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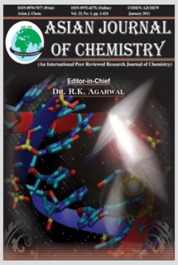

Synthesis, Characterization and Antimicrobial Studies of Novel Derivatives of Phenol and Their Co(II), Ni(II), Cu(II) and Zn(II) Chloro Complexes

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The synthesis, characterization and antimicrobial studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes of N-[(5-amino-2-hydroxyphenyl)(phenyl)methyl]-N-phenylacetamide (PBA) and N-[(5-amino-2-hydroxyphenyl)(phenyl)methyl]nicotinamide (PBN) are reported here. Analytical methods such as TLC, melting point, magnetic and molar conductance and spectral studies such as IR, ^{1}H NMR, ^{13}C NMR, mass, electronic and EPR spectral studies were employed for the characterization. Analytical data show the composition of the metal complexes as $[M(PBA)_2(H_2O)_2]$ and $[M(PBN)_2(H_2O)_2]$ [M = Co(II), Ni(II), Cu(II) and Zn(II)]. Both the ligands and their metal complexes have been tested for *in vitro* to evaluate their activity against certain micro organisms.

Key Words: Phenolic derivatives, Multi-component product, 4-Aminophenol, Metal complexes, Microbial studies.

INTRODUCTION

Extensive studies have been made on the synthesis and characterization of metal complexes of ligands containing N and O donor atoms that are known to possess antimicrobial, antiviral, antifungal and anticonvulsant activities. They are also used as powerful pesticides and insecticides apart from other biological applications. Metal chelates of certain multidentate compounds have been prepared through multi-component reaction.

Multi-component reaction is a chemical reaction in which three or more compounds react to form a single product[1]. The importance of multi-component reactions for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused.

The present paper describes the synthesis and characterization of Co(II), Ni(II), Cu(II) and Zn(II) complexes of ligands N-[(5-amino-2-hydroxyphenyl)(phenyl)methyl]-N-phenylacetamide (PBA) and N-[(5-amino-2-hydroxyphenyl)-(phenyl)-methyl]nicotinamide (PBN).

EXPERIMENTAL

The melting points of the compounds were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC using silica gel G coated glass plates with chloroform and ethyl acetate (1:1) as irrigant and iodine vapour as visualizing agent. Elemental analysis was worked out using Varion EL III C, H, N available at Sophisticated test and instrumentation centre (STIC), Cochin. ^{1}H NMR and ^{13}C NMR spectra of compounds were recorded on a Brucker 300 MHz model in DMSO using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL-8X 102. Molar conductivity in DMF at room temperature was measured by Elico Conductivity Bridge with a tip type cell having a cell constant of 1.03. Magnetic measurements at room temperature were carried out by Gauoy method. Thermogravimetric analyses of complexes were carried out in nitrogen atmosphere on Perkin-Elmer thermal analyzer instrument at the STIC, Cochin, in the temperature range of 0-800 °C at heating range of 10 °C/min. The EPR spectral studies were made in JEOL-DPS-2000 at Central University, Pondicherry.

General preparation of N-[(5-amino-2-hydroxyphenyl)(phenyl)methyl]-N-phenylacetamide (PBA) and N-[(5-amino-2-hydroxyphenyl)(phenyl)methyl]nicotinamide (PBN): To a mixture 4-aminophenol (0.015 mol) and benzaldehyde (0.015 mol), the compounds like acetanilide and nicotinamide in methanol (0.015 mol) were added drop wise and the reaction mixture was stirred in an ice-bath constantly for *ca.* 2 h. The solid separated on cooling was recrystallized from methanol and chloroform[2]. The analytical data are given in Table-1.

