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Synthesis, spectro-analytical, computational and biological studies of novel 6-methyl-3-(1-(4-oxo-2-phenylquinazolin-3(4H)-ylimino) ethyl)-2H-pyran-2, 4(3H)-dione and its Co (II), Cu (II) and Hg (II) metal complexes

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Abstract: *A novel 6-methyl-3-(1-(4-oxo-2-phenylquinazolin-3(4H)-ylimino) ethyl)-2H-pyran-2, 4(3H)-dione (MOPQIEP) was prepared and characterized on the basis of Mass, IR, UV-Vis and ^{1}H-NMR spectral data. The solid metal complexes of the title compound were synthesized with chlorides of Co (II), Cu (II) and Hg (II) salts and characterized by Mass, IR, TGA, DTA, SEM, EDX and Magnetic Susceptibility measurements. The HyperChem.7.5 software was used for quantum chemical calculations using semi empirical method. The IR data and the energies of frontier orbitals and their corresponding contour maps of HOMO and LUMO for title compound were computed by means of single point PM3 method. ^{1}H NMR data is generated by TANDO 1 method. The IR and NMR data computed were in good agreement with the experimentally recorded values. The pKa value was computed by employing ChemAxon software. The computed pKa value and contour maps of frontier orbitals for the compound under study envisaged potential binding sites for metal ion coordination. The spectro-analytical analyses of its metal complexes, revealed oxygen of carbonyl group from quinazolinone and enol oxygen of pyran through deprotonation and 'N' from azomethine group as donor sites. Further the title compound and its metal complexes were tested for biological activity. The studies revealed more pronounced antimicrobial activity in mercury complex compared to the candidate compound, while with copper and cobalt complexes the activity is not significant. The experimental studies on super coiled plasmid PBR 322 DNA carried out with the title compound and its complexes inferred that only Cu (II) metal complex has the cleavage activity.*

Key words: *TGA - DTA, SEM, EDX and DNA cleavage studies.*

I. Introduction

Heterocyclic compounds are broadly disseminated in nature and played a vital role in life in many ways. Quinazolinones are the heterocyclic compounds showing broad spectrum of biological significance such as anticancer [1], antitumour [2], antifungal [3,4], antibacterial [5,6], antitubercular [7], antihistaminic [8], anti-inflammatory [9], anticonvulsant [10], immunotropic [11], hypolipidemic [12], antiulcer [13], analgesic [14,15] and CNS depressant [16] activities. The compound 3-acetyl-6-methyl-2H-Pyran-2, 4(3H)-dione upon complexation with transition metals exhibited numerous biological applications [17-20]. Interaction of imine bases with transition metals often increases the biological activity [21] of the imine base. In recent years there has been an enormous attention on transition metal complexes prepared from imine bases. The functional imine group (C=N) has great importance for the biological activity [22,23] of the metal complexes and has vital role in coordination chemistry. Keeping in view the importance of quinazolinones, we focused on the synthesis of 6-methyl-3-(1-(4-oxo-2-phenylquinazolin-3(4H)-ylimino) ethyl)-2H-pyran-2, 4(3H)-dione (MOPQIEP) and its metal complexes and their characterization by employing various spectro-analytical techniques. Further an attempt is made to explore the biological activity and DNA cleavage studies on the title compound and its metal complexes.

II. Materials And Methods

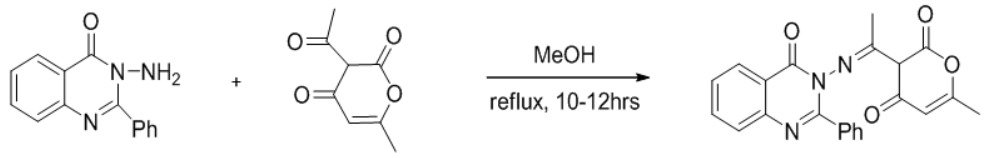
2.1 Physical Measurements

All the reagents used were of analytical grade. Polmon apparatus (Model No.MP-90) was used to determine melting point. IR spectra (KBr) of MOPQIEP and its metal complexes were recorded on a Perkin-Elmer 337 Spectrophotometer. The UV–Vis spectra were recorded in the wavelength range (200-900 nm) on Schimadzu UV Spectrophotometer. ^{1}H –NMR spectra were recorded on Bruker WH (270 MHz) instrument and the mass spectral data were obtained from Shimadzu LCMS-2010A. The Particle size and morphology of title

compound and its complexes were recorded on Zeiss Scanning Electron Microscope. Elemental analyses of the metal complexes were recorded on INCA EDX instrument. Magnetic susceptibilities were measured on a Guoy Balance (model 7550) at room temperature. Thermo- gravimetric analyses were carried out by using a Shimadzu TGA-50H in nitrogen atmosphere.

