

Synthesis and Pharmacological Activity of Metal Complexes having Hydrazinobenzimidazole Based Ligands

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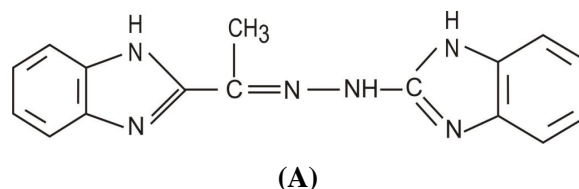
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ABSTRACT: The complexes of N¹-{(1E)-1H-benzimidazol-2-yl) ethylidene 2-hydrazinobenzimidazole} (BahbH) with some transition metal ions of composition, M(BahbH)₂Cl₂ (M=Mn^{II}, Co^{II}, Ni^{II}), [M (BahbH)X₂] (M=Cu^{II} and X=Cl⁻ or Br⁻, when M=Zn^{II}, Cd^{II}, X=Cl or I) Cu (BahbH)I, Ag (BahbH) NO₃, [M(BahbH)₂] SO₄.nH₂O (M=Mn^{II}, Co^{II} or Ni^{II} and n=1 or 2) have been prepared and characterized by elemental analysis, and studies of IR, UV, Magnetic susceptibility values and electrical conductance measurements at room temperature. The magnetic and spectral properties of Mn^{II}, Co^{II} and Ni^{II} complexes are consistent with octahedral structure. The complexes [M(BahbH)X₂] have five coordinated pseudo trigonal bipyramidal structure. The ligand and its complexes with Cu^{II}, Mn^{II}, Fe^{II}, Zn^{II}, Cd^{II} and Ag^I were screened for their antifungal and antibacterial activities. The complexes showed positive antifungal and two strains of Proteins mirabilis and Bacillus subtilis.

Keywords: Metal complexes; antifungal activity; antimicrobial activity; Magnetic susceptibility; Electrical Conductance; Benzimidazole and Schiff base.

INTRODUCTION: Imidazole nuclei of benzimidazole and substituted benzimidazole are important pharmacophore and a privileged structure in medicinal chemistry and possesses wide spectrum of medicinal activity.¹⁻³ One of the important benzimidazole in nature is α -ribosyl 5,6-dimethyl benzimidazole which is an axial ligand for cobalt (III) in vitamin-12. In which imidazole part provides an important binding sites in biological system displaying a vital role in metal protein interaction.⁴⁻⁵ The benzimidazole derivatives have trendy structure employed in various field of agriculture, material science, fuel cells and pharmaceutical industries. Nexium is effective proton pump inhibitor used to treat peptic ulcers and gastroesophageal reflux disease which is benzimidazole derivative. In 1872, when Hobercker reported⁶ the first synthesis of 2, 5-and 2, 6-dimethyl benzimidazole, he had never suspected that benzimidazole scaffold would become such a preeminent structure. In recent two decades thousands of benzimidazole derivatives have been prepared and their complexing behaviour and pharmacological properties have been studied.⁷⁻⁸ Benzimidazole de-

rivatives have wide spectrum of pharmacological activity. The complexes of benzimidazole and its derivatives have extensively been studied.⁹⁻¹⁶ The industrial utility, medicinal activity and prominent complexing ability of benzimidazole created immense interest for further studies on complexes. The schiff base of [(1H-benzimidazol-2-yl) ethanone with 2-hydrazinobenzimidazole (BahbH) potent nitrogen donor tridentate benzimidazole derivative (A).



The perusal of literature shows that metal complexes of (BahbH) has not appeared in literature. Intrigued from medicinal and coordinative properties of benzimidazole derivatives I have synthesized and characterized the complexes of BahbH with Mn (II), Co(II), Cu(I), Ag(I), Cu(II), Zn(II) and Cd(II) in solid state. The complexes were prepared, analyzed and

investigated and determined magnetic susceptibility and the electrical conductance value. The electronic absorption spectra and IR-spectra of some representative complexes have also been recorded and explained.

MATERIAL AND METHODS:

Preparation of ligand (BahbH): It was prepared by refluxing equimolar proportion of 2-acetyl benzimidazole and 2-hydrazino benzimidazole in ethanol containing a few drops of glacial acetic acid. The cream white precipitate separated was crystallized in ethanol + THF mixture. M. P. of BahbH was found 253°C. Nitrogen found 28.84% required for BahbH(C₁₆H₁₄N₆) – 28.96%.