Spectral data

N-[(5-Amino-2-hydroxyphenyl)(phenyl)methyl]-N-phenylacetamide (PBA): IR (KBr, ν_{max}, cm^{-1}): 3460 (phenolic-

OH str.), 3245 (NH_2, str.), 1678 (C=O), 1118 (C-N-C). ^1H NMR (DMSO) δ: 9.5 (s, H, OH), 8.6 (s, 2H, NH_2), 6.7-7.5 (m, aromatic), 5.2 (s, H, CH). ^{13}C NMR (DMSO) δ: 177 (C=O), 128 (Ar), 31 (CH). MS: m/z: 329.

N-[(5-Amino-2-hydroxyphenyl)(phenyl)methyl]-nicotinamide (PBN): IR (KBr, ν_{max}, cm^{-1}): 3457 (phenolic-OH str.), 3236 (NH_2, str.), 1659 (C=O), 1527 (amide-II). ^1H NMR (DMSO) δ: 9.6 (s, H, OH), 8.8 (s, 2H, NH_2), 6.7-7.5 (m, Ar), 6.5 (s, NH-CO) 5.3 (s, H, CH). ^{13}C NMR (DMSO) δ: 176 (C=O), 128 (Ar CH), 32 (CH) MS: m/z: 322.

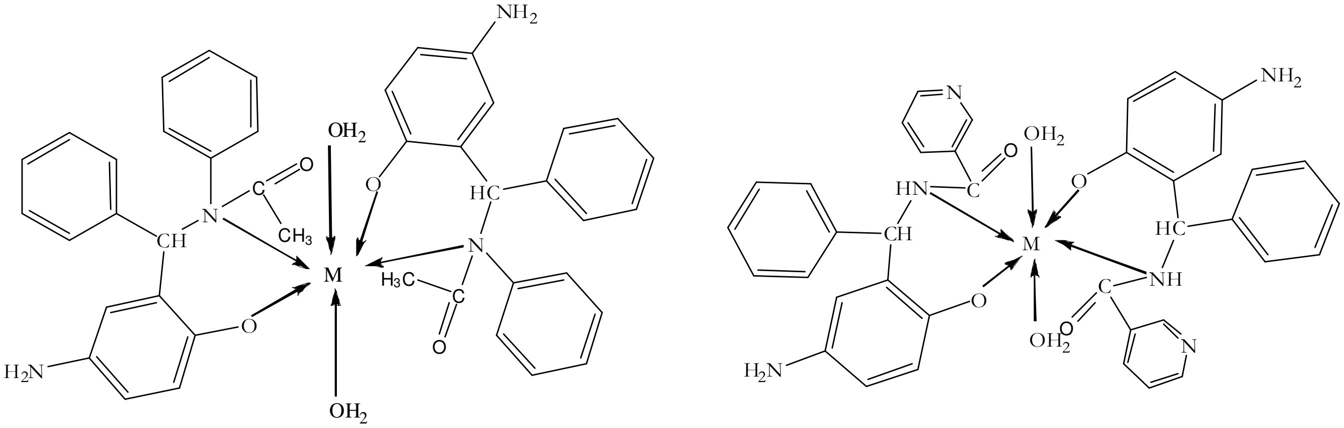
Metal complexes of PBA and PBN: The complexes have been prepared by mixing the methanolic solutions of the corresponding metal salt $MCl_2{\cdot}nH_2O$ [M = Co(II), Ni(II), Cu(II) and Zn(II)] (0.01 mol) to the methanolic solution of ligands PBA/PBN (0.02 mol) in 1:2 mole ratio, respectively. The resulting mixture was refluxed on a water bath for *ca.* 2-3 h. On cooling the refluxate, the coloured solid formed was filtered, washed repeatedly with ether and dried under reduced pressure over anhydrous $CaCl_2$ in desiccator.

Antimicrobial activities: Antimicrobial activities of the ligands and their metal complexes have been studied against bacteria gram positive *S. aureus*, *B. substilis*, gram negative *E. coli*, *P. aeruginosa* and fungi against *C. albicans* by disc diffusion method using nutrient agar as medium for bacteria and Potato Dextrose Agar (PDA) for fungi. 20 mL of media is poured into the sterilized petridishes and kept at room temperature for some time. After after a few minutes, the medium gets solidified in plates. Then this is incubation for 12 h followed by inoculated with microorganisms using sterile swabs. The test solutions are prepared by dissolving the compounds in DMSO. In typical procedure, a well made on the agar medium is inoculated with microorganisms and it is filled with the test solution using micropipette and the plate is incubated at 35 °C for 24-48 h. The zone of inhibition was measured in mm and the activities are compared with ciprofloxacin 1 μg/disc for bacteria and clotrimazole 10 μg/disc for fungi as standard drugs[3].

