Synthesis, Characterization, Chelating Properties and Anti-Fungal Activity of 2-(4-Phenylpiperazinyl) Methyl-3-(8-Quinolinol-5-Yl)- 4(3h)-Quinazolinone

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Abstract: A new quinazolinone derivative namely 2-(4-phenylpiperazinyl)methyl-3-(8-quinolinol-5-yl)- 4(3h)-quinazolinone(HL) was prepared and characterized. Various transition metal (Cu²⁺, Co²⁺, Ni²⁺, Zn²⁺, Mn²⁺) chelates of HL were prepared and characterized by metal ligand (M:L) ratio, IR and reflectance spectral studies, magnetic moment, and antimicrobial activity.

Key words: Synthesis, Characterization, Chelating properties and anti-fungal activity.

Introduction

Report shows that various scientists investigated the quinazolone derivatives as biological and pharmaceutical agents. Most of quinazolone containing phenyl group at 3 position. The area in which the quinazolones containing metal chelating moiety(i.e. ligand) say 8-hydroxy quinoline has not been developed inspite of the 8-hydroxy quinoline is well known metal precipitant. Hence it was aimed to explore the field of quinazolone-8-hydroxy quinoline combined molecules. The present paper comprises the synthesis, characterization, chelating properties and microbial activity of the quinazolone compound having following synthetic route.
Scheme-I

N-chloroacetyl anthranilic acid + 5-Amino-8-quinolinol

\[
\text{POCl}_3, \text{TOLUENE} \rightarrow 2\text{-chloromethyl-3-(8-quinolinol-5-yl)-4-3(H)(quinazolinone)}
\]

\[
\text{DRY PYRIDINE} \rightarrow 2\text{-}(4\text{-phenyl piperazinyl)methyl-3-(8-quinolinol-5-yl)-4-(3H) quinazolinone (HL)}
\]

\[
\text{METAL SALT} \rightarrow \text{METAL CHELATES OF HL}
\]

Where Mt: Cu\(^{2+}\), Co\(^{2+}\), Ni\(^{2+}\), Zn\(^{2+}\), Mn\(^{2+}\)
**Experimental**

**Materials**

5-Amino-8-quinolinol was prepared accordingly to literature method. N-phenyl piperazine was obtained from Enzal Chemicals, Ankleshwar. All other chemicals were used of pure grade.

**Synthesis**

2-chloromethyl-3-(8-quinolinol-5-yl)-4-(3H)(quinazolinone):

A mixture of N-chloroacetyl anthranilic acid (0.1 mole) and 5-amino-8-quinolinol (0.1 mole) and PCl$_3$ (0.1 mole) in dry toluene was refluxed under anhydrous condition for 9 hours. The reaction was kept up to cooling and PCl$_3$ was decomposed by cold water. Then toluene was distilled off to get the product. It was filtered, washed with NaHCO$_3$ (10% solution) and then cold water. It was yellow-brown amorphous powder. Melting point 217°-218° C (uncorrected). N % Calculated 12.44. Found 12.35. Calculated 10.52 Found 10.4

**Synthesis of 2-(4-phenyl piperazinyl)methyl-3-8-quinolinol-5-yl-4-(3H) quinazolinone(HL):**

A mixture of 2-chloromethyl-3-(8-quinolinol-5-yl)-4(3H) quinazolinone (0.05 mole) and N-phenyl piperazine (0.05 mole) in dry pyridine was refluxed for 10 hours. Pyridine was distilled off as much as possible and the residue was poured in to a little crushed ice. It was filtered, washed with water and air-dried. The yield was 80%. Melting Point = 230°-231° (uncorrected).

**Preparation of metal chelates of HL:**

The Cu$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Zn$^{2+}$ and Mn$^{2+}$ metal chelates of HL ligand were prepared in the similar manner. The general procedure is as follows:

The HL (0.02 mole) was suspended in formic acid(10 ml). Then water is added till the HL dissolved completely. Then the solution is added in to the metal acetate (0.01 mole) solution in water (100 ml). The resultant mixture was added by sodium acetate. The precipitates of chelates were settle down and digested on hot water bath for 2 hours. The precipitate of metal chelates were filtered off, washed and air-dried. It was amorphaus, dark coloured powder. Yield was quantitive. It did not melt or decomposed up to 230° C. The details of all chelates are presented in Table-1.

