

Synthesis, Characterization and Antifungal Activity of Metal Complexes having Hydrazinobenzimidazole Based Ligands

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(Received 22 Mar, 2019; Accepted 08 May, 2019; Published 15 May, 2019)

ABSTRACT: The synthesis, characterization and antifungal activity of some transition metal complexes of N¹–{(1E)-1H-benzimidazol-2-yl) benzylidene-2-hydrazinobenzimidazole} (Bbhbz) of composition M(Bbhbz)X₂ (X=Cl⁻ or Br⁻) for Cu²⁺ and (X= Cl⁻, Br⁻, I⁻ and NCS) for Zn²⁺ or Cd²⁺ and M(Bbhbz)X₂ (M= Ni²⁺, Co²⁺ or Mn²⁺ and X=Cl or 1/2SO₄) have been reported. The electrical conductance, Magnetic Susceptibility, IR and electronic absorption spectra of mono ligated complexes M(Bbhbz)X₂ are consistent with five coordinated trigonal bipyramidal structure while those of bis ligated complexes M(Bbhbz)X₂ (M= Mn²⁺, Ni²⁺ and Co²⁺) are pseudo octahedral. The antifungal activity of ligand and some of its complexes have been investigated by radial growth method. Copper(II) and Cadmium(II) complexes showed much antifungal activity than those of ligand and its other complexes.

Keywords: Synthesis; Benzimidazole; Antifungal activity; Metal Complexes; Chemotherapeutic; Electrical Conductance; Magnetic Moment; Schiff base and Elemental analyses.

INTRODUCTION: Heterocyclic compounds are known to play an important role in drug discovery, since the majority of therapeutic drugs contain a heterocyclic unit. Within the vast range of heterocycles, benzimidazoles were found to have trendy structures employed in several areas such as material science, for example, in fuel cells¹ or in the pharmaceutical industry. A successful example is Nexium, a proton pump inhibitor² used to treat peptic ulcers and gastroesophageal reflux disease, which became one of the most widely prescribed drugs. In 1872, when Hobercker reported³ the first benzimidazole synthesis, of 2,5- and 2,6-dimethylbenzimidazole, he never suspected that benzimidazole scaffold would become such a preeminent structure.

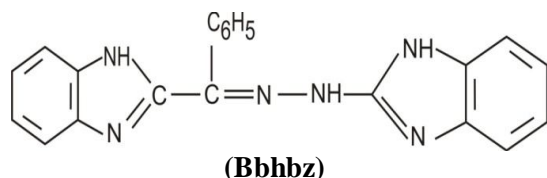
1,2-Disubstituted benzimidazoles and their derivatives represent an important branch of this family. These structures were reported as valuable bioactive structures, such as specific angiotensin II receptor type I selective antagonists,⁴ or hepatitis B virus NSSB polymerase inhibitors.⁵ Furthermore, they exhibit several other pharmacological activities including antidiabetic,⁶ antihistamine,⁷ analgesic,⁸ antiviral,⁹ chemotherapeutic,¹⁰ antifungal,¹¹ and antiparasitic¹² applications.

The relevance of these compounds can be demonstrated by the profusion of pharmaceutical products in the market.

Moreover, 1, 2-disubstituted benzimidazoles were also described as intermediates for dyes and polymers,¹³ and have frequently been used as ligands.¹⁴ In addition, there have also been reports of their use as possible precursors for aminoboronic acids with an interest as bifunctional organic catalysts.¹⁵

Undoubtedly, benzimidazoles are important scaffolds, thus substantial efforts have been made to the search for new synthetic strategies to assemble this structure, both in solution¹⁶ and in the solid phase.¹⁷ Solid-phase synthesis is extremely useful for combinatorial approaches towards novel benzimidazole libraries with increased structural complexity. While methods to prepare 1- or 2-substituted benzimidazoles have highly increased during the last years,¹⁸ the assembly of 1,2-disubstituted benzimidazoles remains an intricate task.¹⁹ The classical and most common methods to assemble benzimidazoles involve the condensation of o-phenylenediamine with aldehydes, carboxylic acids, or their derivatives (nitrites, amidates, orthoesters).²⁰

