



Research Article

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## Synthesis and antifungal activity of novel metal chelates based on 8-hydroxyquinoline and piperazine ring

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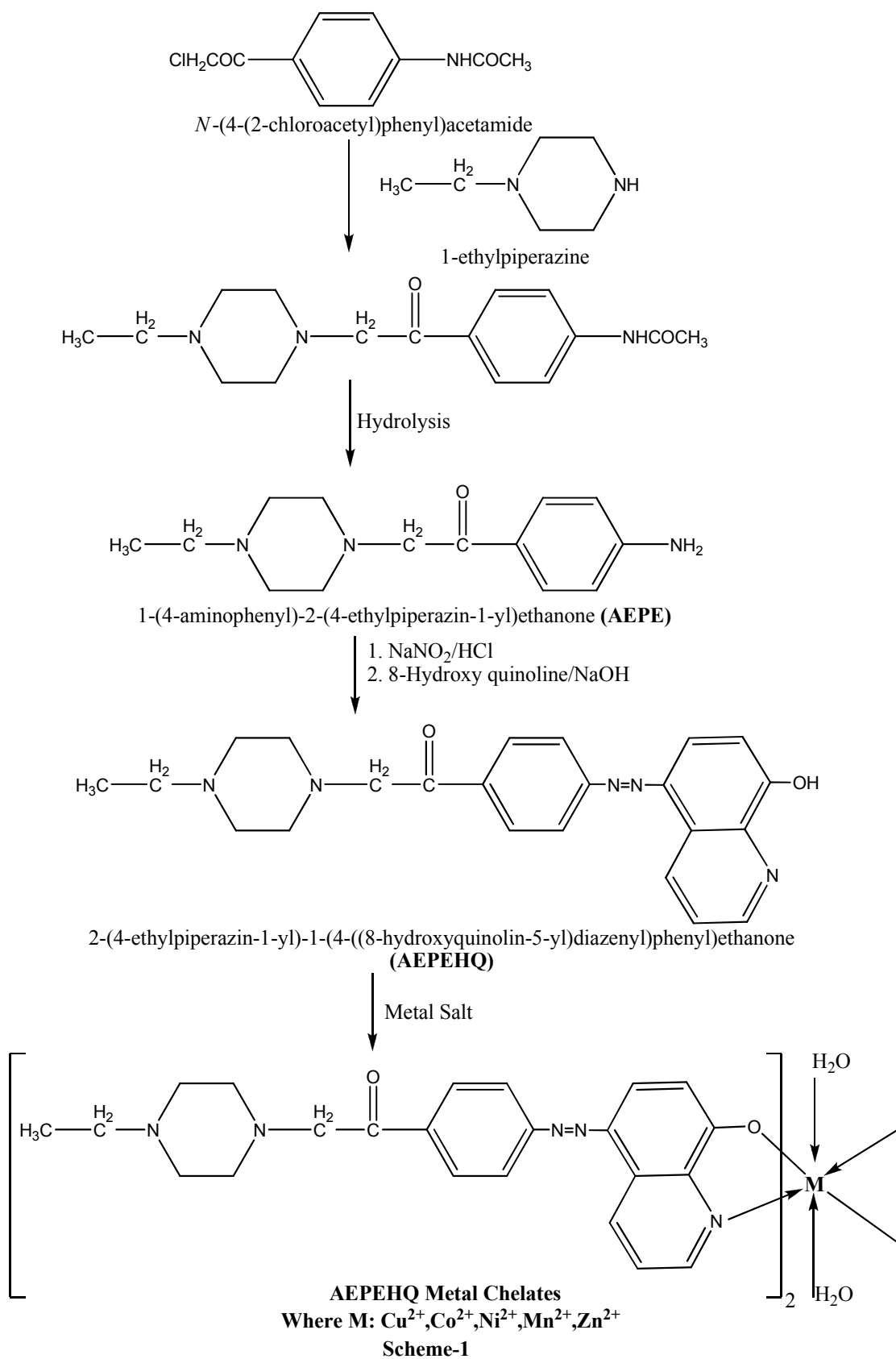
### ABSTRACT