RESULTS AND DISCUSSION

4-Aminophenol and benzaldehyde react with compounds such as acetanilide and nicotinamide to form PBA and PBN. The structures of the compounds PBA and PBN were established by analytical and spectral methods.

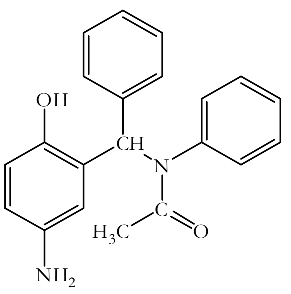
By using the compounds PBA and PBN as ligands the metal complexes have been prepared. The elemental analyses show 1:2 (metal:ligand) stoichiometry for all the complexes and the values are given in Table-1. They correspond well with the general formula ML_2, where M = Co(II), Ni(II), Cu(II) and Zn(II); L = $(PBA)_2$ and $(PBN)_2$. The absence of chloride is evident from Volhard's test. All the complexes are insoluble in water, benzene and carbon tetrachloride, but soluble in DMF. Molar conductance values of metal complexes in DMF at a concentration of 10^{-3} M at room temperature are in the range 10-35 Ω^{-1} cm^2 mol^{-1} suggesting them to be non-electrolyte[4,5]. The low conduc-tance of the chelates supports the non-electrolytic nature of the metal complexes.



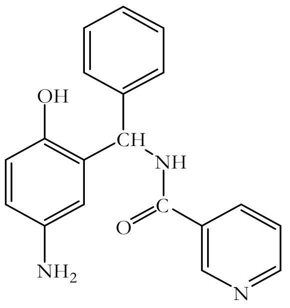
M = Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}

TABLE-1
ANALYTICAL DATA

Compound	Colour	μ_{eff} (BM)	Molar conductance (10^{-3} M) Ω^{-1} cm^2 mol^{-1}	Elemental analysis (%): Found (calcd.)			
				C	H	N	M
PBA	Colourless	–	–	74.85 (75.88)	6.00 (6.06)	8.39 (8.43)	–
$[Co(PBA)_2(H_2O)_2]$	Light brown	4.03	4.2	65.87 (66.57)	5.49 (5.59)	7.39 (7.35)	7.74 (7.78)
$[Ni(PBA)_2(H_2O)_2]$	Dark grey	3.07	2.9	66.56 (66.59)	5.62 (5.59)	7.39 (7.40)	7.65 (7.75)
$[Cu(PBA)_2(H_2O)_2]$	Dark green	2.04	6.4	66.19 (66.17)	5.23 (5.55)	7.22 (7.35)	8.44 (8.34)
$[Zn(PBA)_2(H_2O)_2]$	Colourless	Diamag.	5.3	65.97 (66.01)	5.62 (5.54)	7.30 (7.33)	8.43 (8.56)
PBN	Colourless	–	–	71.43 (71.46)	5.34 (5.37)	13.14 (13.16)	–
$[Co(PBN)_2(H_2O)_2]$	Light brown	4.10	4.7	62.29 (62.38)	4.88 (4.96)	11.35 (11.49)	8.00 (8.05)
$[Ni(PBN)_2(H_2O)_2]$	Dark grey	3.11	3.0	62.38 (62.40)	4.92 (4.96)	11.38 (11.49)	7.96 (8.02)
$[Cu(PBN)_2(H_2O)_2]$	Dark green	1.98	8.0	61.89 (61.99)	4.98 (4.93)	11.38 (11.41)	8.59 (8.63)
$[Zn(PBN)_2(H_2O)_2]$	Colourless	Diamag.	5.1	61.80 (61.83)	4.90 (4.92)	11.42 (11.39)	8.83 (8.86)



