SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 6-BROMO-2[(4-PHENYL)-1-YL] METHYL]-3-[8-HYDROXY QUINOLINE -5-YL]-3 QUINAZOLIN -4-ONE LIGAND AND ITS METAL CHELATES

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ABSTRACT

The novel ligand HL11 was synthesized using anthranilic acid and it was undergo the chelating reaction with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) to prepare transition metal chelates. These chelates were characterized by physicochemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, FT-IR, NMR and electronic spectral data. The stoichiometry of the complex has been found to be 1:2 (Metal: ligand). An octahedral geometry around Co(II), Ni(II) and Mn(II), distorted octahedral geometry around Cu(II) and tetrahedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates was conducted against various fungi.

Key words: 8-Hydroxy quinoline ligand, Complexes, Electronic, NMR spectral studies, Antifungal activity

INTRODUCTION

The heterocyclic nitrogen compounds especially quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs. A Quinazolin-4-one derivative possesses biological activities such as antifungal. The 8-hydroxyquinoline and quinazolin-4-one molecules into one molecule have not received any attention in spite of well-defined applications of both the molecules. Hence it was thought to explore the study of quinazolin-4-one 8-hydroxyquinoline merged molecules as ligand HL11 with their complexes with Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) metal ion. Antifungal activity of the ligand and its metal chelates has also been studied.

Scheme I: General structure of formation of chelates
EXPERIMENTAL

All the chemicals used were of pure grade (Merck and B.D.H). Double distilled water was used throughout the experiment. The melting point of ligand was determined by open capillary method and were found to be uncorrected.

Synthesis of BPHMQ ligand, (HL11): The 5-bromo anthranilic acid was converted into 5-bromo N-chloroacetyl anthranilic acid by means of chloroacetyl chloride then it refluxed with 5-amino-8-hydroxy quinol in 1-dioxane under anhydrous condition for 4 hrs. The reaction mixture was allowed to cool and phosphorous trichloride was decomposed by titrating with cold water. Then, 1, 4-dioxane was distilled off to get the product, 6-bromo-2-chloromethyl-3-[8-hydroxy quinolin-5-yl]-3(H)-quinazolin-4-one. It was filtered and washed with small portion of sodium bicarbonate solution (10%) after then extensively with cold water. The mixture of 6-bromo-2-chloromethyl-3-[8-hydroxy quinolin-5-yl]-3(H)-quinazolin-4-one and 1-phenyl piperazine in dry pyridine was refluxed for 12 hrs. Pyridine was distilled off as much as possible and the residue was poured into little crushed ice with stirring. The product, HL11 i.e. 6‐bromo‐2‐chloromethyl‐3‐(8‐hydroxy quinolin‐5‐yl)‐3(H)‐quinazolin‐4‐one was separated out, filtered and washed with water and finally with ethanol. The air dried product was quantitative. Melting point for HL11, >230°C.

Synthesis of Chelates: A dried ligand sample HL11 (0.01 M) was stirred in 85 % (v/v) formic acid and then it was diluted with water until complete dissolution. The resultant solution was designated as reagent solution. This solution was used for preparation of chelates with particular ligand with transition metal ions. The formic acid solution of ligand was added drop wise to a solution of Cu(NO3)2.6H2O, Ni(NO3)2.6H2O, Co(NO3)2.6H2O, MnCl2.6H2O, Zn(NO3)2.6H2O (0.005 mole) in 100 ml of water with constant stirring. The resultant pH 4.5 [for Cu(II)], pH 6.0 [for Ni(II) and Co(II)] and pH 5.6 [for Mn(II) and Zn(II)] were maintained by addition of sodium acetate. A dark colored solid precipitated out. It was allowed to separate and digested on water bath at 70 °C for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone then dried. The percentage yield of chelates was in the range of 59-75 %. All the chelates were powdered well and dried at 70°C over a period of 24 h.

The C, H and N contents of metal chelates were determined on elemental analyzer Thermonfingers 1101 Flash EA. The metal contents were estimated using standard methods11. The molar conductance of the complexes in DMF (10-3 M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. The NMR spectra of ligand was recorded on Bruker NMR spectrophotometer. PMR chemical shifts were recorded in δ – value using TMS as an internal standard in CDCl3/D2O. The IR spectra (KBr) were recorded in the range 4000-600 cm-1 on a Nicolet-760 spectrophotometer. The percentage of inhibition of fungi was calculated after 5 days using the formula given below:

\[
\text{Percentage of inhibition} = 100 \times \frac{(X - Y)}{X}
\]

Where X= area of colony in control plate (without sample) and Y = area of colony in test plate.