2.2 Synthesis of Ligand

To the solution of 3-amino-2-phenylquinazolin-4(3H)-one (0.66 m mol) dissolved in methanol (10ml), 3-acetyl-6-methyl-2H-Pyran-2, 4(3H)-dione (0.66 m mol) was added. The mixture was heated at 60-70 °C on magnetic stirrer for 10-12 hrs. The completion of reaction was monitored by TLC. The reaction mixture was cooled and poured in ice cold water. An yellow crystalline solid separated out upon cooling. The solid obtained was filtered, dried in vacuum and recrystallized from methanol. The compound was obtained in 81% yield with m.p 144 °C.



2.3 Synthesis of Metal Complexes

To a hot solution of the ligand MOPQIEP in chloroform, equimolar amount of metal chlorides of Co (II), Cu (II) and Hg (II) solution in methanol was added drop wise with stirring. The resulting mixture was refluxed on magnetic stirrer for 10-12 hours. The solid separated was filtered, washed thoroughly with water, hot methanol, petroleum ether and dried over calcium chloride in vacuum desiccators.

2.4 Computational Studies

The structure of the compound was built using HyperChem.7.5 software [24-26]. The final geometry was obtained with the semi-empirical PM3 method followed by optimization using the Polak-Ribiere algorithm until the root mean square gradient was 0.1 kcal/mole with 540 numbers of maximum cycles in HyperChem program. Further the IR and ^{1}H-NMR data of the compound was computed and compared with the observed values. ChemAxon tools [27] were employed to study the conformers and for the calculation of pKa values of title compound.

III. Results And Discussion

3.1 Spectral Studies

Mass, IR and NMR spectra of MOPQIEP are presented in Fig. 01, 02, 03 & 04. The mass spectrum of the MOPQIEP exhibited prominent (M+1) and (M+Na) adduct peaks at 388 and 410 m/z respectively. The IR spectrum displayed bands at 1659, 1637 and 1604 cm^{-1} corresponding to the stretching frequencies of ν (C=O). The strong bands at 1589 cm^{-1} and 1541 cm^{-1} are attributable to ν (C=N) vibrations [28]. The medium intensity peaks in the region of 1471–1373 cm^{-1} are attributable to ν (C=C) aromatic stretching vibrations. The peaks at 1159 cm^{-1}, 3061 cm^{-1} are attributed to (C-O-C) and aromatic ν (C-H) stretching vibrations. The UV spectrum showed two peaks at wavelengths 252 nm and 260 nm attributable to n→ π* (C=O) and π→ π* (C=C) transitions respectively. The ^{1}H-NMR spectrum of the title compound in $CDCl_3$ recorded a multiplet at δ 7.41(m, 4H) ppm, δ 7.83 (m, 5H) ppm corresponding to aromatic protons. The peaks appearing at δ 2.1 (s, 3H) and δ 2.4 (s, 3H) ppm are ascribed to the aliphatic protons of methyl groups. The peaks recorded at δ 5.6 (s, 1H) ppm and δ 4.6 (s, 1H) ppm corresponds to HC = C proton and active metylene CH proton of pyran ring [29-32] respectively. The ^{13}C NMR spectral data of the title compound under analysis indicates signals corresponding to aromatic carbons which appeared at δ 120-150 ppm. The signals observed at δ 20 and 32 ppm to the carbons of methyl group. The peaks at δ 208 and 182 ppm are attributed to carbonyl carbon and lactone carbon respectively. The peaks corresponding to the carbons of C=N appeared at δ161, 170 ppm and alkenyl (C = C) carbons are recorded at δ 103 and104 ppm.