PBA



PBN

It is observed that the bands appearing at 1118 cm^{-1} due to ν(C-N-C) in the PBA spectrum is shifted to lower side by 30-40 cm^{-1} in the spectra of the complexes indicating the coordination of tertiary N-atom to the central metal ion. A band around 3460 cm^{-1} and a band at 1375 cm^{-1} in the ligand spectrum are assignable to phenolic ν(OH) stretching and phenolic -OH deformation[6]. These bands are absent in the spectra of complexes indicating deprotonation and coordination to the metal. This is further supported by shift of phenolic ν(C-O) at 1280 cm^{-1} in the ligand to the higher frequency by *ca.* 30-40 cm^{-1} in complex. A medium intensity band at 738 ± 05 cm^{-1} [ν(OH) rocking] in the spectra of Co(II) and Cu(II) complexes, are assignable to coordinated anion. The new bands of weak intensity at 500 ± 15 and 455 ± 20 cm^{-1} in complexes have been assigned to ν(M-O) and ν(M-N), respectively[7].

A band at 3332 cm^{-1} assigned to ν(N-H) in the spectra of ligand (PBN) has been shifted to lower frequency around 10-20 cm^{-1} in the spectra of the complexes indicating the coordination of N-atom of NH to the central metal ion. A broad band at 3380 cm^{-1} corresponds to stretching modes of ν(OH) of phenolic group. A sharp band at 1352 cm^{-1} corres-ponds to -OH deformation. The broad and sharp bands of OH have been found absent in the spectra of complexes. An intense band at 1242 cm^{-1} in the ligand due to the phenolic C-O, shifts to higher value of 1264 ± 05 cm^{-1} in the complexes. This finding suggests the deprotonation of the phenolic-OH after its chelation with metal. A weak band in the range 750-743 cm^{-1} [ν(OH), rocking] in the spectra of complexes, are assignable to coordinated anion. The new bands of weak intensity at 500 ± 15 and 455 ± 20 cm^{-1} in the complexes have been assigned to ν(M-O) and ν(M-N), respectively. A broad band around 3450 cm^{-1} is observed in all the complexes indicating the presence of lattice/coordinated water molecules as confirmed by thermal analysis.

Electronic spectra: Electronic spectra of Co(II) complexes showed two bands in the 14200-14650 and 21350-21700 cm^{-1} regions, which may reasonably be assigned to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4A_{1g}(F) \rightarrow {}^4T_{2g}(P)$ transitions, respectively, suggesting an octahedral geometry around the cobalt(II) ion[8]. The Ni(II) complexes exhibit two bands in their electronic spectra in the regions 14850-15900 and 23745-24000 cm^{-1} and they may be assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transitions, respectively, suggesting octahedral geometry around the nickel(II) ions. The Cu(II) complexes showed bands in the regions 12600-16310 and 15850 cm^{-1} and they may be assigned to $^2E_g \rightarrow {}^2T_{2g}$ and $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ transitions, suggesting a octahedral geometry around the copper(II) ion. The magnetic moment values further confirm the proposed geometry.

^{1}H NMR spectra: ^{1}H NMR spectra of Zn(II) chloro complexes of PBA and PBN have been recorded in DMSO-d_6. The disappearance of peak at δ 9.5 due to OH proton in the spectra of both PBA and PBN complexes indicates the deprotonation of phenolic OH after its chelation with metal. This confirms the coordination of O-atom of phenol. In the spectrum of Zn(II) complex of PBN, a broad signal was observed at δ 7.2 due to NH proton and it is shifted from δ 6.5 of ligand indicating the coordination of NH group.

