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# A NEW MANNICH BASE *N*-[PHENYL(PYRROLIDIN-1-YL)METHYL]ACETAMIDE - SYNTHESIS, SPECTRAL PROPERTIES, ANTIBACTERIAL AND ANTIFUNGAL STUDIES OF SOME OF ITS METAL COMPLEXES

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## ABSTRACT

A new Mannich base ligand: *N*-[Phenyl(pyrrolidin-1-yl)methyl]acetamide(PBA) was prepared and characterized by elemental analysis and various spectral studies. Some metal complexes of a ligand with $Co^{II}$, $Ni^{II}$ and $Cu^{II}$ have been synthesized and characterized by elemental analysis, molar conductance values, magnetic susceptibility measurements and various spectral studies. The spectral data reveals that the ligand acts as bidentate and tridentate coordination to the metal ion through the CNC nitrogen, carbonyl oxygen and amido nitrogen atoms. Based on the magnetic and electronic studies, all the complexes are high spin octahedral geometry. The conductance measurements indicate that the non-electrolytic nature of the complexes. The biological activities of the ligand and complexes have been screened *in vitro* against some bacteria and pathogenic fungi to study their capacity to inhibit their growth.

**KEYWORDS:** aminomethyl, pharmacological, polycrystalline, tetragonal, distorted, liphophilic.

## INTRODUCTION

Nitrogen containing biologically active compounds are of high interests as pharmaceutical products.[1,2] The Mannich reaction is one of the most basic and useful methods for the synthesis of such compounds and has been widely used to introduce aminomethyl group into a variety of organic compounds. Mannich base derivatives with bridge *N*-atom have been found to possess a broad range of biological activities including antimicrobial[3], antitumor[4], anti-inflammatory[5], antipyretic and antimalarial[6,7] and some of them were used as complexing agents.[8-10] At the present time, metal based drugs are an important source of novel molecules with therapeutic activity.[11-14] Furthermore, coordination compounds with transition metals have been investigated in the last few decades after the discovery of cisplatin because they have shown good antineoplastic activity and less toxicity.[15,16] Literature survey shows that a large number of transition metal complexes of amides have been found to be associated with diverse pharmacological activities.[17] Complexes of transition metals with amides in proteins and peptides are utilized in numerous biological processes, such as oxygen conveyer, electron transfer and oxidation. In these processes, the enzymatic active site, which is very specific, forms complexes with divalent metal ions.[18]

In view of these points and in continuation of our work, we report herein the synthesis, spectral properties, antibacterial and antifungal studies of a new Mannich base *N*-[Phenyl(pyrrolidin-1-yl)methyl]acetamide and some of its transition metal complexes

## Experimental

High purity acetamide(Merk), benzaldehyde(Merk), pyrrolidine(Merk) were used as supplied. All other solvents and metal salts used were of A.R. grade and used as received.

Micro elemental data were obtained with Carlo Erba 1108 elemental analyzer at RSIC, CDRI, Lucknow. Metal contents were estimated by usual procedure after digesting the complexes with con. $HNO_3$ and the results were further confirmed by atomic absorption spectrophotometer.[19] The conductance data were obtained in ~$10^{-3}$ M DMF solution of the complexes at room temperature using a systronics direct reading digital conductivity meter. IR spectra were recorded using a spectrum-one Perkin Elmer FT-IR spectrometer by using KBr pellets. The UV-Visible region were recorded in DMF solution using double beam UV-Visible spectrometer(Perkin EZ-301). The $^1$H and $^{13}$C NMR of the ligand were recorded on a bruker instrument and on a JEOL GSX-400 spectrometer. The FAB mass recorded for the ligand was carried out using a JEOL GC-mate mass spectrometer. The room temperature magnetic susceptibility measurements of the complexes were made by using a Gouy magnetic balance calibrated using mercury(II)tetrathiocyanatocobaltate(II). The biological activities of ligand and complexes were screened by the disc diffusion technique under prefectly sterile conditions.

### Synthesis of the Ligand

*N*-[Phenyl(pyrrolidin-1-yl)methyl]acetamide(PBA) was synthesized by employing the Mannich condensation[20] reaction between acetamide, benzaldehyde and pyrrolidine in 1:1:1 mol ratio. Acetamide was dissolved in ethanol and mixed with benzaldehdye and pyrrolidine with constant stirring in an ice bath. After 12 days a pale yellow solid was obtained and then washed with distilled water. The compound was dried at 60$^{o}$C in an air oven and recrystallised from ethanol. The percentage yield was 78 and the melting temperature is 120-124$^{o}$C. It is insoluble in water but completely soluble in organic solvents.