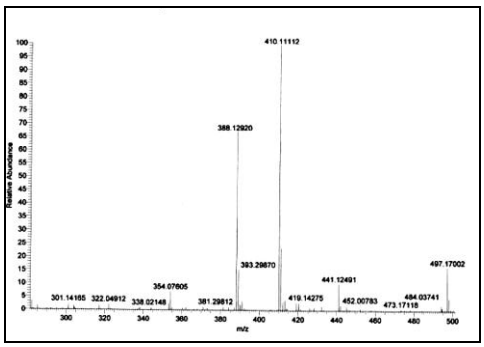


Fig.01 Mass spectrum of MOPQIEP

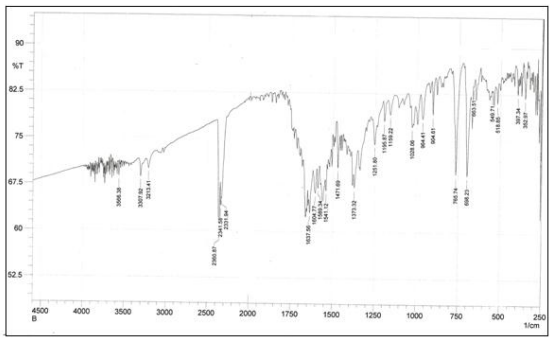


Fig.02 IR spectrum of MOPQIEP

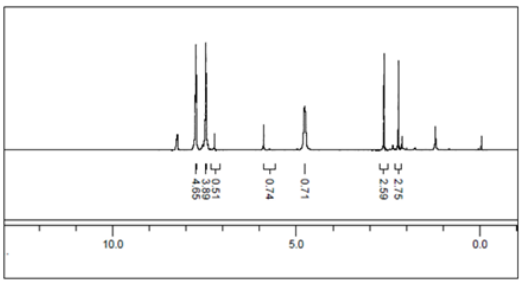


Fig. 03 [1] H NMR spectrum of MOPQIEP

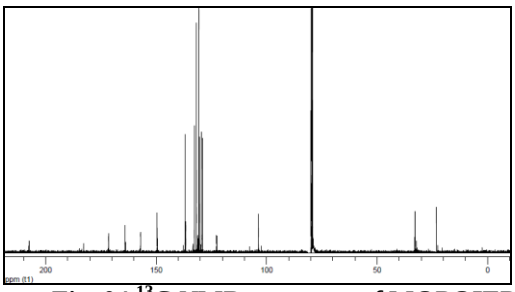


Fig. 04 [13]C NMR spectrum of MOPQIEP

In present investigation further an attempt is made to correlate the experimental spectral data with computed data [33]. For generating computed data the structure of MOPQIEP was optimized by using semi empirical single point PM3 method. Geometry optimized structure is shown in Fig.05.

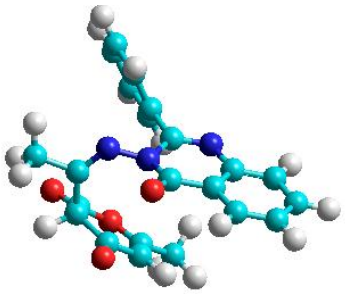


Fig.05 Geometry Optimized Structure of MOPQIEP

The computed IR and ^{1}H-NMR spectral data is compared with the experimentally recorded data (table.01).

Table.01 IR Spectrum of MOPQIEP (Experimental) / (Computed*)

Compound	**ν (cm^{-1})**						
	ν (CH) aliphatic	**ν (C=O) pyran**	**ν (C=O) Quinazolinone ring**	**ν (C=N)**		**ν (C=C) aromatic**	**ν (CH) aromatic**
				Quinazolinone ring	**imine**		
MOPQIEP	2978	1637	1604	1589	1541	1471-1373	3061
MOPQIEP*	2944-2886	1905	1874	1726	1825	1777-1817	3003-3041

The comparison of IR data reveals a good agreement of stretching frequency values with non polar covalent bonds and deviation with polar covalent and conjugated bonds. This can be attributable to the fact that polarization and resonance properties influence the force constant values of corresponding bonds. Thus the results infer that some variations in the experimental and computed values enable to understand the properties of molecules.

