



ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF A SCHIFF BASE AND ITS METAL COMPLEXES DERIVED FROM 3-AMINO-5-BROMOBENZOFURAN-2-CARBOXAMIDE - SYNTHESIS AND CHARACTERIZATION

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Article Received on
11 March 2015,

Revised on 02 April 2015,
Accepted on 23 April 2015

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ABSTRACT

New metal complexes of Co(II), Ni(II), Cu(II) Zn(II) Cd(II) and Hg(II) were synthesized from a Schiff base (L) formed by the condensation of 3-amino-5-bromobenzofuran-2-carboxamide and 2-hydroxy-5-(phenyldiazenyl)benzaldehyde. Newly synthesized metal complexes subjected to various spectral characterization and screened for their antibacterial and antifungal activities. Investigation of their biological activities shows that complexes are more active than its corresponding ligand.

KEYWORDS: Schiff base, Metal Complexes, Spectral studies, Biological activity.

INTRODUCTION

Schiff bases of benzofuran and its derivatives attracted the chemists worldwide due to their easy synthesis, high stability and having excellent chemical, biological and pharmaceutical properties such as antibacterial and antifungal.^[1] DNA cleavage, antioxidant properties^[2] Besides this Schiff base have also fluorescence properties.^[3] The fast development in the field of coordination chemistry has been dominating among the research field in inorganic and bioinorganic chemistry. In recent years, several coordination compounds of transition and non-transition metal ions with a wide variety of ligands having excellent biological and chemical properties have been reported.

In view of the importance of the benzofuran Schiff base and its metal complexes in the animal kingdom and in continuation of our work on the study of Schiff base and their metal

complexes, herein we report new Schiff base formed by the fusion of biologically active heterocyclic aldehyde 2-hydroxy-5-((phenyldiazenyl)benzaldehyde with 3-amino-5-bromobenzofuran-2-carboxamide could result in valuable chemical and biological properties. Furthermore, insertion of metal ions like Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) could result in synthesizing more biologically active compounds and also for the design of new therapeutic agents with a special significance in medicinal chemistry.^[4] All the synthesized compounds have been studied by various spectroscopic techniques such as UV-Vis, IR, NMR, Mass and EPR and evaluated for their antibacterial and antifungal activities.

1. EXPERIMENTAL

All the chemicals used are of AR grade with a highest purity available. 3-amino-5-bromobenzofuran-2-carboxamide synthesized according to the literature procedure.^[5] The metal and the chloride content were determined according to the *Vogel's procedure*.^[6]

1.1. SYNTHESIS OF SCHIFF BASE[L]

5-bromo-3-(((2-hydroxy-5-((phenyldiazenyl)benzylidene)amino)benzofuran-2-carboxamide

A mixture of 3-amino-5-bromobenzofuran-2-carboxamide (0.1 mol) and 2-hydroxy-5-((phenyldiazenyl)benzaldehyde (0.1 mol) in ethanol (30 mL) are refluxed on water bath for about 8h in presence of a few drops of glacial acetic acid with occasional shaking. The product that was separated out as crystalline solids on cooling was collected and recrystallized from ethanol.

$C_{22}H_{15}BrN_4O_3$ [L]: Molecular Weight = 463.45, mp = 240°C, Yield= 69%.

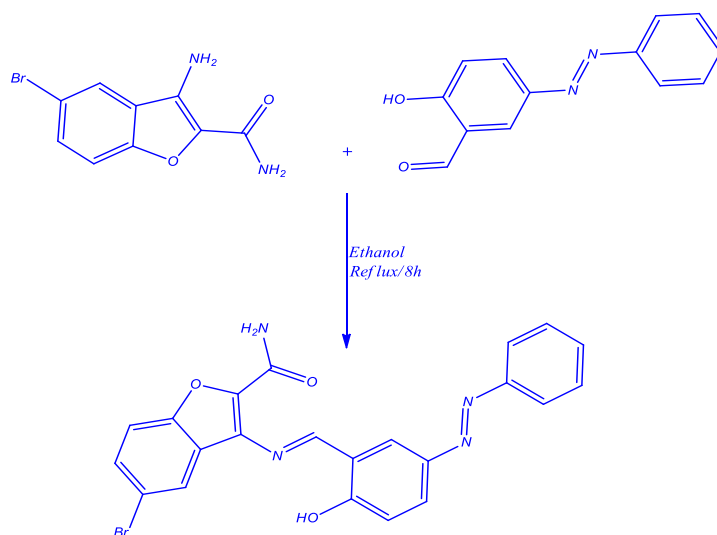


Figure- 1. Synthesis of Schiff base [L].