### Synthesis of the Complexes

The hot methanolic solution of the metal salts was added slowly with constant stirring to the hot ethanolic solution of the ligand in 2:1 mol ratio. The insoluble complexes[20] formed were filtered, washed with appropriate solvent to remove the unreacted metal and ligand, then dried.

### Antibacterial and Antifungal Screening

Antibacterial activities of PBA and their complexes ($Co^{II}$, $Ni^{II}$ and $Cu^{II}$ sulphates) were tested *in vitro* against six bacterial species *(Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi*(gram -ve) and *Bacillus subtilis, Streptococcus pyogenes, Staphylococcus aureus*(gram +ve)), by disc diffusion method[21] using agar nutrient as medium and gentamycin as control. The paper disc containing the compound (10, 20 and 30 µg/disc) was placed on the surface of the nutrient agar plate previously spread with 0.1 mL of sterilized culture of microorganism. After incubating this at 37$^{o}$C for 24 hrs, the diameter of inhibition zone around the paper disc was measured.

*Aspergillus niger* and *Aspergillus flavus* are the fungus common in decaying vegetation and are the commonest contaminants in the laboratory. The antifungal activities of the compounds were determined by potato dextrose agar medium in disc diffusion method. The zone of inhibition in mm exhibited by various sulphato complexes of PBA against *A.niger* and *A.flavus* are tabulated.

## RESULTS AND DISCUSSION

IR spectrum of PBA shows a sharp band at 3306 $cm^{-1}$ is assigned to $\nu_{NH}$ stretching vibration of the secondary amide group.[22] The medium bands at 3053 & 3035, 2821 and 2971&2876 $cm^{-1}$ are attributed to aromatic, aliphatic and alicyclic (C-H) stretching vibrations respectively. The strong band at 1646 $cm^{-1}$ may be attributed to the $\nu_{C=O}$ stretching mode. The medium absorption band appears at 1149 $cm^{-1}$ may be assigned to the new C-N-C bond formed due to the formation of Mannich base by the insertion of pyrrolidinobenzyl group on acetamide. The absorption band at 1126 & 1077 $cm^{-1}$ assigned to the C-N-C frequency of pyrrolidine.

UV-Visible spectrum of the compound in DMF registers an intense split bands centered at 287 and 226 nm which are presumably due to $n \rightarrow \pi^*$ transition of the carbonyl group and $\pi \rightarrow \pi^*$ transition of the carbonyl group and the benzene ring.[23]

The $^1H$ NMR spectrum shows the signal at δ8.42 ppm may be assigned to the secondary amide NH proton. The methyl proton shows a singlet at δ1.89 ppm. The multiplet in the range δ7.39-7.26 ppm is attributed to the protons of the benzene ring.[24] The protons at δ7.39, 7.33 and 7.26 ppm may assigned to the CH protons of benzene ring at 2&6, 3&5 and 4 positions respectively. The chemical shift of the protons of $N(CH_2)_2$ at $\alpha, \alpha^1$ group of pyrrolidine ring occurs at δ2.51 ppm and and the $\beta, \beta^1$ group of pyrrolidine occurs at δ1.65 ppm.

According to the $^{13}C$ NMR spectrum obtained, the carbonyl carbon shows a signal at δ169.62 ppm. The signals observed between δ141.62-127.68 ppm are due to aromatic carbons of phenyl group. The resonance signals at δ141.62, 128.56, 127.99 and 127.68 ppm are assigned to the carbons of the phenyl group at 1, 2&6, 3&5 and 4 positions respectively. The substituted carbon of the aromatic ring can be distinguished by its decreased[24] peak height(δ141.62 ppm). The signals observed at δ49.23 and 23.59 ppm is due to at $\alpha, \alpha^1$ and at $\beta, \beta^1$ carbons of pyrrolidine ring.

The mass spectrum of PBA was obtained on electron ionization mode[25] shows a very weak molecular ion peak at m/z = 218, which confirms the assigned molecular mass to this Mannich base. Thereupon on fragmentation it records intense signals at m/z = 127 & m/z = 99, which are due to the removal of $C_6H_5CH_2^-$ and $CHO^-$ groups respectively. Finally the signal at m/z = 70 is due to the presence of pyrrolidine ion. Based on the data obtained from various physical and chemical studies, the molecular structure of PBA is shown below..