Table.02 ^{1}H-NMR Spectrum of MOPQIEP (Experimental) / (Computed*)

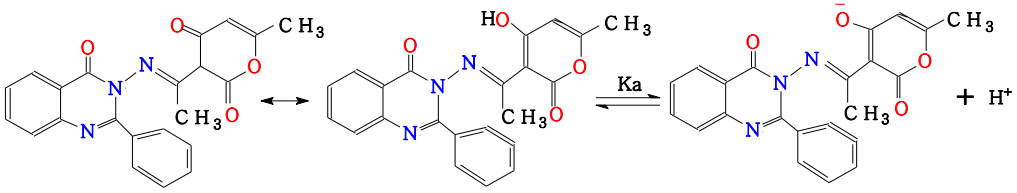
Compound	δ ($CH_{aromatic}$)		δ (HC=C)	δ (CH_3, CH_3)	δ (CH active methylene of pyran ring)
	phenyl	quinazolinone			
MOPQIEP	7.83	7.41	5.68	2.1, 2.44	4.68
MOPQIEP*	8.01	7.21	7.57	2.76, 4.29	5.62

The ^{1}H-NMR spectral data confirms the greater correlation between experimental and computed values with less variation. The variation in δ (HC=C) value is ascribable to resonance in the pyran ring (table.02).

3.2 Structural Properties

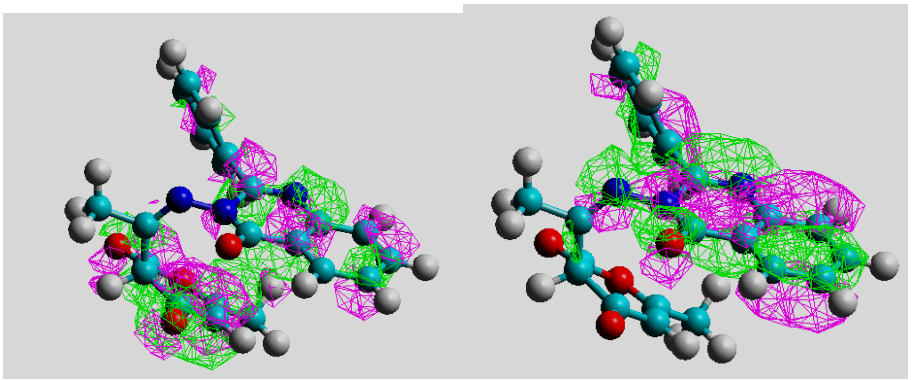
Keto–Enol Tautomerism

The structure is built and optimized employing ChemAxon Marvin sketch tools. The computational analysis indicated the possibility for enolic form of title compound and then subsequent proton dissociation of enol OH corresponding to 6.90 pKa value. The ionized form shows O, N, O^- donor sites which are potentially suitable for chelation with metal ions.



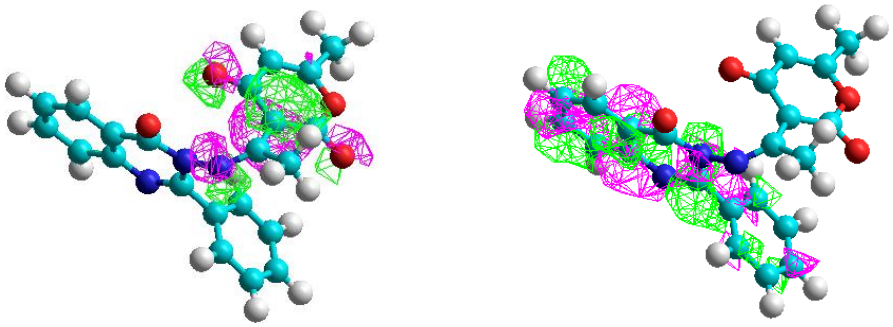
Orbital and Electrostatic Properties

As the quantum chemical calculations enable to understand donor and acceptor properties of molecules, in the present investigation the chelation properties of MOPQIEP in both molecular and ionized forms are explored. The contour maps of highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) and corresponding binding energy values were computed using semi empirical single point PM3 method (Fig. 06 & 07). From binding energy values it is evident that the ionized form with relatively lower value can readily donate electrons than neutral form of MOPQIEP. The difference in HOMO and LUMO levels is less in ionized form indicating more reactivity and ability to bind with metal ion.