Due to extensive field of utility of benzimidazole derivatives in industries, medicine and Coordination chemistry the preparation and characterization of new derivatives of benzimidazole molecule created interest in the studies of their metal complexes. In present investigation I have prepared and characterized the complexes of some metal ions with Schiff base of 2-benzoylbenzimidazole with 2-hydrazinobenzimidazole. (Bbhbz)



The ligand (1H-benzimidazol-2-yl) benzoyl-2-hydrazinobenzimidazole (Bbhbz) contains a bulky phenyl ring in (1H-benzimidazol-2-yl) acetyl 2-hydrazino (1H-benzimidazole) in place of methyl group. Bbhbz is also a potential-tridentate – N,N,N-donor coordinating molecule and can behave as tripod ligand. The hydrazinyl part of benzimidazole ring donor nitrogen is not coplanar with acetyl or benzoyl part chelating nitrogen atoms due to lone pair of electron present at hydrazine NH-nitrogen. Thus the donor behavior of ligand will be interesting.

In pursuance of our interest to investigate the synthesis, characterization and microbial potentiality of coordination complexes of substituted benzimidazole derivatives we report here the synthesis and antifungal activity of complexes of 2- Hydrazinobenzimidazole derivatives with some bivalent metal ions.

MATERIAL AND METHODS:

Preparation of Cu(Bbhbz) X_2 (X= Cl or Br): About 10 millimole of Cu(II) halide (CuCl $_2$ 2H $_2$ O, or CuBr $_2$) was dissolved in 20-25ml of methanol and treated with hot methanolic solution of 10 millimole of ligand (30ml methanol) and hot solution was refluxed on steam bath for about 25 minutes with stirring and cooled to room temperature. On skretching the solution coloured product separated. The complexes were collected on Buchner funnel, washed with ice cold methanol and dried in desiccators over CaCl $_2$.

Preparation of M(Bbhbz) Cl_2 (M= Zn^{II} or Cd^{II}): About 10 millimole of a aqueous methanolic solution of metal chloride in about 20 ml was added to hot methanolic solution of 10 millimole of ligand with stirring. The mixed solution was heated on steam bath when cream coloured complex separated gradually. The products were collected washed with cold methanol and dried as above.

Preparation of [ML $_2$] Cl_2 (M= Co^{II}, Ni^{II}, or Mn^{II}): About 10 millimole of metal chloride and 20 millimole of ligand were separately dissolved in about 20 and 30ml of methanol and clear solutions were mixed together with stirring and refluxed on steam bath in a R.B. flask for 30-35 minutes. The resulting solution sometime gave precipitate or complexes were obtained as concentrating the refluxed solution to a small volume. The product separated were left overnight and collected on a filter. The products were washed with cold methanol and dried in a desiccator over CaCl $_2$.

Preparation of [ML $_2$] SO_4 (M = Co^{II}, Ni^{II}, and Cu^{II}): The complex Sulphate of Co(II), Ni(II) and Cu(II) were prepared as above but due to poor solubility of metal sulphate in dry methanol. The metal sulphate solutions were prepared in aqueous methanol (20ml) and ligand (20 millimole) in about 35ml hot methanol. The metal solution were mixed with stirring drop wise in hot solution of ligand and mixed solutions were refluxed on steam bath and concentrated to small volume (10ml) and chilled over night. The complex sulphate separated as the crystalline precipitate. The products were collected on filter washed with cold dry methanol and dried in air and finally in air oven at 50-60°C.

The dried samples were analyzed and analytical results of samples are recorded in Table-1. The colour and magnetic susceptibility value (μ_{eff}) at room temperature (304°K) were measured and recorded in Table-1. The electrical conductance (qualitative) of complexes in Dimethylformamide at room temperature (28-29°C) were measured and approximate molar conductance value of complexes are recorded in Table-1. The infrared spectra of ligand and its representative complexes were recorded in KBr disc and their diagnostics band positions of complexes are given in IR-spectral studies data. The electronic absorption band position with their probable assignment is given in Table-2.