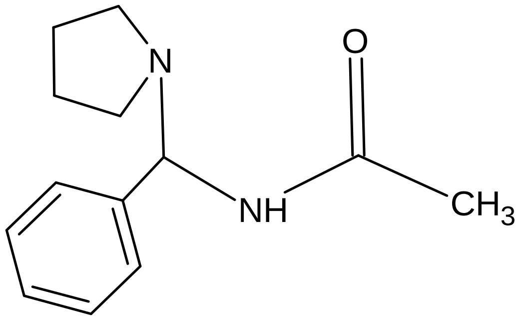

**Fig I: N-[Phenyl(pyrrolidin-1-yl)methyl]acetamide(PBA).**

To find out the stoichiometry of the complexes, the percentage of the metal ions, anions and CHN were determined.[26] The molar conductance values are seen that all the complexes are non-electrolytes. The CHN analysis values having good agreement with the calculated values and are presented in Table I.

In the IR spectra of all the PBA complexes, the stretching frequencies of C=O and C-N-C bonds are found lowered showing that both carbonyl oxygen and CNC nitrogen atoms are coordinated to the metal ions. So the ligand acts as ON donor.[27] But in Ni(II) nitrato complex, in addition to the C=O and C-N-C bonds the amido NH bond also shifted to lower frequency, which indicates the tridentate bonding nature of the ligand. The IR spectrum of the sulphato complexes shows the presence of coordinated sulphato group. The bands at the ranges of 1150, 1000 and 900 $cm^{-1}$ are due $\nu_3$ of sulphato group and $\nu_4$ splits up into its components at the ranges of 650, 600 and 580 $cm^{-1}$ in the complex. The frequencies 750($\nu_1$) and 500($\nu_2$) $cm^{-1}$ are also observed. These frequencies are due to the bidentate chelation[27] of sulphato group. The bands around 3300-3500, 1600-1650, 800-880, 600-690 and 460-530 $cm^{-1}$ found only in the spectra of $Co^{II}$, $Ni^{II}$ and $Cu^{II}$ sulphato, $Cu^{II}$ nitrato complexes of PBA indicates the presence of coordinated water molecule.

The $Co^{II}$ nitrato complex exhibits electronic transition[28] bands at 3916 $cm^{-1}$ due to $^4A_2(F)\rightarrow{}^4T_2(F)(\nu_1)$ transition, at 6747 $cm^{-1}$ due to $^4A_2(F)\rightarrow{}^4T_1(F)(\nu_2)$ transition, at 15101 $cm^{-1}$ due to $^4A_2(F)\rightarrow{}^4T_1(P)(\nu_3)$ and the bands at 23435 & 31647 $cm^{-1}$ due to charge transfer transitions respectively. The $\nu_2/\nu_1$ ratio for $Co^{II}$ nitrato complex is below 1.72. The $Co^{II}$ sulphato complex exhibit electronic transition bands at 7109($\nu_1$), 15281($\nu_2$), 18346($\nu_3$) and 32875 $cm^{-1}$ respectively due to $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)(\nu_1)$, $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)(\nu_2)$, $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)(\nu_3)$ and charge transfer transitions[28] respectively. The $\nu_3/\nu_1$ ratio for $Co^{II}$ sulphato complex is 2.58. The order of Dq values among the $Co^{II}$ complex as found to be

$Co(NO_3)_2$.PBA < $CoSO_4$.PBA.$2H_2O$. The Dq value for the octahedral sulphato complex is greater than that of the tetrahedral $Co^{II}$ complex as expected. The effective magnetic moment of nitrato complex is 3.85 B.M. which is expected for tetrahedral geometry and for the sulphato complex is 5.23 B.M. which is expected for octahedral $Co^{II}$ complex.