**Measurement:**

The elemental analysis for C, H, and N were carried out on Carlo Erba elemental analyzer (Italy). IR spectra of HL and the coordination metal chelates were scanned on a Perkin Elmer FTIR Spectrophotometer in KBr. The metal content of the metal chelates were performed by decomposing a weighed amount of each coordination metal chelates followed by EDTA titration as reported in literature. Magnetic susceptibility measurements of all the coordination metal chelates were carried out at room temperature by the Gouy method. Mercury tetrathiocyanatocobaltate(II). Hg[Co(NCS)$_4$]$^+$ was used as a calibrant. The diffused reflectance spectra of solid coordination metal chelates were recorded on a Backman DK-2A Spectrophotometer with a solid reflectance attachments. MgO was employed as the reflectance compound.

**Anti-fungal activity:**

The fungicidal activity of all the compounds were studied at 1000 ppm concentration in Vitro. Plant pathogenic organisms used were. Penicillium Expansum, Botrydepladia Thiobromine, Nigrospora Sp. The antifungal activity of all the samples were measured on each of these plant pathogenic strains on a potato dextrose agar(PDA) medium. Such a PDA medium contained potato 200 gms, dextrose 20 gms, agar 20 gms and water 1 litre. 5 days old culter were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120°C for 15 min. at 15 atm pressure. These medium were poured into sterile petri plate and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after 5 days using the formula given below.

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

Where, X : Area of colony in control plate, Y : Area of colony in test plate

The fungicidal activity displayed various compound as shown in Table-2.
Results and Discussion

The ligand was synthesized as shown in the Scheme-1. HL is a amorphous yellow powder, soluble only in DMSO and DMF. The results of elemental analysis of the ligand reported in Table-1 are consistant with the predicted structure as shown in Scheme-1. Examination of IR spectrum (not shown) of HL reveals that a broad band of phenolic hydroxyl stretching is observed at 3300-3500 cm$^{-1}$ as well as additional absorption band at 1427, 1481, 1508 and 1602 cm$^{-1}$ characteristics of the 8-hydroxy quinoline moiety$^{10}$. The weak bands at 2920 and 2850 cm$^{-1}$ are arised from CH$_2$ piperazine ring and CH$_3$ group. The bands due to aromatic ring are observed at their respectable positions. The strong band at 1690 and 1630 are attribute respectively to C=O and C=N bands$^{11}$.

The metal chelates of HL with the metal ions Cu$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Zn$^{2+}$, Mn$^{2+}$ vary in dark colours. On the basis of the proposed structure as shown in scheme-1, the molecular formula of the HL ligand is C$_{28}$H$_{32}$N$_{5}$O$_{2}$. Which upon chelation coordinates with one central metal atom at four coordination sites and with tow water molecules. Therefore, the general molecular formula of the resulting metal chelat is given by [C$_{28}$H$_{32}$N$_{5}$O$_{2}$]M.2H$_2$O. This has been confirmed by results of elemental analysis of all the five metal chelates and their parent ligand. The data of elemental analysis reported in Table-1 are in arrangement with the calculated values of C, H, and N based on the above mentioned molecular formula of parent ligand as well as coordination metal chelates.

Inspection of the IR Spectra(not shown) of metal chelates reveals that all the spectra are identical in all respects. The comparison of IR spectrum of the parent ligand HL with that of its each metal chelates has revealed certain characteristics differences. One of the significant difference to be expected in all respects. The comparison of IR spectrum of the parent ligand HL with that of its each metal chelate is given by [C$_{28}$H$_{32}$N$_{5}$O$_{2}$]M.2H$_2$O. This has been confirmed by results of elemental analysis of all the five metal chelates and their parent ligand. The data of elemental analysis reported in Table-1 are in arrangement with the calculated values of C, H, and N based on the above mentioned molecular formula of parent ligand as well as coordination metal chelates.