RESULTS AND DISCUSSION: The results of elemental analysis of complexes corresponds to molecular formula Cu(Bbhbz) X_2 (X= Cl, or Br), Zn(Bbhbz) Cl_2 , Cd(Bbhbz) Cl_2 , [M(Bbhbz) $_2$] Cl_2 (M = Mn^{II}, Co^{II}, Ni^{II}), [M(Bbhbz) $_2$] SO_4 (M = Co^{II}, Ni^{II} or Cu^{II}). The complexes are stable in air and their solutions except Zn(II) and Cd(II) complexes, the complexes of Mn(II), Co(II), Ni(II) and Cd(II) are paramagnetic. The magnetic moment value of Mn(II) complex [Mn(Bbhbz) $_2$] Cl_2 at 304°K was found to be 5.92 BM. The magnetic moment value corresponds to high spin octahedral Mn(II) complexes.²¹ The mag-

netic moment value of copper (II) complexes $\text{Cu}(\text{Bbhbz})\text{X}_2$ ($\text{X} = \text{Cl}$ or Br) and $[\text{Cu}(\text{Bbhbz})_2]\text{SO}_4$ occur in the range of 1.83 - 1.89 BM indicating that copper (II) is magnetically dilute and there is no Cu-Cu interaction in complexes. The complexes are either five coordinated $\text{Cu}(\text{Bbhbz})\text{X}_2$ and six coordinated distorted octahedral in $[\text{Cu}(\text{Bbhbz})_2]\text{SO}_4$. The magnetic moment values of Ni(II) complexes occur in the range 3.27-3.32 BM at 304°K which found in the range of six coordinated octahedral complexes for nickel(II) ions.²² The magnetic moment value of cobalt (II) complexes in planar field occur in the range of 2.2 - 2.5 BM and those of tetrahedral complexes between 4.2 - 4.7 BM. Cobalt(III) complexes are with exception of $[\text{CoF}_6]^{3-}$ and $[\text{CoF}_4(\text{OH})_2]^{3-}$ the most of the complexes are diamagnetic but high spin cobalt (II) complexes (d^3 system) usually show magnetic moment value in the range of 4.9 to 5.2 BM.²³ In present complexes $[\text{Co}(\text{Bbhbz})_2]\text{Cl}_2$ and $[\text{Co}(\text{Bbhbz})_2]\text{SO}_4$ the room temperature magnetic moment value 5.02 BM and 5.12 MB respectively indicating high spin octahedral environment of ligand around Co(II) ion.

The complexes in general are less soluble or insoluble in methanol and ethanol but dissolve in dioxane but highly soluble in Dimethylformamide. The electrical conductance value of $\text{Cu}(\text{Bbhbz})\text{X}_2$ ($\text{X} = \text{Cl}$ or Br) and $\text{M}(\text{Bbhbz})\text{Cl}_2$ ($\text{M} = \text{Zn}^{\text{II}}$ or Cd^{II}) at room temperature (28°C) show negligible molar conductance value ($\lambda_{\alpha} = 12-18 \text{ ohm}^{-1}\text{mol}^{-1}\text{cm}^2$) suggesting non-ionic character and halides are coordinated to metal atom. The bis ligated complexes $[\text{M}(\text{Bbhbz})_2]\text{Cl}_2$ ($\text{M} = \text{Mn}^{\text{II}}$, Co^{II} or Ni^{II}) and $[\text{M}(\text{Bbhbz})_2]\text{SO}_4$ ($\text{M} = \text{Mn}^{\text{II}}$, Co^{II} , Ni^{II} or Cu^{II}) display electrical conductance value between 148-158 $\text{ohm}^{-1}\text{mol}^{-1}\text{cm}^2$ indicating that complexes are ionic in nature and the halide or sulphate in complexes are ionic and not involved in coordination.²⁴

