

## **STUDIES ON NOVEL HETEROCYCLIC COMPOUNDS HAVING METAL CHELATING GROUP**

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### **ABSTRACT**

Biginelli Reaction between 5-formyl-8-hydroxyquinolinol (FHQ), urea and methyl aceto acetate in the presence of acid was gave methyl 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (PYHQ), which was then react with aniline yield 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (PYAHQ). The novel ligand characterized by elemental analysis and spectral studies. The transition metal chelates viz.  $\text{Cu}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Mn}^{2+}$  and  $\text{Zn}^{2+}$  of PYAHQ were prepared and characterized by metal-ligand (M:L) ratio, IR and reflectance spectroscopies and magnetic properties. The antifungal activity of PYAHQ and its metal chelates was screened against various fungi. The results showed that all these samples were good antifungal agents.

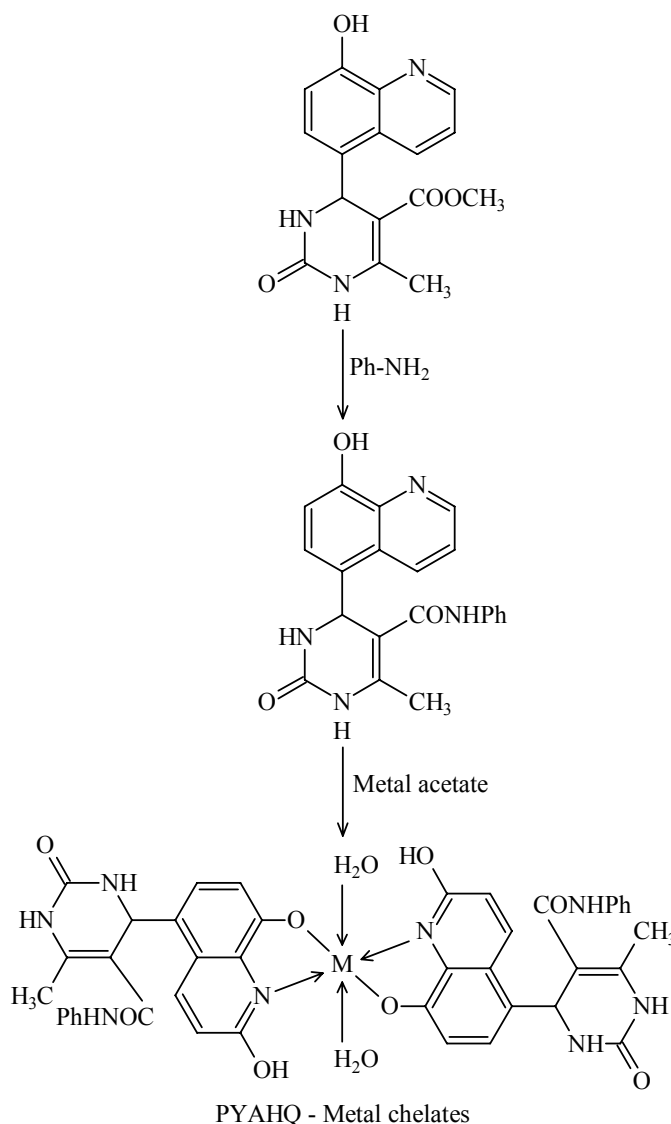
**Key words:** Biginelli reaction, 5-Formyl-8-hydroxy quinolinol, Pyrimidine derivative, Magnetic moment, Antifungal properties.

### **INTRODUCTION**

8-Hydroxyquinoline, a well-known complexing agent able to chelate a wide number of metal ions. 8-Hydroxyquinoline is well known as an analytical reagent<sup>1-4</sup>. Several 8-quinolinol derivatives are also reported for dyeing of textiles<sup>5</sup>. One of the derivative say 5-formyl-8-hydroxyquinolinol (FHQ) can be synthesized easily and studied extensively for number of derivatives. Some of the ions exchanging resins are also reported with good potentiality<sup>6,7</sup>. Heterocyclic compounds are essential for life. Pyrimidine has played a vital role in the manufacture of various biologically active drugs as antimicrobial, calcium channel blockers, antitubercular, antibacterial, anti-inflammatory<sup>8-16</sup>. The reaction of pyrimidine derivatives with HQ has not been reported so far. Hence, such type of heterocyclic ring and 8-HQ into one molecule may afford good biological active compound. The present communications discuss about syntheses, characterization and antifungal properties of 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (PYAHQ) (**Scheme 1**).