1.2 Preparation of metal complexes of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) with the Schiff base [L]

The Metal chloride (0.01 mol) was mixed with a Schiff base (0.01 mol) in an ethanolic medium 30 mL and reaction mixture was refluxed for about 3h on water a bath, then an aqueous solution of sodium acetate was added to the mixture to adjust the pH between 5 to 6 and further refluxed for about an hour. The complexes separated were filtered off, washed with distilled water, then with alcohol, and finally dried in vacuum over fused calcium chloride.

2. PHYSICAL MEASUREMENTS

The FTIR spectra of a Schiff base and its *Co(II)*, *Ni(II)*, *Cu(II)*, *Zn(II)*, *Cd(II)* and *Hg(II)* metal complexes were recorded in KBr pellets in the range of 4000 – 400 cm^{-1} . The proton magnetic resonance spectra of Schiff base ligand was recorded on 'AMX-400 NMR Spectrometer at 'SAIF Punjab University, Chandigarh' using TMS as an internal standard and DMSO- d_6 as a solvent. The electronic spectra of the *Co(II)*, *Ni(II)* and *Cu(II)* complexes were recorded on an Elico-SL-164 double beam UV-Visible spectrophotometer in the range 200 – 900 nm in DMF (10^{-3} M) solution. Molar conductivity measurement was recorded on an Elico CM-180 conductivity bridge in DMF (10^{-3} M) solution using dip-type conductivity cell fitted with a platinum electrode and the magnetic susceptibility measurement was made at room temperature on Gouy balance using $\text{Hg}[\text{Co}(\text{NCS})_4]$ as the calibrant. In the light of interesting antimicrobial activities, the synthesized ligands and their metal complexes were screened for their antibacterial activity by agar diffusion method^[7-9] at *Dept. of Microbiology, Gulbarga University, Karnataka*.

3. RESULTS AND DISCUSSION

The analytical results show that the metal complexes are of the type ML_2 for the complexes of *Co/Ni/Cu* and ML for *Zn/Cd/Hg*) (Table-1) and possess 1:2 and 1:1 Metal–Ligand ratio respectively. Low molar conductance values indicate the nearly non-electrolytic or least electrolytic nature of the synthesized complexes. All the complexes are light colored, stable and non-hygroscopic at NTP having high ($>300^\circ\text{C}$) melting points.

3.1 UV-VIS Spectral Studies

On the basis of electronic spectral data of the *Co(II)*, *Ni(II)* and *Cu(II)* complexes the ligand field parameters such as Dq , B' , β , $\beta\%$, L.F.S.E and ν_2/ν_1 ratio^[10] were calculated and recorded in the Table-2. The *Co (II)* ion possesses the electronic structure 3d^7 and occurs in

both octahedral and tetrahedral geometry. The present Co(II) complexes exhibit absorption bands in the region 16012 and 19370 cm^{-1} in DMF (10^{-3} M) solution corresponding to $^4\text{T}_{1\text{g}}$ (F) \rightarrow $^4\text{A}_{2\text{g}}$ (F) (ν_2) and $^4\text{T}_{1\text{g}}$ (F) \rightarrow $^4\text{T}_{2\text{g}}$ (F) (ν_3) transitions respectively, in an octahedral environment.^[11] However, the ν_1 band could not be observed due to the limited spectral range of the instrument used and hence these values were calculated using band fitting procedure^[12] and found to be at 7463 cm^{-1} . The electronic spectra of Ni(II) complexes, under present investigation exhibit bands in at 15801 and 26200 cm^{-1} in DMF (10^{-3} M) solution. These transitions are assigned to $^3\text{A}_{2\text{g}}$ (F) \rightarrow $^3\text{T}_{1\text{g}}$ (F) ν_2 and $^3\text{A}_{2\text{g}}$ (F) \rightarrow $^3\text{T}_{1\text{g}}$ (P) (ν_3) respectively, in an octahedral environment. The Cu(II) complex under present investigation exhibit a single broad asymmetric band in the region 14263-16200 cm^{-1} the asymmetry being on the lower energy side. These observations suggest that all the Cu(II) complexes have a tetragonally distorted octahedral structure and this is in accordance with the experimental findings of Orgal and Dunita.^[13] The broadness of the band may be due to dynamic Jahn–Teller distortion. (Table -2). The octahedral geometry^[14] was further supported by the values of ligand field parameters, such as the Racah interelectronic repulsion parameter (B'), ligand field splitting energy (10 Dq), covalency factor (β), and ligand field stabilization energy (LFSE).^[15] The B' values for the complexes were lower than the free ion values, which is an indication of the orbital overlap and delocalization of d-orbitals.