The electronic absorption spectrum of ligand Bbhbz shows three medium to strong band in ultraviolet region located at 262, 273 and 332 nm. These electronic transition are assigned to benzimidazole ring and hydrazone ($=\text{C}=\text{N}-\text{NH}$), $\pi-\pi^*$ and $n-\pi^*$ transitions. In the complexes these transitions are eclipsed due to charge transfer transition in complexes. The electronic absorption spectra of Zn(II) and Cd(II) complexes display strong charge transfer band below 380 nm and ligand absorptions are observed in charge transfer band. The electronic absorption spectrum of $\text{Cu}(\text{Bbhbz})\text{Cl}_2$ shows a medium band at 440-450 nm and broad asymmetric band near 650-670 nm these transition are assigned to ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{2g}$ and ${}^2\text{B}_{1g} \rightarrow {}^2\text{B}_{2g}$, ${}^2\text{E}_g$ transitions in tetragonal distorted field. The strong

electronic absorptions below 380 nm in complexes are attributed to charge transfer transition. The electronic absorption of Ni(II) complex $[\text{Ni}(\text{Bbhbz})_2]\text{Cl}_2$ in methanol in the range 300-850 nm range shows medium band at 390-400 nm and a weak and at 580-585 nm and these transitions are assigned to ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{F})$ and ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$ transitions in approximately octahedral field.²⁵ The electronic absorption spectrum of cobalt (II) complex $[\text{Co}(\text{Bbhbz})_2]\text{Cl}_2$ shows strong absorption below 400 nm due to charge transfer absorption and medium to weak is and near 450-460 nm and 520-530 nm assignable to ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$ and ${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$ transitions is approximately octahedral field.²⁶ Thus from magnetic and spectral evidences octahedral structure are suggested for bis ligated Cu(II), Mn(II), Co(II) and Ni(II) Complexes $[\text{M}(\text{Bbhbz})_2]\text{Cl}_2$ and $[\text{M}(\text{Bbhbz})_2]\text{SO}_4$.

Antifungal activity of ligand and its complexes:

The ligand (Bbhbz) and its Complexes $[\text{M}(\text{Bbhbz})]\text{Cl}_2$ ($\text{M} = \text{Cu}^{2+}$, Zn^{2+} or Cd^{2+}) and $[\text{M}(\text{Bbhbz})_2]\text{Cl}_2$ ($\text{M} = \text{Mn}^{2+}$, Co^{2+} or Ni^{2+}) were screened for fungi *Candida albicans* (CA), *Aspergillus niger* (AN), *Aspergillus fumigates* (AF), *F. oxysporum* (FO) and *R. phaseoli* (RP). The screening medium having composition 20g Starch, 20g agar-agar, 20g glucose dissolved in 1litre distilled water were made. To this 50 and 100ppm concentration of ligand and its complexes were made in DMSO. The medium were poured in petri disc and percentage inhibitions of fungi growth are shown in Table-3. It was found that the Bbhbz complexes of Cu(II) and Cd(II) show much antifungal activity than pure ligand and its other complexes. The reference used for antifungal activity was Mycostatin.

IR spectral Studies: IR spectra of (1H-Benzimidazol-2-yl) benzoyl-2-hydrazinobenzimidazole (Bbhbz) shows N-H Stretch at 3420cm^{-1} and C-H stretch at 2927 cm^{-1} . The ν (C=N) of ligand is observed at 1631cm^{-1} and imidazole ring ν (C=N) at 1595cm^{-1} . These (C=N) stretches are shifted to lower vibration in complexes and observed $1585-1591\text{cm}^{-1}$. The (N-H) bending vibration of ligand is observed at 1502cm^{-1} and the band is not affected appreciably in complexes indicating that (N-H) of imidazole and N-H of hydrazone part is not involved in bonding. The (C-H) bending band of ligand located at 1407 and 1335 cm^{-1} are not affected in complexes. The ν (N-N), ν (C-N) and ν (C-C) vibrations of ligand and complexes are located at 1251 , 1216 , 1129 and 1057 cm^{-1} .²⁷ The (C-H) out of plane bending bond of phenyl ring is observed at 769cm^{-1} . The phenyl and benzimidazole²⁸⁻²⁹ ring deformation vibrations of ligand are located at 659 , 601 and 529 cm^{-1} . The IR spectra $[\text{Co}(\text{Bbhbz})_2]\text{Cl}_2$ and