Preparation of [Cu (BahbH) X₂] (X = Cl or Br & M = Cu²⁺, Cd²⁺ Zn²⁺): About 10 millimole of Copper (II) halide was dissolved in 20 ml of dry methanol and treated with hot methanolic solution of ligand (10 millimole in 20 ml). The resulting solution was heated on steam bath at 60-65°C with constant stirring when fine crystalline greenish yellow CuLCl₂ and brownish yellow CuLBr₂ separated on cooling and stretching the wall of the container. The products were collected on a filter and washed with ice cold methanol and dried in a desiccator over CaCl₂.

Preparation of [ML₂Cl₂] (M = Co^{II}, Ni^{II} and Mn^{II}): About 20 millimole of appropriate metal chloride was dissolved in 25 ml hot methanol and added with constant stirring to 40 millimole of (BahbH) dissolved in 30 ml of dry methanol. The mixed solutions were refluxed in R. B. flask for one hour and resulting solutions were concentrated when desired complex chloride separated as adding cold ether. The products were collected on a filter, then washed with ether and dried in a desiccator in vacuum. The dried products are fairly stable in dry air and dissolve in aqueous ethanol and aqueous methanol.

Preparation of Cu(I) complex [Cu(BahbH)I]: About 10 millimole of copper (II) sulphate was dissolved in 20 ml hot water and treated with excess of KI (potassium iodide) with stirring. The liberated I₂ was removed by adding required amount of Na₂S₂O₃. The colourless solution containing white precipitate of Cu₂I₂ was filtered and washed with hot water and air free methanol. The separated Cu₂I₂ was suspended in 20 ml methanol and kept in CO₂ atmosphere. The methanolic suspension of Cu₂I₂ was treated with 10 millimole of ligand dissolved in 30 ml hot methanol. The resulting product was refluxed for one hour when Cu₂I₂ went into solution to give yellow solution from which cream yellow prod-

uct separated on concentration and cooling. The complex was collected on a filter washed with air free methanol and dried in vacuum desiccator over CaCl₂. The dry product is fairly stable but get oxidised in moist air.

Preparation of Ag (BahbH) NO₃: About 20 millimole of silver nitrate was dissolved in 10 ml hot water and added drop-wise with constant stirring to hot solution of 20 millimole of BahbH dissolved in 30 ml ethanol. The cream yellow product separated slowly. The product was digested on steam bath (60-70°C) for fifteen minutes and collected on a filter. The product was washed with ethanol, ether and dried in a desiccator over CaCl₂. The product is fairly stable and dissolves in DMF, DMSO and pyridine.

Preparation of ML₂ SO₄ nH₂O (M = Mn^{II}, Co^{II}, Ni^{II} and Cu^{II} n = 2 or 1): About 10 millimole of hydrated metal sulphate was dissolved in 15 ml aqueous methanol and added slowly with constant stirring to 20 millimole of (BahbH) in 30 ml methanol. The resulting solution was heated when complex sulphate separated, gradually. The products were digested on steam bath at 60-65°C for half an hour and cooled in ice for one hour. The products separated were collected on filter, washed with methanol and ether and finally dried in a desiccator over CaCl₂.

Preparation of MLX₂ (M = Zn^{II} or Cd^{II} and X = Cl or I): The chloride and iodide of zinc(II) and Cd(II) are soluble in methanol. About 20 millimole of appropriate metal chloride was dissolved in 20 ml hot methanol and treated with 20 millimole of ligand dissolved in 30-40 ml hot methanol.

The resulting solutions were refluxed on a steam bath for 30 minutes and concentrated to half of its bulk when crystalline cream coloured precipitate started separating. The resulting products were cooled in ice and separated complexes were collected on buchner funnel. The products here washed with a few drops of methanol and excess of ether. The collected products were dried over CaCl₂ in a vacuum desiccator. The yield of product was 80-85%.

The complexes were analysed for metal, nitrogen and sulphate or halide and recorded in Table-I. The prominent band positions of IR spectra and their probable assignments are shown in Table 2 and 3.