RESULTS AND DISCUSSION

The complexes are microcrystalline colored powder having melting points higher than the ligand. They are stable in air at room temperature. All compounds gave satisfactory elemental analysis, suggesting 1:2 [metal: ligand] stoichiometry. Elemental and molar conductance data were shown in Table-1. The result indicates that there are less ionic in DMF. The molar conductance values found to be 21.68, 8.80, 8.12, 7.96 and 7.68 Ohm-1cm2·mol-1 for Co(II), Ni(II), Zn(II), Cu(II) and Mn(II) respectively. So, the electrical conductivity of these chelates was found in the decreasing order: Co > Ni > Zn > Cu > Mn. The very low values of chelates indicates that they are non-electrolytic12 and monomeric in nature. The low conductance values may be attributed to the large cations11.

Infrared spectra: FT-IR spectrum of ligand HL11 showed a broad band extended from 3400 to 2600 cm-1 which might be responsible to phenolic band bonded to N atom of 8-hydroxy quinoline moiety12. The inflesxtious at 2923, 2852 and 1470 cm-1 are due to aromatic CH and methylene bridge of group and piperazine ring 13. The strong band at 1710 cm-1 was attributed to CO of quinazoline 4-one moiety. Several bands appeared between 1500-1600 cm-1 region may arise from aromatic breathing. The IR band at ~ 1580 cm-1 (C=N of 8-quinolinol system) of HL11 ligand shifted to higher frequency ~1600 in the spectra of metal chelates indicating involvement of nitrogen in the chelate formation12,15. Most of bands appeared in the spectra of corresponding ligand were observed at their metal chelates. Only a new band at 1095 cm-1 had appeared in the spectra of metal chelates. This may be assigned to v(C-O-M) bond formation. All the complexes show additional bands at 840-850 cm-1 indicating the presence of coordinated water15 (Figure-1).

Table 1: Analytical and physical data of ligand and its metal chelates

<table>
<thead>
<tr>
<th>Ligand / Mol Formula</th>
<th>M. W. (g/mole)</th>
<th>Yield (%)</th>
<th>Elemental Analysis (%)</th>
<th>Observed µe (B.M) (Expected)</th>
<th>An (Ohm-1cm2·mol-1)</th>
</tr>
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<tbody>
<tr>
<td>HL11</td>
<td>542.00</td>
<td>59</td>
<td>62.30  4.40  13.01  14.70</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CuH2N4O4Br</td>
<td>568.00</td>
<td>60</td>
<td>56.80  4.20  21.68  21.50</td>
<td>-</td>
<td>-</td>
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<tr>
<td>(HL11)2Cu2+</td>
<td>1181.54</td>
<td>69</td>
<td>56.87  4.23  11.80  21.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Co6H11N3O2Cl2Br5</td>
<td>1176.69</td>
<td>69</td>
<td>56.90  4.10  21.68  21.50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(HL11)2Co2+</td>
<td>1118.54</td>
<td>69</td>
<td>(57.10) 4.24  11.80  21.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zn6H11N3O2Cl2Br5</td>
<td>1176.90</td>
<td>72</td>
<td>57.00  4.10  11.80  21.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(HL11)2Zn2+</td>
<td>1172.90</td>
<td>59</td>
<td>(57.09) 4.24  11.80  21.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mn6H11N3O2Cl2Br5</td>
<td>1183.39</td>
<td>75</td>
<td>(57.29) 4.26  11.90  21.68</td>
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<td>-</td>
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<tr>
<td>(HL11)2Mn2+</td>
<td>1172.90</td>
<td>59</td>
<td>(57.20) 4.20  11.90  21.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ni6H11N3O2Cl2Br5</td>
<td>1183.39</td>
<td>75</td>
<td>(56.78) 4.22  11.83  21.68</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Percentage of inhibition = 100 (X-Y) / X

Where X= area of colony in control plate (without sample) and Y = area of colony in test plate.
Table 2: Antifungal activity of ligand HL11 and its metal chelates