Table-1. Analytical and Physico-chemical data of the ligand [L] and its metal complexes

Empirical formula	Mol Wt.	M.P (°C)	Yield (%)	Elemental analysis (%) found(calculated)					μ_{eff} B.M	Δ_M^\dagger
				C	H	N	M	Cl		
(L)	463	233	68	56.10 (57.04)	3.09 (3.26)	12.01 (12.09)	----	----	----	----
[Co(L) ₂]	984	>300	65	53.20 (53.73)	2.30 (2.87)	11.10 (11.39)	5.78 (5.99)	----	4.77	13.14
[Ni(L) ₂]	983	>300	68	53.01 (53.75)	2.20 (2.87)	11.00 (11.40)	5.97 (5.97)	----	2.82	15.01
[Cu(L) ₂]	988	>300	73	53.01 (53.48)	2.70 (2.86)	11.30 (11.34)	6.20 (6.43)	----	1.65	11.85
[Zn(L)Cl ₂]	598	>300	76	44.01 (44.15)	2.03 (2.36)	8.99 (9.36)	10.88 (10.92)	11.52 (11.85)	----	16.16
[Cd(L)Cl ₂]	646	>300	69	40.88 (40.93)	1.89 (2.19)	8.56 (8.68)	17.22 (17.41)	10.82 (10.98)	----	14.58
[Hg(L)Cl ₂]	734	>300	85	35.83 (36.01)	1.75 (1.92)	7.22 (7.64)	27.01 (27.34)	09.42 (09.66)	----	11.09
$^\dagger \text{ohm}^{-1} \text{cm}^2 \text{mole}^{-1}$										

Table-2. Electronic spectral bands and ligand field parameters of the Co(II), Ni(II) and Cu(II) complexes in DMF (10^{-3} M) Solution

Complexes	Transitions (cm ⁻¹)			Dq (cm ⁻¹)	B'(cm ⁻¹)	β	β%	ν ₂ / ν ₁	LFSC (K.cal)
	ν ₁ *	ν ₂	ν ₃						
[Co(L) ₂]	7463	16012	19370	855	866	0.89	10.79	2.14	14.66
[Ni(L) ₂]	9758	15801	26200	976	848	0.82	18.43	1.62	33.46
[Cu(L) ₂]	14263-16200			1523	---	---	---	---	26.11
*Calculated values									

3.2. IR Spectral Studies

Infrared spectral analysis of ligands and their complexes has an immense importance in the evaluation of nature, of the metal ligand bond, molecular symmetry, electronic distribution and stability of the complexes.^[16-19] The important IR spectral bands for the synthesized ligand (L) and its metal complexes are depicted in the (Table-3). In the IR spectra of the ligand the most characteristic frequency appeared at 1690 cm^{-1} assigned to the νCO stretch of $-\text{CONH}_2$ group, further this frequency shifted to a lower value in the complexes indicating coordination to the metal ion through the oxygen atom. The strong band at 1619 cm^{-1} assigned to the $-\text{C}=\text{N}$ group this frequency changes to the lower value in complexes. This indicates there is an involvement of the nitrogen atom of the azomethine group in the coordination to a metal ion. The frequency observed at the 3468 cm^{-1} in free ligand, which is the characteristic frequency of the $-\text{OH}$ group gets disappeared in the spectra of the metal complexes supports the deprotonation of the hydroxyl group. The intense bands observed in the region $1170\text{-}1226\text{ cm}^{-1}$ are due to the $n(\text{C-O-C})$ stretch of the benzofuran ring.^[20]