RESULTS AND DISCUSSION: The analytical results of complexes of Cu(II) and Cu(I) corresponds with composition Cu (BahbH) X₂ (X = Cl or Br) and Cu (BahbH) I. In case of sulphate the composition of complex corresponds to Cu (BahbH)₂.SO₄.H₂O. The

analytical results of Co(II), Mn(II) and Ni(II) complexes corresponds to composition $M(\text{BahbH})_2\text{Cl}_2$ ($M = \text{Co}^{\text{II}}$ or Mn^{II}) and $M(\text{BahbH})_2\text{SO}_4 \cdot \text{H}_2\text{O}$ ($M = \text{Co}^{\text{II}}$, Ni^{II} or Mn^{II}). The zinc (II) and cadmium (II) halide complexes corresponds to composition $M(\text{BahbH})\text{X}_2$

($\text{X} = \text{Cl}$ or I). The complexes are fairly stable in air and hydrated complexes. $[\text{M}(\text{BahbH})_2] \cdot \text{SO}_4 \cdot 2\text{H}_2\text{O}$, $\text{Cu}(\text{BahbH})_2\text{SO}_4 \cdot \text{H}_2\text{O}$ loss H_2O on heating between 60-120°C without change in morphology and lusture of the complexes indicating that H_2O are not coordinated to metal atoms.

Table 1: Analytical result and Magnetic moment value of complexes at 304°K in BM.

Compound	% elemental Results found (Cal)			Magnetic Moment Values
	%M	Nitrogen	Anions	
CuLCl ₂	14.84 (14.83)	13.00 (13.06)	16.49 (16.56)	1.82
CuLBr ₂	12.10 (12.04)	10.59 (10.62)	30.29 (30.31)	1.83
CuLI	10.91 (10.88)	9.59 (9.60)	21.81 (21.75)	Diamagnetic
AgL(NO ₃)	22.50 (22.42)	15.19 (15.25)	–	Diamagnetic
MnL ₂ Cl ₂	7.71 (7.69)	15.67 (15.69)	10.00 (9.95)	5.88
MnL ₂ SO ₄ ·2H ₂ O	7.25 (7.21)	14.55 (14.53)	12.51 (12.45)	5.91
CoL ₂ Cl ₂	8.19 (8.21)	15.55 (15.60)	9.95 (9.89)	4.98
CoL ₂ SO ₄ ·2H ₂ O	7.12 (7.06)	14.51 (14.45)	12.45 (12.39)	4.86
NiL ₂ Cl ₂	8.22 (8.19)	15.71 (15.60)	9.95 (9.89)	3.25
NiL ₂ SO ₄ ·2H ₂ O	7.61 (7.58)	14.51 (14.46)	12.43 (12.39)	3.16
CuL ₂ SO ₄ ·2H ₂ O	8.26 (8.15)	14.41 (14.37)	12.29 (12.31)	1.89
ZnLCl ₂	15.23 (15.19)	12.98 (13.01)	16.62 (16.49)	Diamagnetic
CdLCl ₂	23.58 (23.54)	11.91 (11.73)	14.92 (14.87)	Diamagnetic
CdLI ₂	17.21 (17.02)	8.55 (8.48)	38.31 (38.44)	Diamagnetic

$L = \text{BahbH}$

The complexes of Cu(I) and Ag(I) correspond to composition $[\text{Cu}(\text{BahbH})\text{I}]$ and $\text{Ag}(\text{BahbH})\text{NO}_3$. The attempt to prepare $\text{Ag}(\text{BahbH})\text{I}$ was unsuccessful as AgI get separated on treatment with KI .

The complexes of Ag(I) and Cu(I) were diamagnetic where as the complexes of Cu(II), Mn(II), Ni(II) and Co(II) were paramagnetic and magnetic moment values of complexes occur in the range of high-spin octahedral complexes of respective metal ions.¹⁷ The magnetic moment values of Mn(II) complexes (Table 1) occurs in the range 5.88–5.91 BM and those of cobalt (II) in the range 4.86–4.98 BM similar to high spin octahedral cobalt (II) and Mn (II) complexes.¹⁸ The magnetic moment of copper (II) complexes occur in the range 1.82–1.89 BM indicating that there magnetically dilute product.¹⁹ The magnetic moment value of Nickel (II) complexes (3.16 and 3.25BM) are consistent with octahedral geometry.²⁰ The electron absorption spectra of Ni(II) and Cu(II) complexes in ethyl alcohol show medium to weak band between 400-850 nm. Ag(I), Cu(I) and Mn(II) complexes did not show prominent band in visible region. Manganese (II) complexes always show spin forbidden transition hence its complexes seldom display prominent transition in visible region. The Nickel (II) complexes