### **EXPERIMENTAL**

5-formyl-8-hydroxyquinolinol (FHQ) was prepared according to method reported in literature<sup>17</sup>. All chemicals used were of laboratory grade.



Where M:  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Zn}^{2+}$

**Scheme 1**

### Synthesis of methyl 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PYHQ)

A mixture of urea (0.01 mol), 5-formyl-8-hydroxyquinolinol (0.01 mol) and methyl aceto acetate (0.01 mol) in absolute alcohol (20 mL) containing 35% HCl (8 drops) was refluxed for 6-7 hours, the reaction solution allowed to cool. The resulting precipitate was filtered off and washed with 50 % ethanol, dried, recrystallized from ethanol to afford methyl 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PYHQ).

Yield: 73%. m.p. 213-215°C. IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3650 (OH), 3352 (NH), 1675, 1640 (C=O), 2980 ( $\text{CH}_2$ ), 2850, 1630, 1575, 1500, 1470 (aromatic), 1640, 1575, 1475, and 755 (8-quinolinol).  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  (ppm): 2.28 (s, 3 H,  $\text{CH}_3$ , pyrimidine), 3.84 (s, 3 H,  $\text{COCH}_3$ ), 5.21 (s, 1H, pyrimidine), 8.92-7.12 (m, 5 H, Ar-H), 9.60, 9.70 (2 H, 2 NH,  $\text{D}_2\text{O}$  exchangeable), 5.27 (s, 1 H, OH). Anal. Calcd. for  $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_4$  (313): C, 61.34; H, 4.83; N, 13.41%. Found: C, 61.32; H, 4.80; N, 13.40%.

### Synthesis of 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamide(PYAHQ)

In a round bottom flask, the mixture of 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (0.1 mole) and aniline (0.1 mole) was heated under reflux for 6 hrs. Subsequently ethyl alcohol was distilled off and the solid mass obtained. The solid designated as PYAHQ was isolated and dried in air. Yield was 67%. It's m.p. was 186-188°C (uncorrected).

#### Analysis

		C (%)	H (%)	N (%)
Elemental analysis	Calculated	67.37	4.85	14.96
C <sub>21</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> (374)	Found	67.36	4.83	14.93

IR Spectral Features (cm<sup>-1</sup>): 3650 (OH), 3352-3325 (NH), 1640 (C=O), 2980 (CH<sub>2</sub>), 2850, 1630, 1575, 1500, 1470 (aromatic), 1640, 1575, 1475, and 755 (8-quinolinol).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ (ppm): 2.28 (s, 3 H, CH<sub>3</sub>, pyrimidine), 5.21 (s, 1 H, pyrimidine), 8.92-7.08 (m, 10 H, Ar-H), 10.32, 9.60, 9.70 (2 H, 2 NH, D<sub>2</sub>O exchangeable), 5.27 (s, 1 H, OH).

#### Synthesis of metal chelates of PYAHQ

The metal chelates of PYAHQ with Cu<sup>2+</sup>, Co<sup>2+</sup>, Zn<sup>2+</sup>, Mn<sup>2+</sup> and Ni<sup>2+</sup> metal ions were prepared in two steps. All the metal chelates were prepared in an identical procedure.

#### Preparation of PYAHQ solution

PYAHQ (0.05 mol) was taken in 500 mL beaker and formic acid (85% v/v) was added up to slurry formation. To this slurry water was added till the complete dissolution of PODMHQ. It was diluted to 100 mL.

#### Synthesis of PYAHQ -metal-chelates

In a solution of metal acetate (0.005 mol) in acetone: water (50:50 v/v) mixture (40 mL) the 20 mL of above mentioned PYAHQ solution (i.e. containing 0.01 M PYAHQ) was added with vigorous stirring at room temperature. The appropriate pH was adjusted by addition of sodium acetate for complete precipitation of metal chelate. The precipitates were digested on a boiling water bath. The precipitates of chelate were filtered off, washed by water and air-dried.