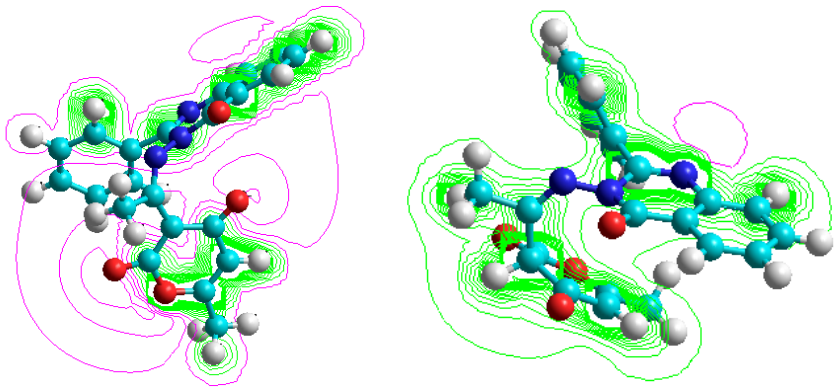
HOMO (Binding energy = 8.9858 eV) **LUMO (Binding energy = - 1.0092 eV)**

Fig.06 The contour maps of highest occupied molecular orbitals and lowest unoccupied molecular orbitals of MOPQIEP



HOMO (Binding energy = 4.89 eV) **LUMO (Binding energy = - 2.27 eV)**

Fig.07 The contour maps of highest occupied molecular orbitals and lowest unoccupied molecular orbitals of ionized form of MOPQIEP



Molecular Form **Ionized Form**

Fig.08 Contour maps of electrostatic potentials of molecular and ionic forms of MOPQIEP

The contour maps of electrostatic potentials in Fig.8 indicates the charge delocalization on to ring nitrogen in molecular form and in ionized form where the ionization has occurred through enol form resulting charge on oxygen, construe delocalization of charge to rest of the moiety.

3.3. Metal Complexes of MOPQIEP

3.3.1 Spectral Studies

The metal complexes were characterized by Mass, IR, TGA-DTA, Magnetic moment measurements, SEM and EDX data.

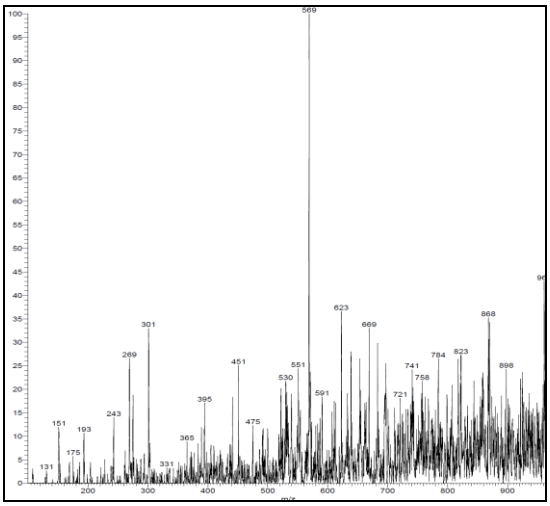


Fig.09 Mass spectrum of Cu (II)-MOPQIEP

Mass spectra provided an essential clue for the elucidation of the structure of the metal complex. The mass spectrum of Cu (II)-MOPQIEP metal complex shows a quasi ion peak at m/z 530 indicates formation of metal complex in 1:1ratio.

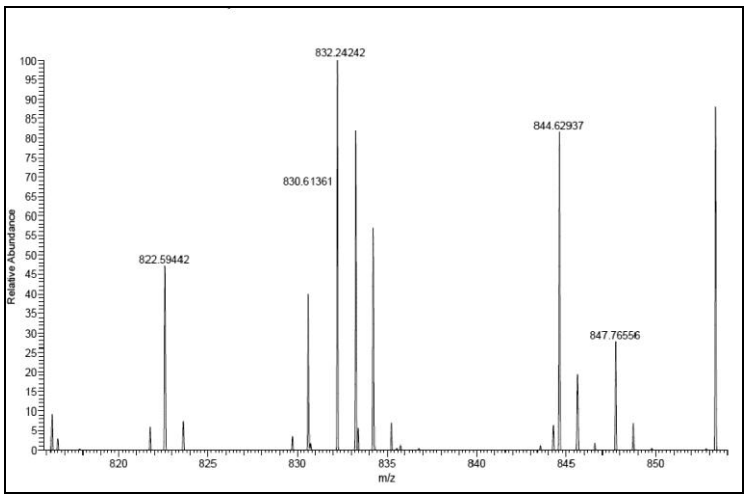


Fig.10 Mass spectrum of Co (II)-MOPQIEP

The mass spectrum of the Co (II)-MOPQIEP metal complex exhibits a dominant peak at m/z 832 which is in accordance with the expected mass. From the mass spectrum it is clear that 1:2 ratio of metal complex is formed.