The $Ni^{II}$ nitrato complex exhibit band at 7435 $cm^{-1}$ due to $^3A_{2g}\rightarrow{}^3T_{2g}$ transition, at 12566 $cm^{-1}$ due to $^3A_{2g}\rightarrow{}^3T_{1g}(F)$ transition and at 24550 $cm^{-1}$ due to $^3A_{2g}\rightarrow{}^3T_{1g}(P)$ transition respectively. The sulphato complex exhibit bands at 3892 $cm^{-1}$ due to $^3T_{1g}(F)\rightarrow{}^3T_{2g}(F)$ transition, at 8405 $cm^{-1}$ due to $^3T_{1g}(F)\rightarrow{}^3A_{2g}(F)$ transition and at 15281 $cm^{-1}$ due to $^3T_{1g}(F)\rightarrow{}^3T_{2g}(P)$ transition respectively. The bands appearing at 26885 $cm^{-1}$ in the sulphato complex of $Ni^{II}$ is attributed to charge transfer transition. The $\nu_2/\nu_1$ ratio for the $Ni^{II}$ nitrato and sulphato complexes are 1.69 and 2.16 respectively. The $\mu_{eff.}$ values for the nitrato and sulphato complexes of $Ni^{II}$ are 3.36 and 3.97 B.M. respectively indicating distorted octahedral environment[29] around $Ni^{II}$ ion in nitrato complex and tetrahedral environment in sulphato complex.

$Cu^{II}$ nitrato complex exhibits two intense bands at 12073 and 29590 $cm^{-1}$ due to $^2E_g\rightarrow{}^2T_{2g}$ and charge transfer transitions respectively. Sulphato complex of $Cu^{II}$ exhibit electronic absorption[21] bands at 9055 $cm^{-1}$ due to $^2B_{1g}\rightarrow{}^2A_{2g}$, 12843 $cm^{-1}$ due to $^2B_{1g}\rightarrow{}^2B_{2g}$, `14790 $cm^{-1}$ $^2E_g\rightarrow{}^2T_{2g}(F)$ and the bands at 24217 & 35789 $cm^{-1}$ are assigned due to charge transfer transitions respectively.[28] The $\mu_{eff}$. value of nitrato (1.80 B.M) and sulphato (1.69 B.M) complexes indicate that they are magnetically diluted and have distorted octahedral geometry.[29]

The X band EPR spectra[30] of polycrystalline nitrato and sulphato complexes of $Cu^{II}$ are recorded at LNT (77K)(Table II). The g values of the nitrato and sulphato complexes are in the trend, $g_{\parallel} > g_{\perp} > g_{DPPh}$ suggesting that the unpaired electron lies predominantly in the $d_{x2-y2}$ orbital and they showed EPR spectra of axial symmetry type indicating planar based distorted octahedral geometry around copper centre. The $g_{\parallel}$ values of nitrato and sulphato complexes are less than 2.30 indicating the covalent nature. The higher $g_{\parallel}$ values may be due to the coordination of $H_2O$ to the $Cu^{II}$ ion in these complexes. The axial symmetry parameter G, which is a measure of interaction between the metal centers in the crystalline solids is less than 4 for complex of $Cu^{II}$ and it show considerable coupling and appreciable misalignment of the local tetragonal axes leading to an exchange interaction of free electron between two copper centers in the solid state. The G value for the nitrato and sulphato complexes of $Cu^{II}$ is

12.0 and 9.3 and this suggests the lack of change interaction between two $Cu^{II}$ centers in the unit cell of the complex. The negative sign of G value in nitrato complex is dropped. Based on the above discussions six coordinated tetragonally distorted octahedral geometry may be assigned to nitrato and sulphato complexes of $Cu^{II}$.

Based on micro elemental analysis, conductance measurements, IR, UV-VIS and magnetic moment measurements, the following are the tentative structures proposed for the complexes (Figures II to VI).