EPR spectra: EPR spectral studies of $[Cu(PBA)_2Cl_2]$ and $[Cu(PBN)_2Cl_2]$ were recorded at room temperature. The $g_{\parallel}$ values of $[Cu(PBA)_2Cl_2]$ and $[Cu(PBN)_2Cl_2]$ are found to be at 2.09 and 2.10, respectively. Kivelson and Neiman[9] have reported that the $g_{\parallel}$ value is < 2.3 for covalent character of the metal-ligand bond and > 2.3 for ionic character. Applying this criterion, the covalent character of the metal-ligand bond in the complexes is confirmed.

Thermal studies: The thermograms of Co(II) complexes with PBA and PBN exhibit decomposition in two stages, one corresponding to dehydration and other to the decomposition with the loss of organic moiety. In TGA dehydration curve a peak corresponding to the loss of water molecule in the temperature range of 110-130 °C was observed. A sharp endothermic peak in DTA curve is obtained in the range 120-140 °C. It may be due to loss of coordinated molecules. In the TGA decomposition curve, a peak corresponding to a loss of organic moiety in the temperature around 250 °C was observed. Broad exothermic peak observed above 350 °C may be due to oxidation. In Ni(II) chloro complex of PBA, a peak observed at 120-140 °C corresponds to the elimination of two coordinated water molecules. Both TGA and DTA curves reveal that decomposition of the anhydrous intermediate occurs at 200-340 °C. The TG curve of Cu(II) chloro complex of PBA is found to be stable upto 120 °C, after this temperature a weight loss starts and it ends upto 150 °C which corresponds to the loss of water molecules. The endothermic peak at the same temperature is corroborating the elimination of water molecule. A broad endothermic peak at the temperature range 230-340 °C indicates decomposition of organic moiety of the intermediate. The Zn(II) chloro complex of PBA shows a sharp fall in temperature in the range of 120-160 °C indicating the presence of coordinated water molecules. The downward peak from 240-260 °C in the DTA pattern may be due to the decomposition of anhydrous complex. The final mass loss observed has been found to agree with the values calculated for the conversion of the complex to its oxide.

Antimicrobial activities: Antimicrobial activities of PBA, PBN and their metal complexes are given in Table-2. It is o bserved that the metal chelates have higher activity than the free ligand, which can be explained on the basis of overtone's concept and chelation theory. According to overtone's[10] concept of cell permeability the lipid membrane that surrounds the cell favours the passage of only lipid soluble material. Thus the liposolubility is an important factor that controls the antimicrobial activity. On chelation the polarity of the metal ion is reduced to a greater extent due to overlap of the ligand ion with donor groups. Further it increases the delocalization of

TABLE-2
ANTIMICROBIAL DATA

Compound	Diameter zone of inhibition (mm)				
	Gram positive		Gram negative		Fungi
	SA	BS	EC	PA	CA
PBA	15	12	12	10	12
$[Co(PBA)_2(H_2O)_2]$	18	13	14	15	11
$[Ni(PBA)_2(H_2O)_2]$	19	18	13	13	04
$[Cu(PBA)_2(H_2O)_2]$	16	15	17	12	14
$[Zn(PBA)_2(H_2O)_2]$	13	NI	07	17	NI
PBN	15	12	13	10	17
$[Co(PBN)_2(H_2O)_2]$	14	09	10	19	05
$[Ni(PBN)_2(H_2O)_2]$	15	17	11	14	13
$[Cu(PBN)_2(H_2O)_2]$	17	18	13	19	19
$[Zn(PBN)_2(H_2O)_2]$	NI	11	NI	12	NI
$CoCl_2$	13	10	09	07	08
$NiCl_2$	11	09	06	09	10
$CuCl_2$	18	07	09	08	11
$ZnCl_2$	12	07	06	12	10
Standard	20	19	16	19	12
Solvent	NI	NI	NI	NI	NI

SA = *S. aureus*; BS = *B. subtilis*; EC = *E. coli*; PA = *P. aeruginosa*; CA = *C. albicans*; Standard = Ciprofloxacin 1 µg/disc for bacteria, Clotrimazole 10 µg/disc for fungi; Solvent = Dimethyl sulfoxime; NI = No inhibition.

electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complexes into the lipid membrane and blocking of metal binding sites on the enzymes of the microorganism.

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