displayed two prominent band located at 420-430 and 580-590 nm assignable to ${}^3\text{A}_{2g} - {}^3\text{T}_{1g}(\text{P})$ and ${}^3\text{A}_{2g} - {}^3\text{T}_{1g}(\text{F})$ transition in weak octahedral field.^[21a] The electronic absorption spectra of $\text{Co}(\text{BahbH})_2\text{Cl}_2$ showed a medium band at 435 nm and a weak transition at 530 nm attributable to ${}^4\text{T}_1 - {}^4\text{T}_{1g}(\text{P})$ and ${}^4\text{T}_{1g} - {}^4\text{A}_{2g}$ transition consistent with octahedral structure of Co^{II} complexes. The U.V spectra of Copper (II) complex $\text{Cu}(\text{BahbH})_2\text{SO}_4 \cdot \text{H}_2\text{O}$ showed a broad band at 590-610 nm assignable to ${}^2\text{T}_{2g} \leftarrow {}^2\text{E}_g$ transition in approximately octahedral field.²⁰

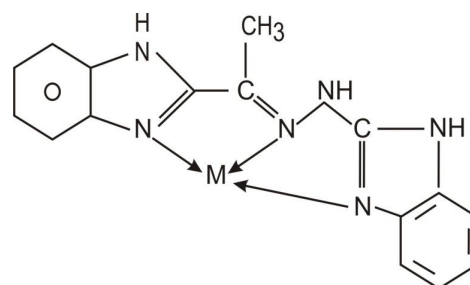
Antifungal and antibacterial activity of ligand and its complexes: The ligand (BahbH) and its complexes $M(\text{BahbH})_2\text{Cl}_2$ ($M = \text{Mn}^{\text{II}}$, Cu^{II} or Fe^{II}) and $[\text{M}(\text{BahbH})\text{Cl}_2]$ ($M = \text{Cu}^{\text{II}}$, Zn^{II} and Cd^{II}) and $\text{Ag}(\text{BahbH})\text{NO}_3$ were screened in vitro for their antimicrobial activity against two strains of bacteria proteus mirabilis and Bacillus subtilis as well as four strains of fungi. {Candida albicans (CA), Aspergillus niger (AN), Rizopus oryzae (RO) and Aspergillus fumigates (AF)}. The complexes were tested at 100µg/ml concentration in DMSO by disc diffusion technique.^{21b} Commercial antibacterial (ciprofloxacin and antifungal Amphotericin B) were also screened under similar condition for comparison. The results

have been reported in the form of inhibition zones and activity index Table 5 and Table 6. The results revealed that the ligand and all the complexes tested showed antifungal activities. The antifungal activity of Cu^{II} , Zn^{II} , and Cd^{II} were moderated and higher than free ligand.

The antibacterial activity of $\text{Cu}(\text{II})$ complexes (Table-VI) are appreciable and encouraging. The activity of $\text{Zn}(\text{II})$ is slightly lower than ciprofloxacin.

Infrared Spectra: The IR spectrum of ligand (1H-benzimidazol-2-yl) ethanone hydrazinobenzimidazole shows NH stretches and CH_3 stretches between $2880\text{--}3245\text{ cm}^{-1}$ located at $3147, 3070, 2927$ and 2847 cm^{-1} (Table 2 and 3). These IR spectral bands are not affected appreciably in its complexes. However, the hydrated complex sulphate display a broad IR absorption in 3μ region and show bands between 3400 to 3000 cm^{-1} attributed from hydrogen bonded $\nu(\text{OH})$ of water molecule. The ligand (BahbH) shows a medium $\nu(\text{C}=\text{N})$ stretching band at 1612 cm^{-1} is assigned to $\nu(\text{C}=\text{N})$ of benzimidazole ring. The N-H bending band of ligand was located at 1525 cm^{-1} and (CH_3) bending band was located at 1468 and 1344 cm^{-1} . These NH and (CH_3) bending bands of ligand is retained in complexes and observed with slight change in intensity and their position. The change can be attributed to change in molecular weight of complex species on formation of complex with metal atoms. The phenyl and imidazole ring skeletal vibration of ligand is observed in finger print region at $1585, 1419, 1344, 1285, 1217, 1153, 1043, 971, 918, 857, 765,$ and 728 cm^{-1} , the deformations vibrations are observed $695, 657, 577$ and 462 cm^{-1} . In complexes these vibrations are slightly affected due to involvement of ligand molecule in bond formation. The IR band at 728 cm^{-1} in free ligand is assigned to phenyl ring out of plane (CH) vibration. In complexes the $\nu(\text{C}=\text{N})$ band is shifted to long frequency due to coordination. The $\nu(\text{C}=\text{N})$ vibration of free ligand is shifted to lower frequency in almost all complexes. The withdrawal of electron cloud of $(\text{C}=\text{N})$ nitrogen forwards metal atom causes the shift of $(\text{C}=\text{N})$ stretching frequency to lower frequency.²²⁻²⁴ This indicated the coordination of imidazole ring tertiary nitrogen to metal atom. The NH stretches and N-H group of imidazole ring show $\beta(\text{NH})$ at 1525 cm^{-1} and it is retained in complexes suggesting that N-H Hydrogen is not deprotonated in complexes and NH nitrogen is not involved in bonding.^[25-34] Thus the IR spectra result of ligand and metal complexes suggests the coordination of ligand through both benzimidazole ring pyridine nitrogen and hydrazino group $(\text{C}=\text{N})$ nitrogen

