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Biological studies of a novel azo based Heterocyclic Schiff base and its transition metal complexes

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ABSTRACT

A new heterocyclic Schiff base ligand bis(2-(pyridin-2-ylimino)phenyl)-4,4'-(diazene-1,2-diyl)dibenzoate (BPPD, L) and its metal complexes with divalent transition metal ions viz., Co(II), Ni(II), Cu(II) and Zn(II) have been synthesized and characterized through IR, NMR and elemental analysis. The ligand and its complexes have been screened for the antibacterial activities towards bacteria Staphylococcus aureus (gram positive) and Escherichia coli (gram negative), and antifungal activities towards fungi Aspergillus niger and Candida albicans. The results showed that the complexes have higher antimicrobial activities than the ligand. The order of antimicrobial activities was Cu(II)L> Zn(II)L>Ni(II)L>Co(II)L>L.

Key words: Heterocyclic Schiff base ligand, transition metal complexes and antimicrobial activities.

INTRODUCTION

Schiff base ligands are potentially capable of forming stable complexes with different metal ions [1]. Because of the facile synthesis of Schiff bases, many ligands of diverse structure types have been synthesized. Schiff base can accommodate different metal centers involving various coordination modes thereby allowing successful synthesis of homo and hetero metallic complexes with varied stereochemistry [2]. Now a days Schiff bases are attracting biochemist as they are known to be medicinally important and are used to design medicinal compounds [3]. It has been reported that the biological active compounds show greater activity when administered as metal complexes than as free organic compound [4]. The azomethine (C=N) linkage in Schiff bases imports in elucidating the mechanism of transamination and resamination reactions in biological system [5,6]. The biomedicinal properties of free organic molecule upon

chelation with suitable metal ion led to the implementation of metal complexes for several biomedical applications as therapeutically active possessing analgesic [7], antipyretic [8], antiinflammatory [9], cytotoxic [10], antiviral [11], antitumorous [12] and antitubercular activity [13] besides their applications as antimicrobrial [14,15].

Considering the above facts in view, a novel heterocyclic Schiff base ligand (BPPD, L) and its complexes with divalent transition metal ions *viz.*, Co(II), Ni(II), Cu(II) and Zn(II) have been synthesized and characterized. The ligand along with its metal(II) complexes were screened for their *in vitro* antibacterial activities against *Staphylococcus aureus* (gram positive) and *Escherichia coli* (gram negative), and antifungal activities towards fungi *Aspergillus niger* and *Candida albicans*.

MATERIALS AND MEHTODS

2.1. Materials and measurements

All chemicals were obtained from Sigma-Aldrich and were used without further purification. Elemental analyses (C, H, N) were performed by the Carlo Erber Micro Analysis (Model-1106). Infrared spectra of the ligand and its metal complexes were recorded on FTIR Perkin Elmer 1710 spectrophotometer using KBr pellets. The electronic spectra of the metal complexes were recorded at 5 x 10^{-3} M in DMSO on an Agilent-8453 diode array spectrometer. ^{1}H NMR spectrum of the ligand was recorded on a Brucker AMX-300 spectrometer in DMSO-d_6. Molar conductance of the complexes was determined in DMSO (10^{-3} M) at room temperature using a Toshniwal digital conductivity meter. Magnetic susceptibility measurements of the metal complexes in powder form were carried out on a Guoy balance. The metal contents of the complexes were determined by an Anti Unicam 929 Model AA spectrometer in solutions prepared by decomposing the compounds in aqua regia followed by in concentrated HCl.

2.2. Synthesis of ligand BPPD

Synthesis of ligand BPPD was initiated from the starting material *p*-nitrobenzoic acid (**I**) as shown in Scheme 1. The synthesis of 4,4'-bis(chlorocarbonyl)azobenzene (**II**) was carried out as per literature [16] method. Then, the dialdehyde (**III**) (1 mmol) was condensed with 2-amino-pyridine (2 mmol) in methanolic medium (50 ml). The mixture was refluxed for 10 hours. A light orange colour precipitates were obtained, which were filtered and washed with methanol followed by ether and then, dried over anhydrous $CaCl_2$ under reduced pressure. The crude product was recrystallized from hot methanol, which gave pure ligand with a yield of 40 %, calculated from the starting compound *p*-nitrobenzoic acid. m.p.,135 °C; IR (KBr pellet, cm^{-1}): 3040, 2895, 1735, 1640, 1545, 1220, 625, 420; ^{1}H NMR (DMSO-d_6; δ ppm): 7.55 (8H, m, C_6H_4), 8.38 (8H, m, C_6H_4), 8.50 (8H, m, Pyridine ring), 8.75 (2H, s, HC=N); Elemental analysis (%): Anal. Calc. for $C_{38}H_{26}N_6O_4$: C, 72.38; H, 4.12; N, 13.33 and found: C, 72.32; H, 4.10; N, 13.30.