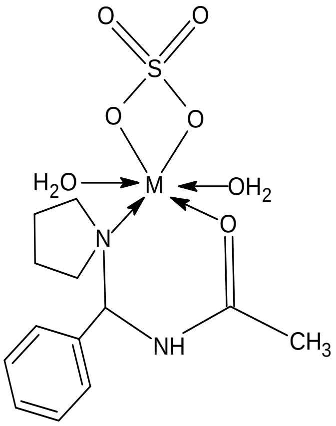

**Fig. II**

**$MSO_4.PBA.2H_2O$**

**M = Co & Cu**

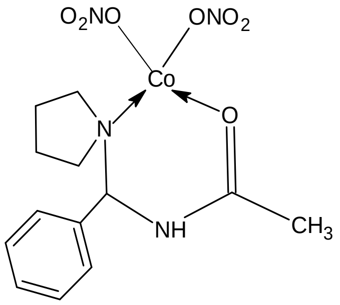

**Fig.. III**

**$Co(NO_3)_2.PBA$**

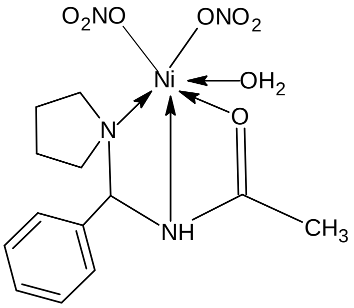

**Fig. IV**

**$Ni(NO_3)_2.PBA.H_2O$**

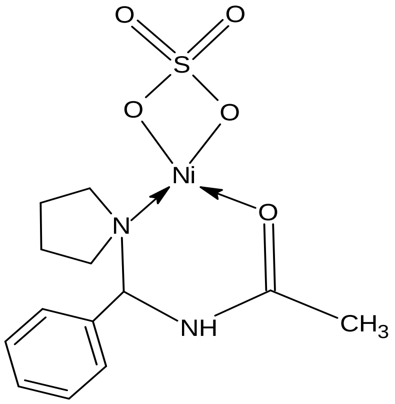

**Fig. V**

**$NiSO_4.PBA$**

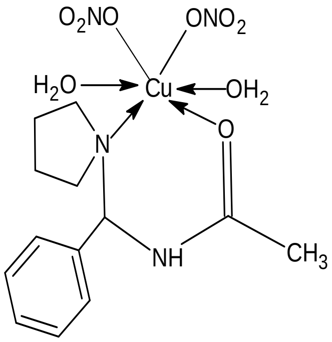

**Fig. VI**

**$Cu(NO_3)_2.PBA.2H_2O$**

A comparison of diameters of the inhibition zones of the compounds investigated and listed in Tables III and IV shows that $Co^{II}$ sulphato complex exhibits highest antibacterial and antifungal activity against all the bacterial and fungal species studied. This is because; they have larger diameters of inhibition zones than even the control gentamycin at the same concentration and identical conditions. The complexes have more antibacterial and antifungal activities than the ligand against all the bacteria and fungi studied. This observation clearly indicates that the chelation increases the activity. The higher activity of the $Co^{II}$ complex may be due to the fact that, $Co^{II}$ is an essential micronutrient during transcription and transformation of nucleic acids. Hence these complexes were shown to inhibit cellular protein and RNA synthesis. In $Co^{II}$ sulphato complex, the unsaturated metal center present, achieves higher coordination number by binding with some of the functional groups of the protein. This leads to the increased uptake of the compound by the bacterium and thereby inhibiting its growth.[31]

The fungi toxicity of the free ligand is less severe than that of the metal chelates. A possible mechanism of toxicity may be speculated in the light of chelation theory.[32] Chelation reduces considerably the polarity of the metal ion mainly because of partial sharing of its positive charge with donor groups and possible π-delocalization of electron over the chelate ring. This increases the liphophilic character of the neutral chelate which favours its permeation through lipoid layers of fungus membranes. Furthermore, the mechanism of action of the compound may involve the formation of hydrogen bond through the uncoordinated hetero atoms O, S and N with the active centers of the cell constituents resulting in the interference with the normal cell process.[32] Presence of lipophilic and polar substituents like C=O, NH, etc., are expected to enhance the fungi toxicity. These compounds have greater chance of interaction with either the nucleotide bases or biologically essential metal ions presents in the biosystem and also coordinatively unsaturated metal present in the metal complexes to achieve higher coordination number especially with some of the enzymatic functional groups.[33] The low activity of some of the complexes may be due to a mismatching of the geometry and charge distribution around the molecule with that around the pores of the fungal cell wall preventing penetration and hence toxic reaction within the pores. As a corollary, the complex cannot reach the desired site of action on the cell wall to interfere with normal cell activity.