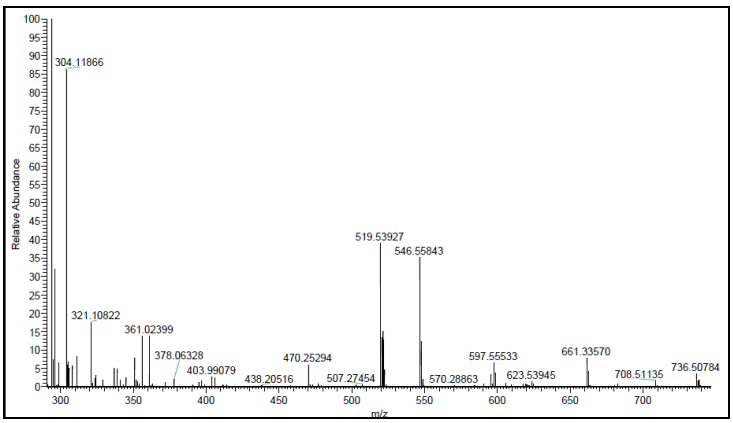


Fig.11 Mass spectrum of Hg (II)-MOPQIEP

Hg (II)-MOPQIEP metal complex shows a quasi ion peak at m/z 661 which is in accordance with the expected mass. From the mass spectrum it is clear that 1:1 ratio of metal complex is formed.