**Table 1: Analysis of PYAHQ ligand and its metal chelates**

Empirical formula	Mol. wt. g/mole	Yield (%)	Elemental analysis							
			C (%)		H (%)		N (%)		M (%)	
			Cald	Found	Cald	Found	Cald	Found	Cald	Found
C <sub>21</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub>	374	67	67.37	67.36	4.85	4.83	14.96	14.93	-	-
C <sub>42</sub> H <sub>34</sub> N <sub>8</sub> O <sub>6</sub> Cu <sup>2+</sup> 2 H <sub>2</sub> O	845.54	72	59.61	59.59	4.49	4.47	13.25	13.24	7.51	7.49
C <sub>42</sub> H <sub>34</sub> N <sub>8</sub> O <sub>6</sub> Co <sup>2+</sup> 2 H <sub>2</sub> O	840.94	68	59.93	59.91	4.52	4.50	13.32	13.30	7.01	6.99
C <sub>42</sub> H <sub>34</sub> N <sub>8</sub> O <sub>6</sub> Ni <sup>2+</sup> 2 H <sub>2</sub> O	840.71	70	59.95	59.94	4.52	4.51	13.32	13.32	6.98	6.96
C <sub>42</sub> H <sub>34</sub> N <sub>8</sub> O <sub>6</sub> Mn <sup>2+</sup> 2 H <sub>2</sub> O	836.94	73	60.22	60.20	4.54	4.51	13.38	13.36	6.56	6.53
C <sub>42</sub> H <sub>34</sub> N <sub>8</sub> O <sub>6</sub> Zn <sup>2+</sup> 2 H <sub>2</sub> O	847.38	66	59.48	59.46	4.48	4.46	13.22	13.21	7.72	7.70

## RESULTS AND DISCUSSION

The elemental contents were determined by Thermo Finigen Flash 1101 EA (Italy) the metals were determined volumetrically by Vogel's method<sup>18</sup>. To a 100 mg chelate sample, each 1 mL of HCl, H<sub>2</sub>SO<sub>4</sub> and HClO<sub>4</sub> were added and then 1 g of NaClO<sub>4</sub> was added. The mixture was evaporated to dryness and the resulting salt was dissolved in double distilled water and diluted to the mark. From this solution, the metal content was determined by titration with standard EDTA solution. Infrared spectra of the synthesized compounds were recorded on Nicolet 760 FT-IR spectrometer. NMR spectrum of PYAHQ was recorded on 60 MHz NMR spectrophotometer. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. Mercury tetrathiocyanatocobalate (II) Hg[Co(NCS)<sub>4</sub>] was used as a calibrant. The electronic spectra of complexes in solid were recorded on at room temperature. MgO was used as reference. Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature<sup>19</sup>.

The synthesis of 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide was performed by a simple reaction of aniline with methyl 4-(8-hydroxyquinolin-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PYHQ), which was prepared by Biginelli Reaction between 5-formyl-8-hydroxyquinolinol (FHQ), Urea and methyl aceto acetate. The resulted PYAHQ ligand was an amorphous brown powder. The C, H, N contents of PYAHQ (Table 1) are consistent with the structure predicted (**Scheme 1**). The IR spectrum of PYAHQ comprises the important bands due to 8-quinolinol. The bands were observed at 1640, 1575, 1475, and 755 cm<sup>-1</sup>.

**Table 2: Spectral features and magnetic moment of PYAHQ metal chelates**

Metal chelates	$\mu_{\text{eff}}$ (BM)	Electronic spectral data (cm <sup>-1</sup> )	Transition
PODMHQ-Cu <sup>2+</sup>	2.55	23454 13216	Charge transfer ${}^2B_{1g} \rightarrow {}^2A_{1g}$
PODMHQ-Ni <sup>2+</sup>	3.71	22599 15373	${}^3A_{1g} \rightarrow {}^3T_{1g}(P)$ ${}^3A_{1g} \rightarrow {}^3T_{1g}(F)$
PODMHQ-Co <sup>2+</sup>	4.77	23736 19106 8927	${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}$ ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$
PODMHQ-Mn <sup>2+</sup>	5.54	23236 19037 16843	${}^6A_{1g} \rightarrow {}^6A_{2g} {}^4E_g$ ${}^6A_{1g} \rightarrow {}^4T_{2g}(4G)$ ${}^6A_{1g} \rightarrow {}^4T_{1g}(PG)$
PODMHQ-Zn <sup>2+</sup>	Diamag.		-----

The broad band due to -OH group appeared at 3650 cm<sup>-1</sup>. In this band, the inflections are observed at 2970, 2930 and 2850 cm<sup>-1</sup>. While the latter two might be attributed to asymmetric and symmetric vibration of CH<sub>2</sub> of AHQ. The NMR spectrum of PYAHQ in DMSO indicates that the singlet of 3 H at 2.28 for CH<sub>3</sub> and 5.21 CH of pyrimidine. While the singlet at 5.27  $\delta$  ppm due to -OH group. The aromatic protons are appeared in multiplicity at 8.92-7.08  $\delta$ . Thus the structure of PYAHQ is confirmed as shown in Scheme 1.