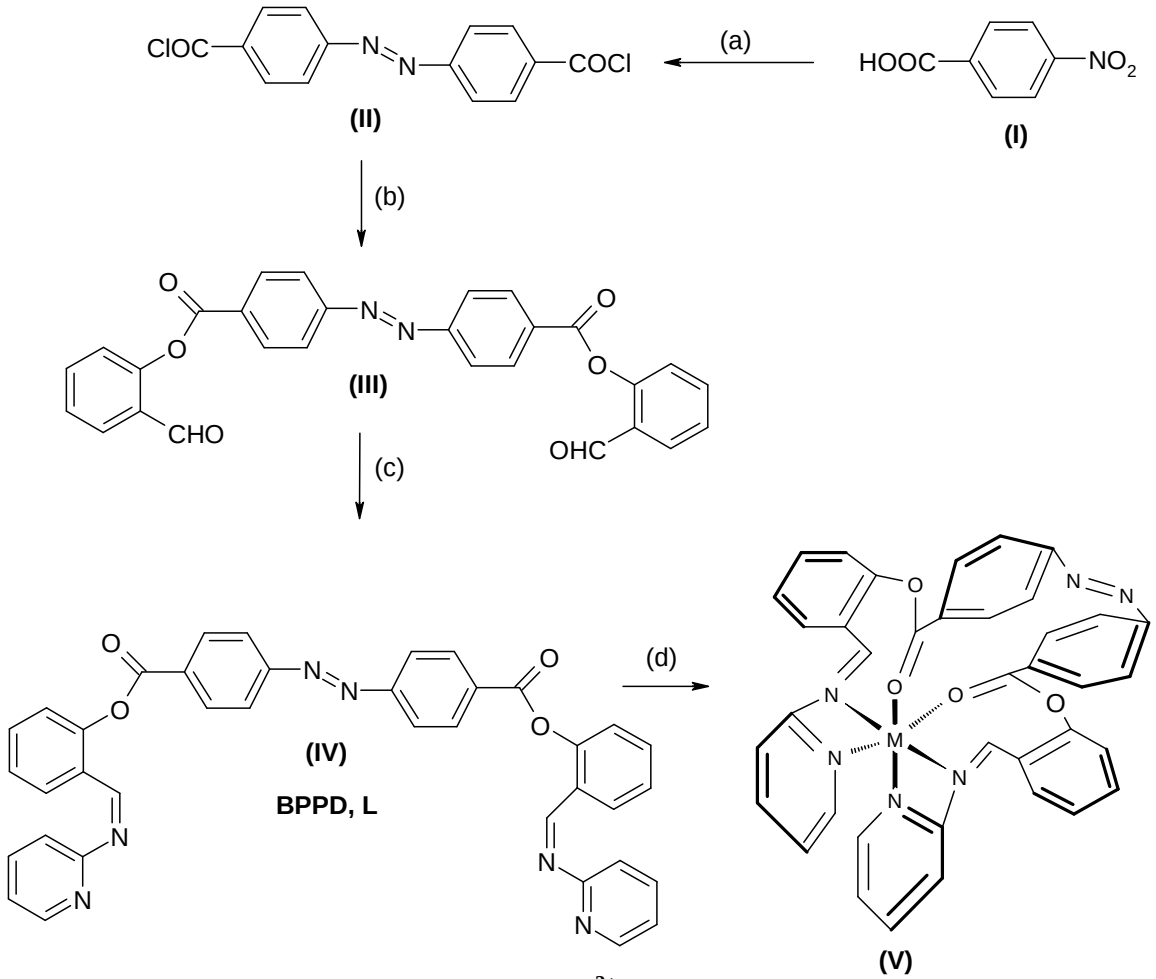
2.3. Synthesis of metal complexes

The metal(II) complexes of the ligand BPPD were prepared by similar procedure. A solution of BPPD (1 mmol) in methanol (20 ml) was added drop wise to a stirred solution of metal ion (1 mmol) in 5 ml of methanol at room temperature and then, the mixture was refluxed for four

hours. The precipitates were filtered and washed with water followed by methanol, ether and then dried in vacuum (yield in %, CoL = 31, NiL = 35, CuL = 37 and ZnL = 34).