Table-3. The important IR frequencies (cm^{-1}) of ligand (L) and its metal complexes

Compound	$\nu(\text{O-H})$	$\nu(\text{C=O})$	$\nu(\text{C=N})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$	$\nu(\text{M-Cl})$
[C ₂₂ H ₁₅ BrN ₄ O ₃](L)	3468	1690	1619	----	----	----
[Co(C ₂₂ H ₁₄ BrN ₄ O ₃) ₂]	----	1682	1525	513	442	----
[Ni(C ₂₂ H ₁₄ BrN ₄ O ₃) ₂]	----	1662	1611	544	453	----
[Cu(C ₂₂ H ₁₄ BrN ₄ O ₃) ₂] _n	----	1613	1525	528	455	----
[Zn(C ₂₂ H ₁₄ BrN ₄ O ₃)Cl ₂]	----	1652	1606	542	450	395
[Cd(C ₂₂ H ₁₄ BrN ₄ O ₃)Cl ₂]	----	1645	1590	541	468	382
[Hg(C ₂₂ H ₁₄ BrN ₄ O ₃)Cl ₂]	----	1660	1594	539	476	366

3.3. NMR Spectral Studies

¹H NMR spectra of Schiff base L (Figure 2) and its Zn(II) complexes were recorded in DMSO-d₆. The signal of the Ar-OH proton appeared at $\delta(10.27)$ is completely disappeared in the spectrum of the complex showing the deprotonation of the $-\text{OH}$ group and formation

of the M-O bond.^[22] The signal at δ (9.49) (s, 1H) is assigned to azomethine proton (-N=CH-) of Schiff base L^[21] this signal shifts to δ (9.05) indicating that nitrogen is involved in the bonding with Zn(II) ion. The signal at δ (8.45) (s, 2H) is assigned to amide proton (-CONH₂)^[20] this value remains unaltered in the spectrum of the complex indicating there is no involvement of the NH₂ group in the bonding with the metal ion. The eleven aromatic protons resonated at δ (7.80–8.14) (m, 11H) shifted downfield in the complex. Thus ¹H NMR spectral observations supplement the assigned geometry.