**Table I: Analytical and Conductance Data for Co$^{II}$, Ni$^{II}$ & Cu$^{II}$ Complexes of PBA.**

| Complex | % C Obs. (Cal.) | % H Obs. (Cal.) | % N Obs. (Cal.) | %Metal Obs. (Cal.) | %Anion Obs. (Cal.) | $\Lambda_M$ ohm$^{-1}$cm$^2$ mol$^{-1}$ |
|---|---|---|---|---|---|---|
| $Co(NO_3)_2$.PBA | 29.93 (30.65) | 3.89 (3.54) | 4.99 (5.50) | 11.25 (11.78) | 23.55 (24.36) | 12.32 |
| $CoSO_4$.PBA.$2H_2O$ | 28.68 (29.16) | 3.58 (3.36) | 5.05 (5.23) | 10.76 (11.01) | 18.29 (17.94) | 27.71 |
| $Ni(NO_3)_2$.PBA.$H_2O$ | 30.11 (29.60) | 3.25 (3.42) | 5.80 (5.31) | 10.61 (11.14) | 23.03 (23.53) | 13.92 |
| $NiSO_4$.PBA | 32.08 (32.43) | 4.00 (3.74) | 6.16 (5.82) | 12.01 (12.20) | 20.28 (19.96) | 35.45 |
| $Cu(NO_3)_2$.PBA.$2H_2O$ | 31.75 (31.45) | 3.69 (3.63) | 5.90 (5.65) | 13.38 (12.81) | 24.77 (25.00) | 18.26 |
| $CuSO_4$.PBA.$2H_2O$ | 30.48 (31.01) | 3.33 (3.58) | 5.95 (5.57) | 12.87 (12.63) | 19.00 (18.59) | 22.47 |

**Table II: EPR Spectral Parameters of Cu$^{II}$ Complexes.**

| Complex | $g_\parallel$ | $g_\perp$ | $g_{av}$ | G |
|---|---|---|---|---|
| $Cu(NO_3)_2$.PBA.$2H_2O$ | 2.16 | 2.02 | 2.09 | 12.0 |
| $CuSO_4$.PBA.$2H_2O$ | 2.12 | 2.01 | 2.06 | 09.3 |

**Table III: Antibacterial Activity of Ligand and its Complexes.**

| Compound | *Escherichia coli* | | | *Pseudomonas aeruginosa* | | | *Salmonella typhi* | | | *Bacillus subtilis* | | | *Streptococcus pyogenes* | | | *Staphylococcus aureus* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Conc. (µg/disc) | 10 | 20 | 30 | 10 | 20 | 30 | 10 | 20 | 30 | 10 | 20 | 30 | 10 | 20 | 30 | 10 | 20 | 30 |
| Control | 08 | 10 | 13 | 11 | 14 | 17 | 09 | 12 | 16 | 11 | 15 | 19 | 10 | 13 | 15 | 12 | 18 | 22 |
| PBA | - | 07 | 11 | 09 | 11 | 12 | 08 | 09 | 13 | - | 10 | 16 | 08 | 11 | 11 | 07 | 12 | 15 |
| $CoSO_4$.PBA.$2H_2O$ | 18 | 21 | 24 | 17 | 22 | 27 | 16 | 21 | 26 | 20 | 24 | 32 | 18 | 20 | 26 | 15 | 22 | 30 |
| $NiSO_4$.PBA.$2H_2O$ | 17 | 20 | 22 | 13 | 16 | 21 | 12 | 20 | 25 | 15 | 18 | 24 | 10 | 16 | 23 | 11 | 15 | 21 |
| $CuSO_4$.2PBA | 18 | 20 | 21 | 17 | 19 | 24 | 14 | 15 | 21 | 12 | 18 | 24 | 16 | 21 | 26 | 12 | 19 | 25 |

**Table IV: Antifungal Activity of Ligand and its Complexes.**

| Compound | *A. niger* | | | *A. flavus* | | |
|---|---|---|---|---|---|---|
| Conc. (µg/disc) | 10 | 20 | 30 | 10 | 20 | 30 |
| Control | 05 | 05 | 09 | 07 | 11 | 12 |
| PBA | 07 | 09 | 11 | 10 | 13 | 15 |
| $CoSO_4$.PBA.$2H_2O$ | 19 | 24 | 31 | 21 | 27 | 36 |
| $NiSO_4$.PBA.$2H_2O$ | 15 | 18 | 25 | 15 | 19 | 27 |
| $CuSO_4$.2PBA | 15 | 20 | 29 | 16 | 18 | 30 |

## CONCLUSION

Based on the spectral data, the ligand acted as bidentate to the metal ion in all the complexes. But in Ni$^{II}$ nitrato complexes, it act as tridentate in nature. From the IR, electronic and magnetic studies, the Ni$^{II}$ complexes exhibit tetrahedral geometry and the other complexes are octahedral geometry. The synthesized ligand and their metal complexes were screened for biological activities. All the compounds showed very good antibacterial and antifungal activities.

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