and ligand behaves as tridentate donor molecule as shown below-



(Tridentate donor)

From the studies of infrared spectra, magnetic susceptibility values, electronic absorption spectral results and molar electrical conductance value the following probable structures are suggested for the complexes of (BahbH = L).

The probable structures of complexes are shown below.

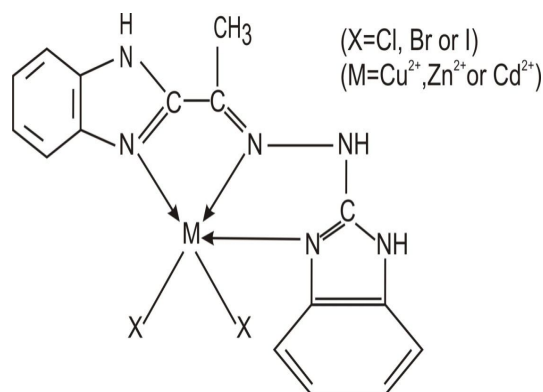


Figure 1: Structure of CuLX_2 ($\text{X}=\text{Cl}$ or Br) and MLX_2 ($\text{M}=\text{Zn}^{2+}$ or Cd^{2+} and $\text{X}=\text{Cl}$ or I).

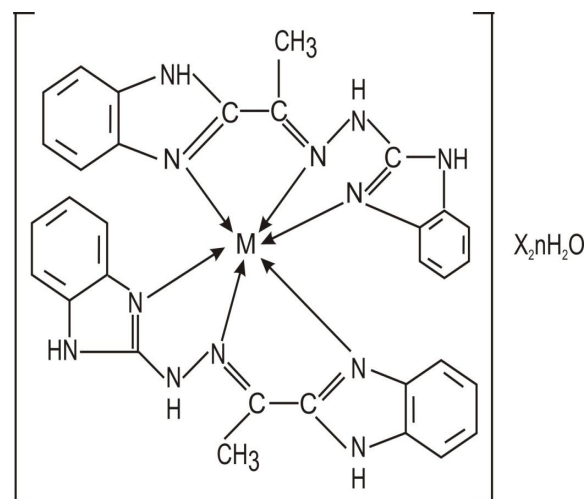


Figure 2: Structure of $[\text{M}(\text{BahbH})_2] \text{X}_2 \cdot n\text{H}_2\text{O}$ ($\text{M}=\text{Mn}^{2+}, \text{Co}^{2+}, \text{Ni}^{2+}, \text{Cu}^{2+}, \text{X}=\text{Cl}$ or $1/2\text{ SO}_4, n=1$ or 2).

Table 2: IR spectral bands positions of Ligand (Bahbh = L) and its complexes in cm^{-1} .

Ligand	NiL_2SO_4 $2\text{H}_2\text{O}$	CoL_2SO_4 $2\text{H}_2\text{O}$	Assignment
3147	3420	3440	$\nu(\text{NH}) + \nu(\text{OH})$
3070	3050	3010	of H_2O
2927	2930	2935	$\nu_{\text{as}} \text{CH}_2$
2847	2840	2836	$\nu_{\text{s}} \text{CH}_2$
1612	1595	1605	$\nu(\text{C}=\text{N})$
1585	1575	1580	$\nu(\text{C}=\text{C})$
1525	1521	1515	$\delta(\text{NH})$
1468	1455	1458	$\delta(\text{CH}_2)$
1419	1412	1420	Phenyl ring ($\text{C}=\text{C}$)
1344	1342	1336	$\delta(\text{CH}_2)$
1285	1283	1281	Phenyl ring
1217	-	1210	$\nu(\text{C}-\text{N})$
1153	1150	1152	$\nu(\text{C}-\text{C})$
1043	1045	1045	CH_2 Scissoring
971	972	970	CH_2 rocking band
918	-	910	Substituted phenyl ring
765	758	762	-
728	712	710 ($\nu\text{C}-\text{S}$)	Skeletal+CH out of plan
695	698	692	Bending band
651	650	641	ring deformation
577	-	-	Vibration
462	455	450	-
-	422	432	(M-N) Stretch

Table 3: IR spectral bands positions of Ligand (Bahbh=L) and its complexes in cm^{-1} .