RESULTS AND DISCUSSION

The synthetic procedure of ligand BPPD and its metal complexes are presented in Scheme 1. The reactions of divalent transition metal ions *viz.*, Co(II), Ni(II), Cu(II) and Zn(II) with the ligand BPPD in 1:1 molar ratio in methanol, yielded the corresponding metal chelates. The physical and analytical data of ligand BPPD and its metal complexes are given in Table 1 and Table 2. All the synthesized compounds are colored and stable to air and moisture. The yields of the complexes (31-37%) are lower than the yield of ligand (40%). The major reason may be due to the steric hindrance. The ligand and its metal complexes are insoluble in common organic solvents but are soluble in DMF and DMSO. All the compounds have elemental analysis consistent with their formulations. The molar conductance values (Table 1) of 283.37-295.22 $ohm^{-1}cm^2mol^{-1}$ in DMSO medium indicate that the metal complexes are 1:2 electrolytes [17].



Scheme 1. Synthesis of BPPD and $[M(BPPD)]^{2+}$, M = Co(II), Ni(II), Cu(II) and Zn(II) (a) HCO_2HNEt_3/Pb, MeOH, r.t, PCl_5/CH_2ClCH_2Cl; (b) Salicylaldehyde, triethylamine, toluene, N_2 atm.; (c) 2-amino-pyridine, MeOH; (d) Acetate salts, MeOH

Table 1. Physical and analytical data of the ligand BPPD (L) and its metal(II) complexes

Compounds	Color	Elemental analyses Expt. (Calc.)				M.P. (°C)	Molar conductance (ohm^{-1} cm^2 mol^{-1})
		C	H	N	M		
BPPD (L)	Light orange	72.32 (72.38)	4.10 (4.12)	13.30 (13.33)	-	135	-
$[Cu(L)](AcO)_2$	Reddish green	65.70 (65.74)	3.71 (3.74)	12.08 (12.11)	9.10 (9.16)	232 (decomp.)	283.37
$[Ni(L)](AcO)_2$	Yellowish green	66.17 (66.21)	3.74 (3.77)	12.14 (12.19)	8.49 (8.52)	310 (decomp.)	294.25
$[Co(L)](AcO)_2$	Reddish brown	66.12 (66.18)	3.75 (3.77)	12.15 (12.19)	8.50 (8.55)	285 (decomp.)	291.63
$[Zn(L)](AcO)_2$	Canary yellow	65.51 (65.57)	3.69 (3.73)	12.02 (12.07)	9.36 (9.40)	233 (decomp.)	295.22

The condensation of 2-amino-pyridine with dialdehyde (**III**) to get BPPD was characterized through the ^1H NMR and IR spectra of the compound. In the infrared spectrum of BPPD (Table 2), the stretching vibrational band due to $\nu_{C=O}$ at 1690 cm^{-1} of dialdehyde was disappeared and appearance of characteristics imine $\nu_{C=N}$ band at 1640 cm^{-1} was observed. Another new band obtained at 2895 cm^{-1} was attributed to ν_{C-H} of the azomethine groups. These observations confirm the condensation of dialdehyde with the primary amine, 2-amino-pyridine. A sharp band due to $\nu_{C=O}$ of the ester groups was observed at 1735 cm^{-1}. Two bands for in-plane and out of plane pyridine ring deformation were observed at 625 and 420 cm^{-1}, respectively. In ^1H NMR spectrum of BPPD, the presence of the azomethine group is also characterized as a singlet at δ = 8.75 ppm. The peak due to pyridyl ring protons was obtained in the form of multiplet at δ = 8.50 ppm. Multiplet due to the aromatic protons linked to the azomethine group was observed at δ = 7.55 ppm, whereas at δ = 8.38 ppm was attributed for the azobenzene protons. The relevant infrared absorption bands due to the coordinated chelates of the complexes with their possible assignment are given in Table 2.

Table 2. Infrared spectra of the ligand BPPD (L) and its metal(II) complexes.

L	$[Cu(L)]^{+2}$	$[Ni(L)]^{+2}$	$[Co(L)]^{+2}$	$[Zn(L)]^{+2}$	Assignments
3040	3035	3030	3030	3035	ν_{C-H} of aromatic ring
2895	2890	2885	2885	2890	ν_{C-H} of azomethine
1735	1615	1620	1620	1615	$\nu_{C=O}$ of ester
1640	1535	1530	1535	1530	$\nu_{C=N}$ of azomethine
1545	1535	1540	1540	1535	$\nu_{C=C}$ of aromatic ring
1220	1215	1210	1210	1215	ν_{C-O} of ester
625	650	660	655	655	In-plane deformation of pyridine ring
420	440	445	450	455	Out of plane deformation of pyridine ring
-	560	565	560	565	ν_{M-O}
-	445	450	450	445	ν_{M-N}
-	330	325	330	325	ν_{M-N}

All the metal chelates showed a sharp band in the region of 1535-1530 cm^{-1} which is attributed to the $\nu_{C=N}$ of azomethine groups, which was shifted towards lower frequency compared to the free ligand band indicating the coordination of azomethine nitrogens in the complexes. A negative shift in the frequency of $\nu_{C=O}$ of the ester groups (1620-1615 cm^{-1}) in the spectra of corresponding metal complexes indicate the coordination of carbonyl oxygens of the ligand to the central metal ion. The shift in the bands due to in plane and out of plane deformation of pyridine of the ligand from 625 and 420 cm^{-1} to 660-650 and 455-440 cm^{-1} (Table 2) respectively in case of metal complexes indicate the coordination of pyridine nitrogens. Also, in the low frequency region, the appearance of new bands in metal chelates at ~560, ~445 and ~330 cm^{-1} may be attributed to the ν_{M-O}, ν_{M-N} and $\nu_{M-N(pyridine)}$, respectively. The ring skeletal vibrational bands of ligand were not affected noticeable upon metal chelation.