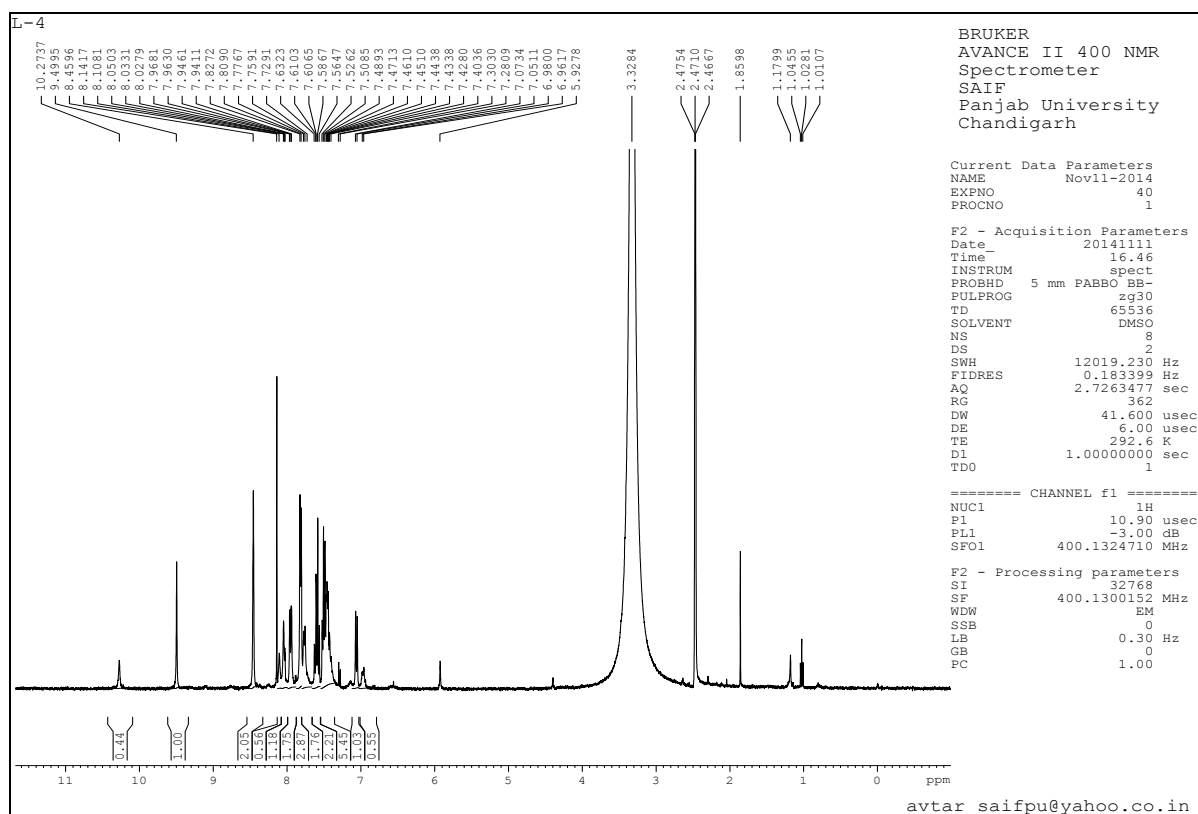


Figure- 2. ¹H-NMR Spectrum of the ligand L

3.4. MASS Spectral Studies

The mass spectrum is a pattern representing the distribution of ions by mass-to-charge ratio and gives valuable information about the molecular mass of the compounds. The LC-MS spectrum of the synthesized ligand (L) (Figure- 2) shows a well-defined peak at m/z = 465 (M+2) which is exactly two mass unit more than that of the molecular mass of the ligand calculated from empirical formula (Table-1), confirming the formation of the ligand (L). The different competitive fragmentation pathways of ligand give the peaks at different mass numbers at 102, 218, 241, 274, 282, 415, 437, 465, 466, 487, 701, 946, 948 and 950. The intensity of these peaks reflects the stability and abundance of the ions.^[23]