<table>
<thead>
<tr>
<th>Samples</th>
<th>Candida Albicans</th>
<th>Botrydepladia Thibronine</th>
<th>Nigrospora Sp.</th>
<th>Aspergillus Fumigatus</th>
<th>Rhizopur Nigricums</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL11</td>
<td>59</td>
<td>69</td>
<td>68</td>
<td>87</td>
<td>70</td>
</tr>
<tr>
<td>(HL11)2Cu2+</td>
<td>80</td>
<td>82</td>
<td>80</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>(HL11)2Ni2+</td>
<td>59</td>
<td>52</td>
<td>56</td>
<td>69</td>
<td>54</td>
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<tr>
<td>(HL11)2Co2+</td>
<td>68</td>
<td>62</td>
<td>63</td>
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<td>67</td>
</tr>
<tr>
<td>(HL11)2Mn2+</td>
<td>70</td>
<td>75</td>
<td>71</td>
<td>72</td>
<td>73</td>
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<tr>
<td>(HL11)2Zn2+</td>
<td>77</td>
<td>69</td>
<td>68</td>
<td>65</td>
<td>63</td>
</tr>
</tbody>
</table>

Fig. 1: IR spectra of ligand HL11

Magnetic moment and Electronic spectra: At room temperature the magnetic moment μeff values for the Co (II) complex is 3.94 B.M (Table-1) suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The electronic spectra of the Co (II) complex display three absorption bands in the range 8542, 19586 and 22489 cm⁻¹, assigned to the transitions τT₁₆(F) ---> τT₂₈(F) (υ₁), τT₁₆(F) ---> τA₂₁(F) (υ₂) and τT₁₆(F) ---> τT₁₆(P) (υ₃) respectively. The values of transition ratio υ₂/υ₁ was 2.29 providing further evidences for octahedral geometry for the Co (II) complexes.

In the Ni (II) complex, μeff value at room temperature is observed to be 3.32 B.M as expected for six coordinated spin free Ni (II) species. The reflectance spectra of the Ni (II) complex, exhibit two strong bands at 14896 and 22800 cm⁻¹, assignable to τA₂₁(F) ---> τT₁₆(F) and τA₂₁(F) ---> τT₄₂(P) respectively. The υ₂/υ₁ ratio for the chelate is 1.53 occurs in the usual range (1.6 –1.82) for octahedral Ni (II) complexes.
chelates\(^{17}\). The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier\(^{18}\).

The Cu(II) complex exhibit normal magnetic moments (1.88 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research workers\(^{19}\). These complex show broad asymmetric bands in the region at 13999 and 25896 cm\(^{-1}\) assignable to \(^2\)B\(_{1g}\) \(\rightarrow\) \(^2\)A\(_{1g}\) and charge transfer transition respectively\(^{20}\). These results reveal the distorted octahedral geometry for these complexes. The former band may be due to \(^2\)E\(_{g}\) \(\rightarrow\) \(^2\)T\(_{2g}\) accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes\(^{21}\). The value of transition ratio \(\nu_2/\nu_1\) was 1.85.

Zn(II) complexes are diamagnetic as expected for d\(^{10}\) systems and have tetrahedral geometry\(^{22}\).

The electronic spectra of the Mn(II) exhibited three spin allowed bands in the region 16458, 18965 and 25489 cm\(^{-1}\) assigned to the transitions \(^4\)A\(_{1g}\) \(\rightarrow\) \(^4\)T\(_{2g}\) \(^{(*G)}\), \(^4\)A\(_{1g}\) \(\rightarrow\) \(^4\)T\(_{2g}\) \(^{(*G)}\) and \(^4\)A\(_{1g}\) \(\rightarrow\) \(^4\)E\(_{g}\) \(^{(*G)}\) respectively, indicating octahedral geometry \(^{23}\). The observed magnetic moment (5.55 B.M.) of the complexes indicates high spin octahedral environment \(^{24}\).

**Antifungal activity:** The ligand and chelates were used for their antimicrobial studies by means of fungi, such as Candida Albicans, Botrydepladia Thibromine, Nigrospora Sp, Aspergillus Fumigatus and Rhizopur Nigricums. Antifungal activity of ligand and its metal chelates shown in Table-2 inhibition of fungal in following decreasing order:

Cu (II) > Mn (II) > Zn (II) > Co (II) > Ni (II).

The substitutions of phenyl rings by chlorine have much more effect on the fungicidal activity. The results suggest that variation in structure on coordination affects the growth of micro organisms and may result in to inhibitory or reduction in toxicology of metal ions towards some organisms \(^{25}\).

**CONCLUSION**

The ligand molecule acts as a hexadentate ligand in all the studied cases of complex. Bonding either among N (4) depending upon the nature of the metal ions. Octahedral structures for Ni (II), Co(II) and Mn(II) complexes, tetrahedral polymeric structure for Zn(II), and distorted octahedral for Cu(II) complex have been tentatively proposed. Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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**REFERENCES**