ZnLCl_2	CdL_2	MnL_2Cl_2	Assignment
3152	3149	3159	$\nu(\text{NH})$ imidazole ring
3047	3040	3051	$\nu(\text{C}-\text{H})$ Phenyl
2940	2935	2936	$\nu_{\text{as}} \text{CH}_2$
2947	2942	2941	$\nu_{\text{s}} \text{CH}_2$
1592	1595	1590	$\nu(\text{C}=\text{N})$
1580	1581	1580	$\nu(\text{C}=\text{C})$
1520	1522	1525	$\delta(\text{NH})$
1462	1460	1462	$\delta(\text{CH}_2)$
1419	1420	1420	Phenyl ring ($\text{C}=\text{N}$)
1342	1340	1345	$\delta(\text{CH}_2)$
1280	1272	1286	Phenyl and imidazole ring
1215	1210	1212	$\nu(\text{C}-\text{N})$
1151	1150	1145	$\nu(\text{C}-\text{C})$
-	-	-	CH_2 rocking
972	955	965	CH_2 Scissoring
917	920	918	Bands
765	761	761	(C-H) out of plane
710	712	708	$\nu(\text{C}-\text{S})$
690	695	695	Ring deform
641	650	652	Vibration
570	572	567	-
435	430	425	$\nu(\text{M}-\text{N})$

Table 4: IR bands of Ligand and its complexes in cm⁻¹.

Ligand(L)	CuLCl ₂	CoL ₂ Cl ₂	Assignment
3147	3155	3145	v(NH) imidazole
3070	3060	3065	v(C-H) Phenyl out
2927	2930	2925	v _{as} (CH ₂)–
2847	2840	2840	v _s (CH ₂)
1612	1605	1601	v(C=N)
1585	1575	1580	v(C=C)
1525	1521	1508	δ(NH) imidazole
1468	1465	1458	δ(CH ₂)
1419	1420	1425	δC–
1344	1344	1340	δ(CH ₂)
1285	1281	1285	v(C–N)
1217	1201	1207	v(C–C)
1153	1150	1155	phenyl ring
1043	1043	1045	Skeletal
971	970	972	Vibration
918	920	920	-
857	855	850	-
765	765	760	phenyl ring (C–H) out of plane
728	720	715	v(C–S–C)
695	699	-	-
651	651	650	ring deformation
577	570	-	Vibrations
462	450	453	-

Table 5: Antifungal activity of ligand and synthesized complexes, zone of Inhibition (mm) activity index.

S. No.	Complexes	Antifungal Activity			
		CA	AN	AF	RO
1	BahbH=L	13	12	9	13
2	CuL ₂ Cl ₂	16	18	15	19
3	FeL ₂ Cl ₂	14	14	12	16
4	MnL ₂ Cl ₂	14	15	13	15
5	ZnLCl ₂	15	17	14	18
6	CdLCl ₂	14	16	13	13
7	CuLCl ₂	16	17	15	16
8	AgLNO ₃	13	14	11	14
9	Amphotericin	20	22	17	24

Candida albicans (CA), *Aspergillus niger* (AN), *Rizopus oryzae* (RO) and *Aspergillus fumigatus* (AF)

Table 6: Antibacterial activity (zone of inhibition).

S. No.	Antibacterial Compounds	Antibacterial Activity	
		Bacillus Subtilis	Proteus mirabilis
1	BahbH	11	12
2	CuL ₂ Cl ₂	18	18
3	MnL ₂ Cl ₂	14	13
4	ZnLCl ₂	19	20
5	CdLCl ₂	16	13
6	AgLNO ₃	17	16
7	Ciprofloxacin	25	24

CONCLUSION: In Summary we have demonstrated synthesis of some new transition metal complexes having Mn^{II} , Co^{II} , Cu^{II} and Mn^{II} with hydrazinobenzimidazole as ligand. We have also successfully screened their antifungal and antibacterial activity and few of them were found to be potent antibacterial and antifungal agents. Our research can open new doors in antimicrobial drug discovery research in near future.

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