The metal and C, H, N contents of metal chelates of PYAHQ (Table 1) are also consistent with the predicted structure. The results show that the metal: ligand (M:L) ratio for all divalent metal chelate is 1:2.

**Table 3: Antifungal activity of pyahqligand and its metal chelates**

Sample	Zone of inhibition of fungus at 1000 ppm (%)			
	<i>Asperginus niger</i>	<i>Botrydeplaia thiobromine</i>	<i>Nigrospora Sp.</i>	<i>Rhisopus Nigricans</i>
PODMHQ	53	68	61	64
PODMHQ-Cu <sup>2+</sup>	75	83	82	78
PODMHQ-Zn <sup>2+</sup>	64	81	81	82
PODMHQ-Ni <sup>2+</sup>	74	80	69	76
PODMHQ-Co <sup>2+</sup>	75	82	74	73
PODMHQ-Mn <sup>2+</sup>	69	79	78	72

The infrared spectra of all the chelates are identical and suggest the formation of all the metalocyclic compound by the absence of band characteristic of free -OH group of parent PYAHQ. The other bands are almost at their respectable positions as appeared in the spectrum of parent-PYAHQ ligand. However, the band due to (M-O) band could not be detected as it may appeared below the range of instrument used. The important IR Spectral data are shown in Table 2.

Magnetic moments of metal chelates are given in Table 2. The diffuse electronic spectrum of Cu<sup>2+</sup> chelates shows two broad bands around 13216 and 23454 cm<sup>-1</sup>. The first band may be due to a <sup>2</sup>B<sub>1g</sub> → <sup>1</sup>A<sub>1g</sub> transition. While the second band may be due to charge transfer. The first band shows structures suggesting a distorted octahedral structure for the Cu<sup>2+</sup> metal chelates. The higher value of the magnetic moment of the Cu<sup>2+</sup> chelate supports the same. The Co<sup>2+</sup> metal chelate gives rise to two absorption bands at 23735 and 19105 cm<sup>-1</sup>, which can be assigned <sup>4</sup>T<sub>1g</sub> → <sup>2</sup>T<sub>2g</sub>, <sup>4</sup>T<sub>1g</sub> → <sup>4</sup>T<sub>1g</sub>(P) transitions, respectively. These absorption bands and the μ<sub>eff</sub> value indicate an octahedral configuration of the Co<sup>2+</sup> metal chelate<sup>14</sup>. The spectrum of Mn<sup>2+</sup> polymeric chelate comprised two bands at 19037 cm<sup>-1</sup> and 23236 cm<sup>-1</sup>. The latter does not have a very long tail. These bands may be assigned to <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>T<sub>2g(G)</sub> and <sup>6</sup>A<sub>1g</sub> → <sup>4</sup>A<sub>2g(G)</sub> transitions, respectively. The high intensity of the bands suggests that they may have some charge transfer character. The magnetic moment is found to be lower than normal range. In the absence of low temperature measurement of magnetic moment it is difficult to attach any significance to this. As the spectrum of the metal chelate of Ni<sup>2+</sup> show two distinct bands at 22599 and 15373 cm<sup>-1</sup> are assigned as <sup>3</sup>A<sub>2g(F)</sub> → <sup>3</sup>T<sub>1g(F)</sub> and <sup>3</sup>A<sub>2g(F)</sub> → <sup>3</sup>T<sub>1g(F)</sub> transition, respectively suggested the octahedral environment for Ni<sup>2+</sup> ion. The observed μ<sub>eff</sub> values in the range 2.55-5.54 B.M. are consistent with the above moiety<sup>20</sup>.

## CONCLUSION

The structure of synthesized compounds were confirmed by elemental, IR and NMR analysis, while magnetic susceptibility and electronic spectra suggest the octahedral geometry for all metal chelate except Zn<sup>2+</sup>, which is diamagnetic in nature. The examination of antifungal activity of PYAHQ ligand and its all chelates (Table 3) reveals that the ligand is moderately toxic against fungi, while all the chelates are more toxic than ligand. Among all the chelates the Cu<sup>2+</sup> chelate is more toxic against fungi.

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