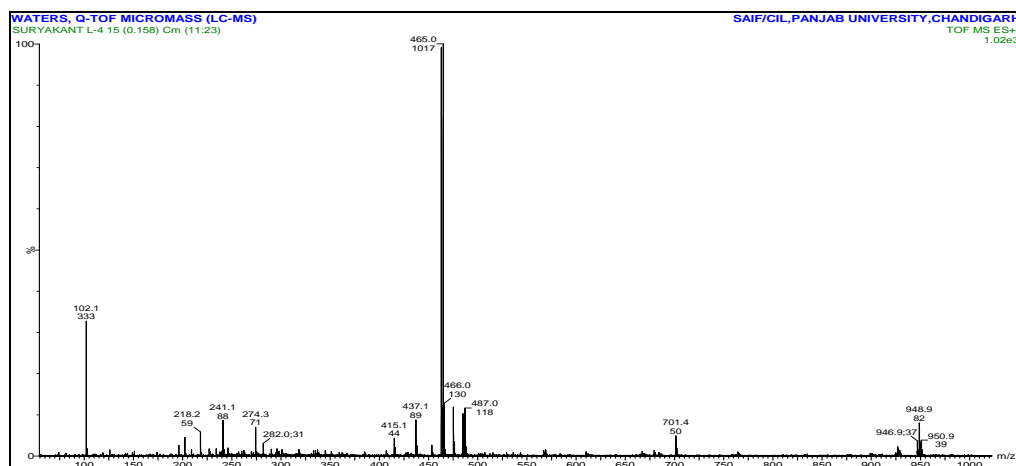


Figure- 3. LCMS Spectrum of the Ligand L

3.5. EPR spectral analysis of Cu(II) complex of ligand[L]

The EPR spectrum of copper complex $[\text{Cu}(\text{C}_{26}\text{H}_{17}\text{N}_4\text{O}_3)_2]$ in a polycrystalline state (Figure.4) was recorded at NTP. The g_{\parallel} and g_{\perp} values were found to be 2.2512 and 2.0630, respectively. The g_{av} was calculated is 2.75. The trend exhibited by the g values ($g_{\parallel} > g_{\perp} > 2.00277$) reveals that the unpaired electrons lie predominantly in the $d_{x^2-y^2}$ orbital with a slight possibility of mixing of d_{z^2} because of low symmetry.^[24] The geometric parameter 'G' is determined as $G = (g_{\parallel} - 2.00277)/(g_{\perp} - 2.00277) = 4.12$ is more than 4 suggesting there is negligible copper-copper exchange interaction in polycrystalline compound.^[25] $g_{iso} = 2.125$, α^2 and β^2 values are 0.63 and 0.53 supports the structure.

3.6. Antibacterial and antifungal activity:

The antibacterial and antifungal activity of Schiff base (L) and its metal(II) complexes have been studied by agar diffusion method in DMF as a solvent against *Escheria coli* and

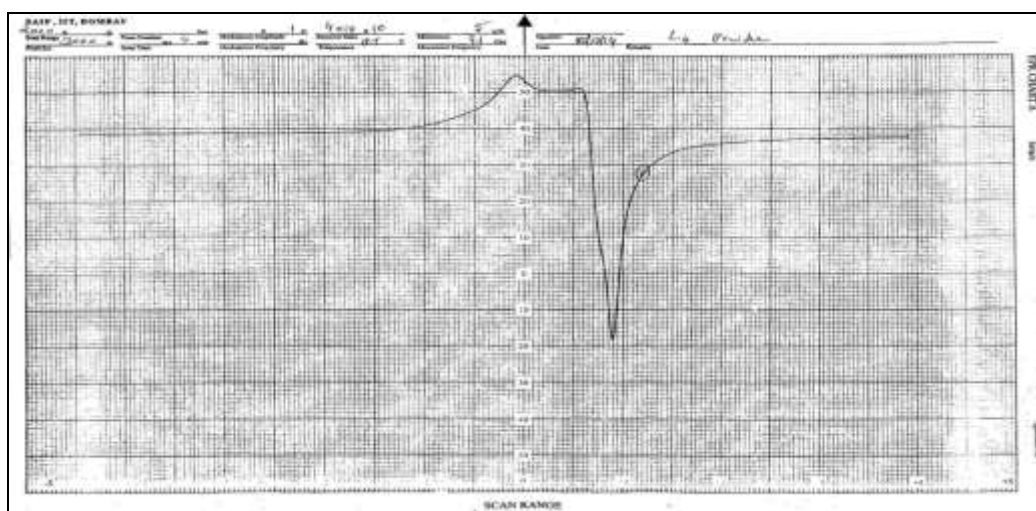


Figure- 4. ESR Spectrum of Copper complex of ligand L

Staphylococcus aureus bacterial species(Figure.5(a)) and *Aspergillus niger* and *Aspergillus flavus* fungal species(Figure.5(b)) at two concentrations concentrations. Gentmycin and Fluconazole are used as a standard antibacterial and antifungal drugs, respectively. The activity of a compound was determined by measuring the diameter of the zone showing complete inhibition of an organism.