1-(4-((8-hydroxyquinolin-5-yl)diazenyl)phenyl)-2-(4-ethylpiperazin-1-yl)ethanone (AEPEHQ) was synthesized by diazotization reaction of 8-hydroxyquinolinol (HQ) and 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone (AEPE), which was characterized by elemental analysis and spectral studies. The transition metal chelates Cu<sup>(II)</sup>, Ni<sup>(II)</sup>, Co<sup>(II)</sup>, Mn<sup>(II)</sup> and Zn<sup>(II)</sup> of AEPEHQ were prepared and characterized by metal-ligand (M:L) ratio, IR, reflectance spectroscopies and magnetic properties. The antifungal activity of AEPEHQ and its metal chelates was screened against various fungi. The results show that all these samples show good antifungal agents.

**Keywords:** 2-(4-ethyl piperazin-1-yl)-1-(4-((8-hydroxy quinolin-5-yl)diazenyl) phenyl)ethanone, 8-hydroxy quinolinol, Spectroscopies study, Magnetic moment and Antifungal properties.

### INTRODUCTION

In recent years, the research on synthesis and study of metal-containing compounds is become an interesting field of chemistry [1]. Organic ligands and their metal complexes played an important role in the development of coordination chemistry, they shows a wide range of applications like, physicochemical as well as biochemically [2-4]. 8-Hydroxyquinoline is well known as an analytical reagent [5,6]. It's various derivatives [7] are also useful in pharmaceuticals. Several azo dyes based on 8-quinolinol are also reported for dyeing of textiles as well as their chelating properties [8,9]. One of the derivative say 5-amino-8- hydroxyquinolinol (AHQ) can be synthesize easily and studied extensively for number of derivatives [10]. Some of the ions exchanging resins are also reported with good potentiality [11-15]. The reaction of these diazo derivatives containing piprazin ring with HQ has not been reported previously. Hence, in continuous of our previous work [16], such type of diazo derivative and 8-HQ into one molecule may afford good biological active compound. The present paper discuss about synthesizes, characterization and antifungal activity of 2-(4-ethylpiperazin-1-yl)-1-(4-((8-hydroxyquinolin-5-yl)diazenyl)phenyl) ethanone (AEPEHQ) (Scheme-1).



## EXPERIMENTAL SECTION

The precursor 8-hydroxyquinoline (**HQ**) was prepared by reported method [17,18]. The 4-chloro acetamido phenacyl chloride (**APC**) was prepared by reported method [19]. All other chemicals used were of laboratory grade.

**Synthesis of 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone (AEPE):**

This was prepared by following method. The solution of 4-chloro acetamido phenacyl chloride (**APC**) (0.1 mole) in acetone was treated with 1-ethylpiperazine (0.1 mole) in acetone at room temperature. The resultant product was filtered and hydrolyzed by 50:50 HCl: Ethanol mixture gives 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone (**AEPE**).

**Synthesis of 2-(4-ethylpiperazin-1-yl)-1-(4-((8-hydroxyquinolin-5-yl)diazanyl)phenyl) ethanone (AEPEHQ):**

A solution of sodium nitrite (0.01) is added dropwise to a stirred and cold solution of 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone (**AEPE**) (0.01mole) in a mixture of con. HCl and water. The reaction mixture is kept in ice-bath. These diazonium salts poured with stirring into a cold solution of 8-Hydroxy quinoline (0.01mole) in sodium hydroxide solution. The reaction mixture was kept in ice-bath for 30minutes. The separated product are known as 2-(4-ethylpiperazin-1-yl)-1-(4-((8-hydroxyquinolin-5-yl)diazanyl)phenyl)ethanone (**AEPEHQ**) filtered, wash and crystallized from ethanol. Yield was 74%. It's m.p. was 233-235°C (uncorrected).