that $[\text{Ni}(\text{Bbhbz})_2]\text{Cl}_2$ and $\text{Zn}(\text{Bbhbz})\text{Cl}_2$ show ν (C=N) vibration in the range $1585\text{-}1591\text{ cm}^{-1}$. The (C-H) out of plane bending band is observed in the range $769\text{-}771\text{ cm}^{-1}$. The IR spectra of $[\text{Co}(\text{Bbhbz})_2]\text{SO}_4$ and $[\text{Ni}(\text{Bbhbz})_2]\text{SO}_4$ shows a strong band of 1105 cm^{-1} and second ν_4 vibration at 641 cm^{-1} typical of ionic sulphate group.³⁰⁻³⁴ The ionic nature of halide and sulphate has also been confirmed from conductance value of complexes.

On the basis of molecular formula, magnetic moment value and spectral studies the probable structure of complexes are shown below.

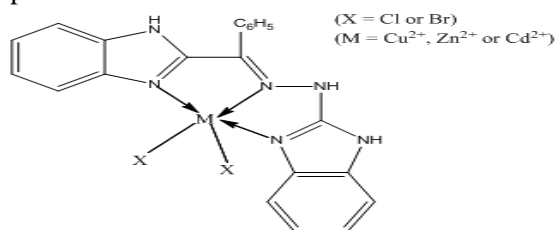


Figure 1: Structure of $[\text{Cu}(\text{Bbhbz})\text{X}_2]$ (X= Cl or Br) and $[\text{M}(\text{Bbhbz})\text{Cl}_2]$ (M = Cu^{II} , Zn^{II} or Cd^{II} and X= Cl or Br).

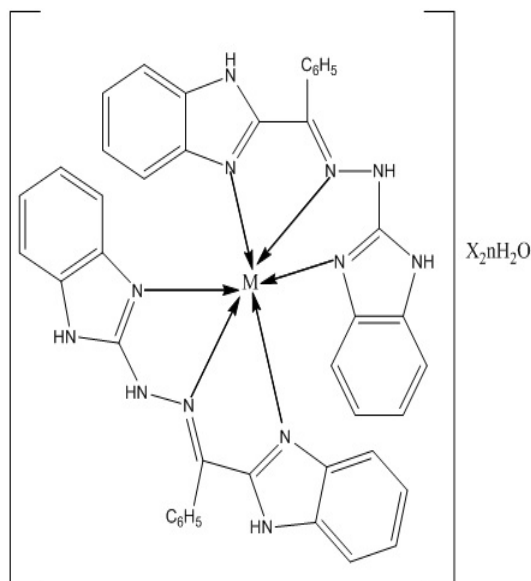


Figure 2: Structure of $[\text{M}(\text{Bbhbz})_2]\text{X}_2$ (M = Mn^{II} , Co^{II} , Ni^{II} or Cu^{II} and $\text{X}_2 = \text{Cl}_2$ or $1/2\text{SO}_4$ n=1 or 2).

Table 1: Results of Elemental analysis and Physical data of Ligands and complexes.

