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

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Abstract: A new quinazolinone derivative namely 2-(4-phenylpiperazinyl)methyl-3-(8-quinololinol-5-yl)- 4(3h)-quinazolinone(HL) was prepared and characterized. Various transition metal (Cu^{2+} , Co^{2+} , Ni^{2+} , Zn^{2+} , Mn^{2+}) 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 agents¹⁻⁶. 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

Experimental

Materials

5-Amino-8-quinolinol was prepared accordingly to literature method ⁷. 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)-4-3(H)(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 $217^\circ\text{--}218^\circ\text{C}$ (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 = $230^\circ\text{--}231^\circ$ (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 amorphous, dark coloured powder. Yield was quantitative. 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 literature⁸. Magnetic susceptibility measurements of all the coordination metal chelates were carried out at room temperature by the Gouy method. Mercury tetrathiocyanatocobaltate(II). $\text{Hg}[\text{Co}(\text{NCS})_4]$ 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 contained⁹ 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.

$$\text{Percentage of Inhibition} = \frac{100 (X - Y)}{X}$$

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 $3300\text{--}3500\text{ cm}^{-1}$ as well as additional absorption band at $1427, 1481, 1508$ and 1602 cm^{-1} characteristics of the 8-hydroxy quinoline moiety¹⁰. The weak bands at 2920 and 2850 cm^{-1} are arised from CH_2 piperazine ring and CH_2 group. The bands due to aromatic ring are observed at their respectable positions. The strong band at 1690 and 1630 are attribute respectively to $\text{C}=\text{O}$ and $\text{C}=\text{N}$ bands¹¹.

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-I**, the molecular formula of the HL ligand is $\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2$. 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 $[\text{C}_{28}\text{H}_{24}\text{N}_5\text{O}_3]_2\text{M} \cdot 2\text{H}_2\text{O}$. 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 between the IR spectrum of the parent ligand and its metal coordinated chelates is the presence of more broadened bands in the region of $3300\text{--}3550\text{ cm}^{-1}$ for the coordination metal chelates as the oxygen of the O-H group of the ligand forms a coordination bond with the metal ions. This is explained by the fact that water molecules might have strongly absorbed to the metal chelates sample during their formation. Another noticeable difference is that the band due to the $\text{C}=\text{N}$ stretching vibration of 8-hydroxy quinoline at 1600 cm^{-1} in the IR spectrum of HL is shifted to lower frequency. The band at 1400 cm^{-1} in the IR spectrum of HL assigned to in-plane OH deformation¹⁰ is shifted towards higher frequency of the spectra of the metal chelates due to the formation of metal –oxygen bands. This has been further confirmed by a weak band at 1105 cm^{-1} corresponding to C-O-M stretching¹⁰. Thus all of these characteristics/features of the IR studies suggested the structure of the metal chelates as shown in **Figure**.

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 (μ_{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 $[\text{CuL}(\text{H}_2\text{O})_2]$ metal chelates shows broad bands at 15878 and 22998 cm^{-1} due to the ${}^2\text{T}_g \rightarrow {}^2\text{T}_g$ transition and charge transfer, respectively, suggesting a distorted octahedral structure for the $[\text{CuL}(\text{H}_2\text{O})_2]$ chelates which is further confirmed by the higher value of μ_{eff} of the $[\text{CuL}(\text{H}_2\text{O})_2]$ chelat. The $[\text{NiL}(\text{H}_2\text{O})_2]$ and $[\text{CoL}(\text{H}_2\text{O})_2]$ chelates gave two absorption bands respectively, at $15623, 22473$ and $16524, 22220\text{ cm}^{-1}$ corresponding to ${}^4\text{T}_{1g} \rightarrow {}^2\text{T}_{1g}$ and ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}(\text{P})$ transitions. Thus, absorption bands of the diffuse, reflectance spectra and the values of the magnetic moments (μ_{eff}) indicate an octahedral configuration for the $[\text{NiL}(\text{H}_2\text{O})_2]$ and $[\text{CoL}(\text{H}_2\text{O})_2]$ chelates. The spectra of $[\text{MnL}(\text{H}_2\text{O})_2]$ shows weak bands at $14666, 19752$ and 25571 cm^{-1} assigned to the transitions ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{1g}$ (4G), ${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}$ (4G) and ${}^6\text{A}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}$, respectively suggesting an octahedral structure for the $[\text{MnL}(\text{H}_2\text{O})_2]$ chelate. As the spectrum of the $[\text{ZnL}(\text{H}_2\text{O})_2]$ polymer is not well resolved, it is not interpreted but its μ_{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 chelats of HL

Compound	Empirical Formula	Formula Weight Gm/mole	Yield (%)	Elemental Analysis % Found/(Calcd.)				μ_{eff} BM
				C	H	N	M	
HL	$\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2$	463	72	72.48 (72.57)	5.37 (5.39)	15.07 (15.11)	-	-
$[\text{CuL}_2(\text{H}_2\text{O})_2]$	$[\text{C}_{28}\text{H}_{24}\text{N}_5\text{O}_3]_2\text{Cu}$	1019.54	83	32.89 (32.95)	2.33 (2.35)	6.81 (6.86)	6.22 (6.23)	1.98
$[\text{CoL}_2(\text{H}_2\text{O})_2]$	$[\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2]_2\text{Co}$	1014.93	89	33.06 (33.10)	2.32 (2.35)	6.87 (6.89)	5.77 (5.80)	4.65
$[\text{NiL}_2(\text{H}_2\text{O})_2]$	$[\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2]_2\text{Ni}$	1014.69	79	33.03 (33.11)	2.30 (2.36)	6.86 (6.89)	5.74 (5.78)	3.11
$[\text{MnL}_2(\text{H}_2\text{O})_2]$	$[\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2]_2\text{Mn}$	1010.93	86	33.22 (33.23)	2.31 (2.37)	6.88 (6.92)	5.41 (5.43)	5.11
$[\text{ZnL}(\text{H}_2\text{O})_2]$	$[\text{C}_{28}\text{H}_{25}\text{N}_5\text{O}_2]_2\text{Zn}$	1021.39	88	32.82 (32.89)	2.33 (2.34)	6.79 (6.85)	6.34 (6.40)	D

Table-2 : Antifungal activity of compounds

Compounds	Zone of inhibition at 1000 ppm(%)		
	Fungus		
	Penicillium Expansum	Botrydepladia Thiobromine	Nigrospora Sp.
HL	71	65	63
$[\text{CuI}(\text{H}_2\text{O})_2]$	82	91	96
$[\text{CoI}(\text{H}_2\text{O})_2]$	76	69	74
$[\text{NiI}(\text{H}_2\text{O})_2]$	73	76	68
$[\text{MnI}(\text{H}_2\text{O})_2]$	77	61	72
$[\text{ZnI}(\text{H}_2\text{O})_2]$	68	65	69

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