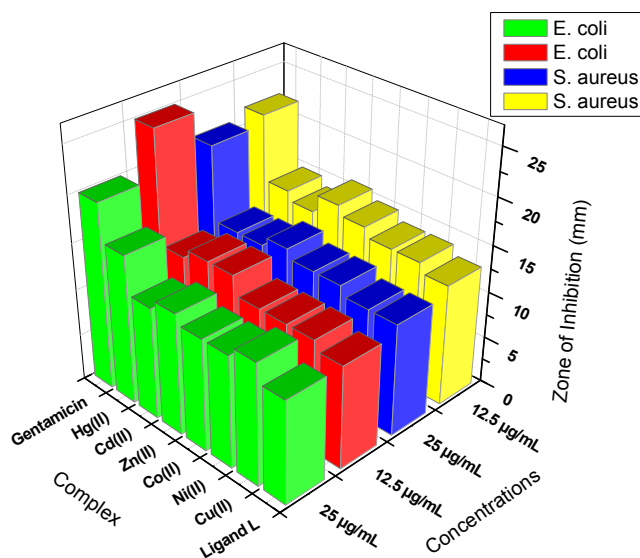


Figure- 5(a). Antibacterial activity study of ligand L and its metal complexes

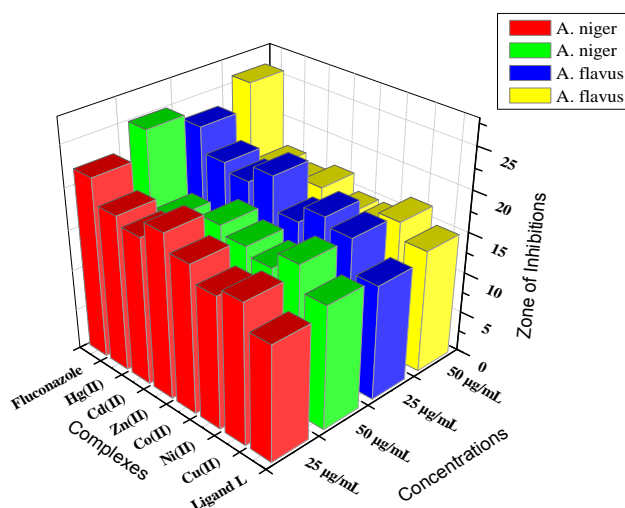
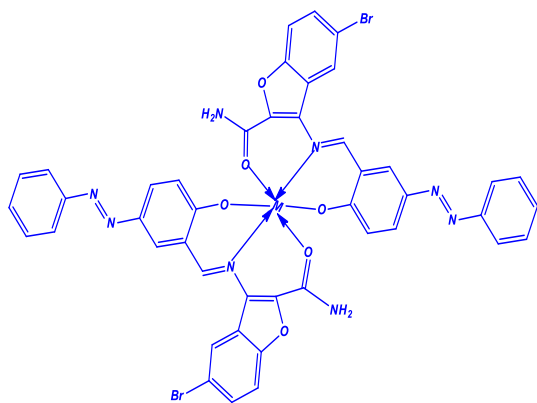
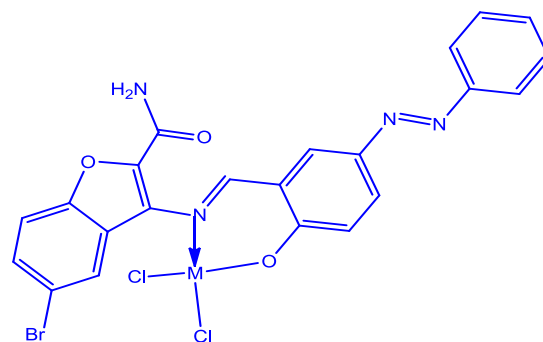


Figure- 5(b). Antifungal activity study of ligand L and its metal complexes

4. CONCLUSION

On the basis of above results we conclude that the newly synthesized Schiff base acts as a neutral tridentate ligand for Co(II), Ni(II) and Cu(II) (Figure-6(a)) and bidentate for Zn(II),

Cd(II) and Hg(II) (Figure-6(b)) coordinating through the oxygen of the amide group, nitrogen of the azomethine group and oxygen of the hydroxyl group. Analytical and spectral investigation reveals probable structures for the complexes as dimeric octahedral for Co(II), Ni(II) and Cu(II) and tetrahedral for Zn(II), Cd(II) and Hg(II). Antibacterial and antifungal activity investigation shows that the metal complexes are more active (Figure- 6,7) than its ligand [L].

**Fig. 6(a)****Fig. 6(b)****Figure-8. Probable structures for complexes**

ACKNOWLEDGEMENT

The authors thank the Head, Department of Chemistry, Gulbarga University for providing laboratory facilities. We also thank SAIF Punjab University (PU), IIT Bombay (MH) and BioGenics (Hubbali) (KA) for providing spectral and biological activity data. One of the author *Sadu Suryakant S.*, also thanks the UGC for providing financial assistance through UGC- (BSR) fellowship.

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