Complexes	Colour	% Found (Calc.)					Magnetic moment values at 304 ^o K	Electrical conductance $\lambda \alpha \text{ ohm}^{-1} \text{ mol}^{-1} \text{ cm}^2$
		Metal	Nitrogen	Carbon	Hydrogen	X ₂ /SO ₄		
L=Bbhbz	-	Metal	Nitrogen	Carbon	Hydrogen	X ₂ /SO ₄	-	-
[CuLCl ₂]	Yellowish	12.89	17.01	51.87	3.40	14.61	1.86BM	12
	Green	(13.05)	(17.26)	(51.78)	(3.28)	(14.58)		
[CuLBr ₂]	Light	10.96	14.42	43.62	2.98	27.61	1.83BM	15
	Brown	(11.04)	(14.60)	(43.80)	(2.78)	(27.76)		
[CuL ₂ SO ₄]	Greenish	9.41	25.03	75.67	4.61	14.21	1.89BM	13
	Yellow	(9.57)	(25.31)	(75.95)	(4.82)	(14.46)		
[CoL ₂ Cl ₂]	Yellowish	19.10	26.31	79.23	4.86	11.21	5.02BM	156
	Brown	(19.29)	(26.48)	(79.46)	(5.04)	(11.19)		
[CoL ₂ SO ₄]	Yellowish	8.71	25.41	76.31	4.62	14.33	5.12BM	148
	Brown	(8.95)	(25.52)	(76.56)	(4.86)	(14.58)		
[NiL ₂ Cl ₂]	Light	9.12	26.31	79.32	4.79	11.02	3.27BM	142
	Blue	(9.28)	(26.53)	(79.61)	(5.65)	(11.21)		
[NiL ₂ SO ₄]	Light	8.73	25.35	76.31	4.71	14.41	3.32	150
	Blue	(8.93)	(25.53)	(76.59)	(4.86)	(14.58)		
[MnL ₂ Cl ₂]	Dull	8.61	26.29	80.01	4.88	11.18	5.92	158
	Yellow	(8.72)	(26.65)	(79.96)	(5.07)	(11.26)		
[ZnLCl ₂]	Cream	13.18	16.92	51.36	3.11	14.23	Diamagnetic	13
	Yellow	(13.38)	(17.19)	(51.58)	(3.27)	(14.53)		
[CdLCl ₂]	Cream	20.81	15.38	47.13	3.01	13.16	Diamagnetic	~18
	Yellow	(20.98)	(15.68)	(47.05)	(2.98)	(13.25)		

Table 2: Electronic absorption band of ligand and complexes with their probable assignment.

Compounds	Electronic band position (in nm)	Assignment
L = Bbhbz	262, 272 323, 332	$\pi-\pi^*$ $n-\pi^*$
Zn(Bbhbz)Cl ₂	380 nm VS	Charge transfer
[Cu(Bbhbz) ₂]SO ₄	380 440-450 650-670	Charge transfer ${}^2B_{1g} \rightarrow {}^2B_{2g}$ ${}^2B_{1g} \rightarrow {}^2B_{2g}, {}^2E_g$
[Ni(Bbhbz) ₂]Cl ₂	390-400 580-585	${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$
[Ni(Bbhbz) ₂]SO ₄	400 570-580	${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$
[Co(Bbhbz) ₂]Cl ₂	450-460 520-530	${}^4T_{1g} \rightarrow {}^4T_{2g}$ ${}^4T_{1g} \rightarrow {}^4A_{2g}$

Table 3: Antifungal activity of ligands and some complexes at 30 ± 1 °C.

Fungi	Conc. in ppm	Bbhbz=L	CuLCl ₂	ZnLCl ₂	CdLCl ₂	MnL ₂ Cl ₂	CoL ₂ Cl ₂	NiL ₂ Cl ₂	Ref
C. Albicans	50	30	60	49	58	48	42	47	81
	100	38	82	65	78	62	61	63	98
A. Niger	50	33	56	48	56	45	47	46	82
	100	45	75	62	75	64	67	62	97
A. Flavus	50	30	57	42	51	47	45	48	85
	100	42	76	60	71	68	66	64	96
R. Phaseoli	50	37	52	41	50	48	42	47	70
	100	42	73	60	72	67	66	63	97
F. Oxysporum	50	31	56	43	55	42	43	45	81
	100	42	78	67	70	68	65	60	98

The reference used for antifungal activity was *Mycostatin*

CONCLUSION: In conclusion, we have reported here a suitable and facile method for preparation of some novel metal complexes having Hydrazinobenzimidazole based ligands. All the prepared complexes were screened for antifungal activity and few of them were found to be potent antifungal agents. All the characterization data and elemental analysis results were in good agreement with illustrated structures of metal complexes. Our present research is very useful from medicinal perspective. Our research can open new doors in antifungal drug discovery research in near future.

ACKNOWLEDGEMENT: Authors acknowledge support from IIT Patna and C. D. R. I. Lucknow for recording IR and UV Spectra. Authors would also like to thank L. N. M. U. Darbhanga for providing the necessary laboratory facilities.

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