Examination of data of the metal content in each compound revealed a 1:2 metal : ligand (ML$_2$) stoichiometry in all of the chelates. Magnetic moment($\mu_{eff}$) of each of the metal chelate is given in Table-1. Examination of these data reveals that all coordination chelates other than, that of Zn(II) are para-magnetic while that of Zn(II) is diamagnetic. The diffuse electronic spectrum of the [CuL(H$_2$O)$_2$] metal chelates shows broad bands at 15878 and 22998 cm$^{-1}$ due to the $^6T_g \rightarrow ^4T_{2g}$ transition and charge transfer, respectively, suggesting a distorted octahedral structure for the [CuL(H$_2$O)$_2$] chelates which is further confirmed by the higher value of $\mu_{eff}$ of the [CuL(H$_2$O)$_2$] chelat. The [NiL(H$_2$O)$_2$] and [CoL(H$_2$O)$_2$] chelates gave two absorption bands respectively, at 15623,22473 and 16524, 22220 cm$^{-1}$ corresponding to $^6T_{1g} \rightarrow ^2T_{1g}$ and $^4T_{1g} \rightarrow ^4T_{1g}(P)$ transitions. Thus, absorption bands of the diffuse, reflectance spectra and the values of the magnetic moments ($\mu_{eff}$) indicate an octahedral configuration for the [NiL(H$_2$O)$_2$] and [CoL(H$_2$O)$_2$] chelates. The spectra of [MnL(H$_2$O)$_2$] shows weak bands at 14666,19752 and 25571 cm$^{-1}$ assigned to the transitions $^6A_{1g} \rightarrow ^2T_{1g}$ (4G), $^6A_{1g} \rightarrow ^2T_{2g}(4G)$ and $^6A_{1g}$ (F) $\rightarrow ^4T_{1g}$, respectively suggesting an octahedral structure for the [MnL(H$_2$O)$_2$] chelate. As the spectrum of the [ZnL(H$_2$O)$_2$] polymer is not well resolved, it is not interpreted but its $\mu_{eff}$ value, shows that it is diamagnetic as expected.

The antifungal activity of all the compounds measured for various plant pathogens. Inspection of the result shown in Table-2 indicates that all compounds are good toxic for fungi. Out of all the compounds Copper chelate is more toxic than others. These compounds almost inhibit the fungi about
70%. Hence, produced metal chelates can be employed as garden fungicides. Further work in this direction is in progress.

**Table-1** Analytical Data of the coordination metal chelates of HL

<table>
<thead>
<tr>
<th>Compound</th>
<th>Empirical Formula</th>
<th>Elemental Analysis %</th>
<th>µ_{eff}</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Found/(Calcd.)</td>
<td>BM</td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>C_{28}H_{22}N_{4}O_{3}</td>
<td>72.48 (72.57)</td>
<td>5.37 (5.39)</td>
<td>15.07 (15.11)</td>
</tr>
<tr>
<td>[CuL _2(H_2O)_2]</td>
<td>[C_{28}H_{22}N_{4}O_{3}]_2Cu</td>
<td>32.89 (32.95)</td>
<td>2.33 (2.35)</td>
<td>6.81 (6.86)</td>
</tr>
<tr>
<td>[CoL _2(H_2O)_2]</td>
<td>[C_{28}H_{22}N_{4}O_{3}]_2Co</td>
<td>33.06 (33.10)</td>
<td>2.32 (2.35)</td>
<td>6.87 (6.89)</td>
</tr>
<tr>
<td>[NiL _2(H_2O)_2]</td>
<td>[C_{28}H_{22}N_{4}O_{3}]_2Ni</td>
<td>33.03 (33.11)</td>
<td>2.30 (2.36)</td>
<td>6.86 (6.89)</td>
</tr>
<tr>
<td>[MnL _2(H_2O)_2]</td>
<td>[C_{28}H_{22}N_{4}O_{3}]_2Mn</td>
<td>33.22 (33.23)</td>
<td>2.31 (2.37)</td>
<td>6.88 (6.92)</td>
</tr>
<tr>
<td>[ZnL(H_2O)_2]</td>
<td>[C_{28}H_{22}N_{4}O_{3}]_2Zn</td>
<td>32.82 (32.89)</td>
<td>2.33 (2.34)</td>
<td>6.79 (6.85)</td>
</tr>
</tbody>
</table>

**Table-2** : Antifungal activity of compounds

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Zone of inhibition at 1000 ppm(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Penicillum Expansum</td>
</tr>
<tr>
<td>HL</td>
<td>71</td>
</tr>
<tr>
<td>[CuI(H_2O)_2]</td>
<td>82</td>
</tr>
<tr>
<td>[CoI(H_2O)_2]</td>
<td>76</td>
</tr>
<tr>
<td>NiI(H_2O)_2</td>
<td>73</td>
</tr>
<tr>
<td>[MnI(H_2O)_2]</td>
<td>77</td>
</tr>
<tr>
<td>ZnI(H_2O)_2</td>
<td>68</td>
</tr>
</tbody>
</table>

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**References**

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