**Analysis:**

		C%	H%	N%
Elemental Analysis	Calculated:	68.47	6.25	17.36
C <sub>23</sub> H <sub>25</sub> N <sub>5</sub> O <sub>2</sub> (403)	Found :	68.4	6.2	17.3

**IR Spectral Features (cm<sup>-1</sup>):** 3635(OH), 3417 (NH), 2972 (CH<sub>2</sub>), 1721 (CO), 2839, 1632, 1466 (aromatic), 1631, 1572, 1479 and 758 (8-Hydroxyquinoline)

**NMR Signals:** δ ppm 8.12-8.25 (m, 4H Ar-H), 6.95-8.87 (m, 5H, Quinoline), 5.51 (s, 1H, OH), 3.70 (s, 2H, N-CH<sub>2</sub>), 2.69 (s, 2H, N-CH<sub>2</sub>-CH<sub>3</sub>), 2.40-2.65 (t, 8H, CH<sub>2</sub>), 1.82 (s, 3H, -CH<sub>3</sub>)

**Synthesis of metal chelates of AEPEHQ:**

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

**Preparation of AEPEHQ solution:**

AEPEHQ (0.01 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 AEPEHQ. It was diluted to 100 ml.

Table-1: ANALYSIS OF AEPEHQ LIGAND AND ITS METAL CHELATES

Empirical Formula	Mol. Wt gm/mole	Yield (%)	Elemental Analysis							
			C%		H%		N%		M%	
			Cald	Found	Cald	Found	Cald	Found	Cald	Found
C <sub>23</sub> H <sub>25</sub> N <sub>5</sub> O <sub>2</sub>	403	74	68.47	68.4	6.25	6.2	17.36	17.3	-	-
C <sub>46</sub> H <sub>48</sub> N <sub>10</sub> O <sub>4</sub> Cu <sup>(II)</sup> 2H <sub>2</sub> O	904.51	65	61.08	61.0	5.79	5.7	15.49	15.4	7.03	7.0
C <sub>46</sub> H <sub>48</sub> N <sub>10</sub> O <sub>4</sub> Co <sup>(II)</sup> 2H <sub>2</sub> O	899.90	68	61.39	61.3	5.82	5.7	15.56	15.5	6.55	6.5
C <sub>46</sub> H <sub>48</sub> N <sub>10</sub> O <sub>4</sub> Ni <sup>(II)</sup> 2H <sub>2</sub> O	899.66	69	61.41	61.3	5.83	5.8	15.57	15.5	6.52	6.4
C <sub>46</sub> H <sub>48</sub> N <sub>10</sub> O <sub>4</sub> Mn <sup>(II)</sup> 2H <sub>2</sub> O	895.91	71	61.67	61.6	5.85	5.8	15.63	15.5	6.13	6.1
C <sub>46</sub> H <sub>48</sub> N <sub>10</sub> O <sub>4</sub> Zn <sup>(II)</sup> 2H <sub>2</sub> O	906.38	67	60.96	60.9	5.78	5.7	15.45	15.4	7.22	7.2

**Synthesis of AEPEHQ-metal-chelates:**

In a solution of metal acetate (0.001 mol) in acetone: water (50:50 v/v) mixture (40 ml) the 20 ml of above mentioned AEPEHQ solution (i.e. containing 0.01 M AEPEHQ) 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.

**MEASUREMENTS:**

The elemental contents were determined by Thermo Finigen Flash1101 EA (Italy) the metals were determined volumetrically by Vogel's method [20]. 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 AEPEHQ was recorded on 60 MHz NMR spectrophotometer. Magnetic susceptibility measurement of the synthesized complexes was carried out on Gouy Balance at room temperature. Mercury tetrathiocyanatocobaltate (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 [21].

**RESULTS AND DISCUSSION**

The synthesis of 2-(4-ethylpiperazin-1-yl)-1-(4-((8-hydroxyquinolin-5-yl)diazanyl)phenyl)ethanone (**AEPEHQ**) was performed by a simple diazotization reaction of 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone (**AEPE**) and 8-hydroxyquinolinol (**HQ**). The resulted AEPEHQ ligand was an amorphous yellow powder. The C,H,N contents of AEPEHQ (**Table-1**) are consistent with the structure predicted (**Scheme-1**). The IR spectrum of AEPEHQ comprises the important bands due to 8-quinolinol. The bands were observed at 1631, 1572, 1479, and 758 cm<sup>-1</sup>.