The electronic spectra of the metal complexes gave characteristics *d-d* transitions to ascertain their structure. The Co(II)-L complex gave three bands at 8400, 17200 and 20500 cm^{-1}, which may be assigned to $^4T_{1g} \rightarrow {}^4T_{2g}$, $^4T_{1g} \rightarrow {}^4A_{2g}$ and $^4T_{1g} \rightarrow {}^4T_{1g}$ transitions, respectively typical of an distorted octahedral geometry [18]. This has been further corroborated by the observed magnetic moment 4.90 BM [19]. The observed magnetic moment corresponds to a high spin octahedral Co(II) complex. The Ni(II)L complex also gave three bands at 8200, 14100 and 25100 cm^{-1} due to $^3A_{2g} \rightarrow {}^3T_{2g}$, $^3A_{2g} \rightarrow {}^3T_{1g}$ and $^3A_{2g} \rightarrow {}^3T_{1g}$ transitions, respectively. The Cu(II)L complex gave only one band due to $^2E_g \rightarrow {}^2T_{2g}$ transition at 17200 cm^{-1}. The electronic spectral data alongwith the observed magnetic moment of Ni(II)L (3.11 BM) and Cu(II)L (1.87 BM) complexes suggested for a distorted octahedral geometry.

4. Antimicrobial activity

The antimicrobial activities of the ligand BPPD and its transition metal complexes were investigated by adopting the serial dilution method [20,21]. Five compounds were evaluated in total for their *in vitro* antibacterial activities against *Staphylococcus aureus* (gram positive), *Escherichia coli* (gram negative) and antifungal activities against *Aspergillus niger* and *Candida albicans*. To determine minimum inhibitory concentration (MIC) values, the sets of two fold serial dilution of the test compounds were prepared in serial dilution method.

The results in Fig.1. reveal that all the compounds showed antifungal and antibacterial activities. It was observed that there was an appreciable increase in the antimicrobial activities in case of metal complexes compared to the uncomplexed ligand, BPPD. Cu(II) chelate was found to be the most effective as evidenced from the comparative study of their MIC values of corresponding chelates. The order of antimicrobial activities was Cu(II)L> Zn(II)L>Ni(II)L>Co(II)L>L.

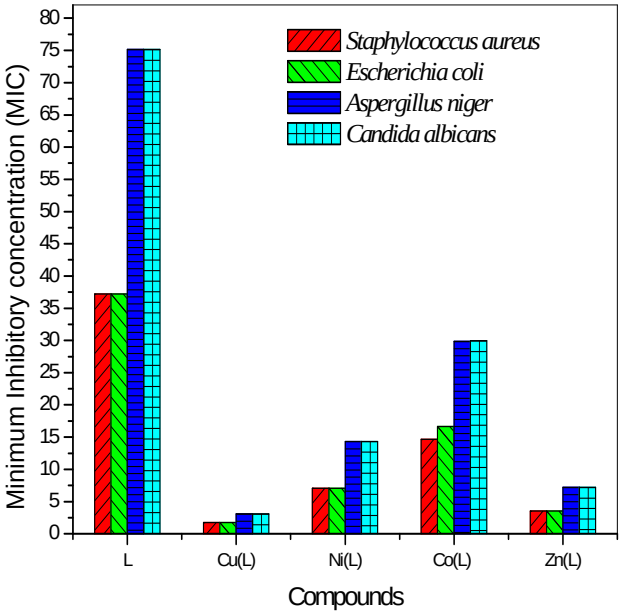


Fig. 1. Minimum Inhibitory concentration (MIC) in molar concentration (1x 10^{-5} M) of the ligand BPPD (L) and its metal complexes (Standard used for the antibacterial and antifungal activity is oxytetracycline and blitox-50 WP, respectively).

CONCLUSION

The ligand BPPD acts as a hexadentate ligand and formed stable complex with Co(II), Ni(II), Cu(II) and Zn(II). The ligand showed antimicrobrial activity but in comparison, the metal complexes of this compound showed a higher efficiency. The Cu(II) chelate showed higher activity in compared to other chelates and the uncomplexed ligand.

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