11	36.50 ± 0.08	36.80 ± 0.05
II	–	36.80 ± 0.03	38.08 ± 0.02	38.20 ± 0.08	38.40 ± 0.01	38.07 ± 0.04	37.90 ± 0.04
III	50	36.70 ± 0.07	38.09 ± 0.04	38.04 ± 0.04	37.70 ± 0.05	37.20 ± 0.07*	36.90 ± 0.08*
IV	100	36.90 ± 0.04	38.06 ± 0.02	38.08 ± 0.06	37.60 ± 0.09	37.10 ± 0.0*	36.80 ± 0.08*
V	Paracetamol (50)	36.80 ± 0.07	38.09 ± 0.09	38.07 ± 0.05	37.50 ± 0.07	37.10 ± 0.07*	36.70 ± 0.07*

Values were expressed as mean ± SD for six rats in each group; *Significantly different from 0 h ($P < 0.05$)

TABLE-3
EFFECT OF Ni(II) COMPLEX ON YEAST-INDUCED PYRETIC IN NORMAL AND EXPERIMENTAL RATS

Treatment groups	Doses (mg/kg body wt)	Before Yeast injection	After Yeast injection	Mean total temperature ± SD (°C)			
				Time after treatment (h)			
		0 h	24 h	0	1	2	3
I	Distilled water	36.80 ± 0.11	36.70 ± 0.10	36.60 ± 0.25	36.80 ± 0.22	36.60 ± 0.20	36.70 ± 0.20
II	–	36.80 ± 0.14	38.64 ± 0.29	38.60 ± 0.21	38.70 ± 0.06	38.30 ± 0.33	38.10 ± 0.03
III	50	36.70 ± 0.29	38.74 ± 0.09	38.70 ± 0.07	38.10 ± 0.07	37.60 ± 0.11*	37.10 ± 0.15*
IV	100	36.90 ± 0.16	38.54 ± 0.09	38.50 ± 0.12	37.80 ± 0.12	37.10 ± 0.14*	36.80 ± 0.10*
V	Paracetamol (50)	36.70 ± 0.13	38.75 ± 0.17	38.70 ± 0.05	37.60 ± 0.11	36.80 ± 0.05*	36.60 ± 0.21*

Values were expressed as mean ± SD for six rats in each group; *Significantly different from 0 h ($P < 0.05$)

CONFLICT OF INTEREST

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

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