The broad band due to -OH group appeared at 3635 cm<sup>-1</sup>. In this band the inflections are observed at 2972, 2984 and 2839 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 AEPEHQ in DMSO indicates that the singlet of 2H at 3.70 and 2.69 for N-CH<sub>2</sub> and N-CH<sub>2</sub>-CH<sub>3</sub> group respectively. While the singlet at 5.51 δ ppm due to -OH group. The aromatic protons are appeared in multiplicity at 8.12-8.25 δ. Also the quinoline protons found in the range 6.95-8.87 δ. The vigorous oxidations of AEPEHQ yield 8-hydroxy quinoline-5-carboxylic acid m.p. 215°C. Thus the structure of AEPEHQ is confirmed as shown in **Scheme-1**.

**TABLE-2: SPECTRAL FEATURUES AND MAGNETIC MOMENT OF AEPEHQ METAL CHELATES**

Metal Chelates	$\mu_{\text{eff}}$ (BM)	Electronic spectral data (cm <sup>-1</sup> )	Transition
AEPEHQ-Cu(II)	2.53	23450 13212	Charge transfer <sup>2</sup> B <sub>1g</sub> → <sup>2</sup> A <sub>1g</sub>
AEPEHQ-Ni(II)	3.71	22595 15369	<sup>3</sup> A <sub>1g</sub> → <sup>3</sup> T <sub>1g</sub> (P) <sup>3</sup> A <sub>1g</sub> → <sup>3</sup> T <sub>1g</sub> (F)
AEPEHQ-Co(II)	4.77	23732 19103 8922	<sup>4</sup> T <sub>1g</sub> (F) → <sup>4</sup> T <sub>2g</sub> (F) <sup>4</sup> T <sub>1g</sub> (F) → <sup>4</sup> T <sub>2g</sub> (P) <sup>4</sup> T <sub>1g</sub> (F) → <sup>4</sup> T <sub>2g</sub> (P)
AEPEHQ-Mn(II)	5.56	23234 19032 16840	<sup>6</sup> A <sub>1g</sub> → <sup>6</sup> A <sub>2g</sub> <sup>4</sup> E <sub>g</sub> <sup>6</sup> A <sub>1g</sub> → <sup>4</sup> T <sub>2g</sub> (4G) <sup>6</sup> A <sub>1g</sub> → <sup>4</sup> T <sub>1g</sub> (PG)
AEPEHQ-Zn(II)	Diamag.		-----

The metal and C,H,N contents of metal chelates of AEPEHQ (**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 AEPEHQ LIGAND AND ITS METAL CHELATES**

Sample	Zone of inhibition of fungus at 1000 ppm (%)			
	<i>Asperginus niger</i>	<i>Botrydeplaia thiobromine</i>	<i>Vigrospora Sp.</i>	<i>Rhisopus Nigricans</i>
AEPEHQ	55	71	66	66
AEPEHQ-Cu(II)	77	86	87	80
AEPEHQ-Zn(II)	66	84	86	84
AEPEHQ-Ni(II)	76	83	74	78
AEPEHQ-Co(II)	77	85	79	75
AEPEHQ-Mn(II)	71	82	83	74

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 AEPEHQ. The other bands are almost at their respectable positions as appeared in the spectrum of parent-AEPEHQ ligand. However, the band due to (M-O) band could not be detected as it may appear 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>(II)</sup> chelates shows two broad bands around 13212 and 23450 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>(II)</sup> metal chelates. The higher value of the magnetic moment of the Cu<sup>(II)</sup> chelate supports the same [23]. The Co<sup>(II)</sup> metal chelate gives rise to two absorption bands at 23732 and 19103cm<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>(II)</sup> metal chelate [24]. The spectrum of Mn<sup>(II)</sup> polymeric chelate comprised two bands at 19032cm<sup>-1</sup> and 23234 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>(II)</sup> show two distinct bands at 15369 and 22595 cm<sup>-1</sup> are assigned as <sup>3</sup>A<sub>1g</sub> → <sup>3</sup>T<sub>1g</sub>(F) and <sup>3</sup>A<sub>1g</sub> → <sup>3</sup>T<sub>1g</sub>(P) transition, respectively suggested the octahedral environment for Ni<sup>(II)</sup> ion. The observed μ<sub>eff</sub> values in the range 2.53-5.56 B.M are consistent with the above moiety [25].

The examination of antifungal activity of AEPEHQ 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>(II)</sup> chelate is more toxic against fungi.

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