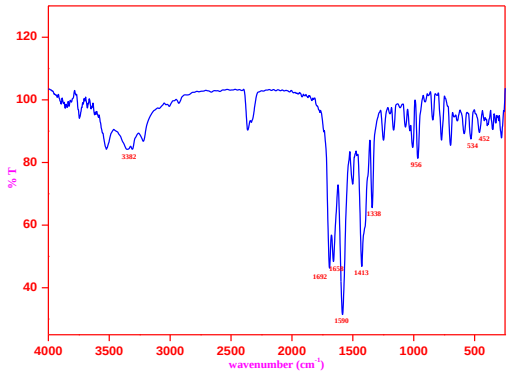


Fig.12 IR spectrum of Co (II)-MOPQIEP

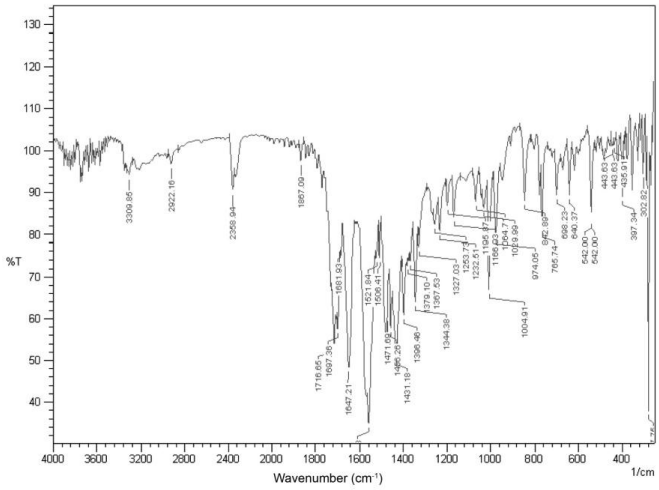


Fig. 13 IR spectrum of Cu (II)-MOPQIEP

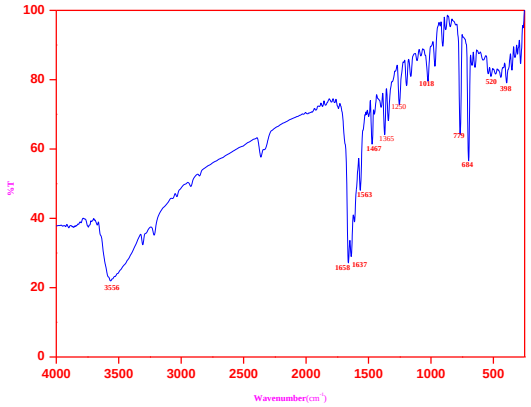


Fig. 14 IR spectrum of Hg (II)-MOPQIEP

The IR spectra of Co (II)-MOPQIEP, Cu (II)-MOPQIEP and Hg (II)-MOPQIEP complexes are presented in Figs. 12, 13 & 14. In Cu (II)-MOPQIEP, Co (II)-MOPQIEP and Hg (II)-MOPQIEP complexes a broad band around 3309 cm^{-1}, 3382 cm^{-1} and 3556 cm^{-1} indicates the presence of coordinated water. Further the existence of coordinated water is confirmed by the appearance of bending modes of water at 842 cm^{-1}, 820-779 cm^{-1} in Cu (II) and Hg (II) complexes. The stretching frequencies of pyran ν (C=O) and quinazolinone ring ν (C=O) are shifted to 1658 cm^{-1},1697 cm^{-1}in Cu (II), 1681 cm^{-1}, 1580 cm^{-1} in Co (II) and 1658 cm^{-1}, 1637 cm^{-1}in Hg (II) complexes, confirms the participation of carbonyl oxygen in bonding with the metal atom [28-31]. The azomethine ν (C=N) vibration are shifted 1647 cm^{-1}, 1550 cm^{-1} and1590 cm^{-1} in Cu (II), CO (II) and Hg (II) metal complexes respectively, indicates the involvement of azomethine-nitrogen to the metal atom [32]. In the IR spectra of all complexes new bands appeared at 442 cm^{-1}, 452 $cm^{-1}$and 398 cm^{-1} are assignable to stretching frequencies of M-N vibrations, while at 542 cm^{-1}, 534 cm^{-1}, 520 cm^{-1} to M-O vibrations [28-32]. The IR spectral data thus ascertains carbonyl oxygen of pyran ring, quinazolinone ring and azomethine-nitrogen group as the binding sites of title chelating agent.

3.3.2. Thermal Studies

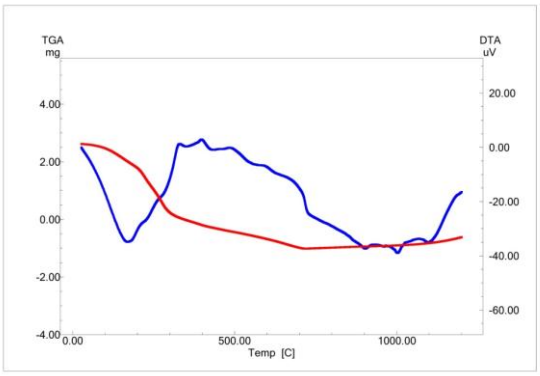


Fig.15 Thermogram of Cu (II)-MOPQIEP

Thermogram of Cu (II)-MOPQIEP (Fig.15.**)** shows weight loss in three steps. The metal complex is stable up to130 °C. Then the weight loss in the temperature range 136 °C to 290 °C, accompanied by energy absorption evident from endothermic peak at t_{min}=169 °C in DTA, corresponds to the loss of coordinated water molecules. The second step of weight loss appeared at 400 °C to 700 °C, and an exothermic peak at t_{min} =349 °C to 680 °C in DTA envisage partial decomposition of the ligand moiety and also phase transition. Above 700 °C there is slight increase of weight which corresponds to the formation of the stable metal oxide and the total loss of organic moiety.

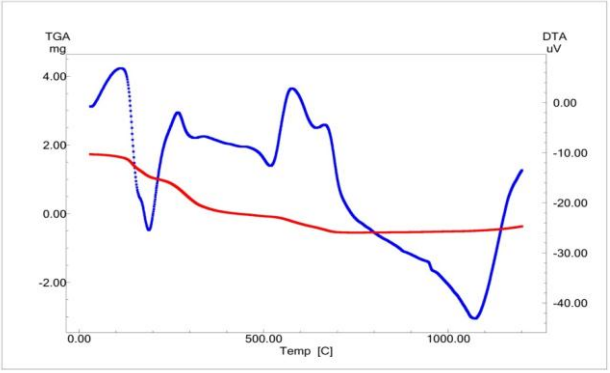


Fig.16 Thermogram of Co (II)-MOPQIEP

TGA curve of Co (II)-MOPQIEP is presented in Fig.16. The steep slope in the temperature range 104 °C and an endothermic peak at t_{min} = 189 °C in DTA curve are probably due to loss of hydrated water. Further decomposition in the region 300 °C to 400 °C and an exothermic peak at t_{min} = 330 °C to 519 °C in DTA correspond to the partial decomposition of ligand. Above 700 °C there is slight increase of weight which corresponds to the formation of the stable metal oxide and the total loss of organic moiety.

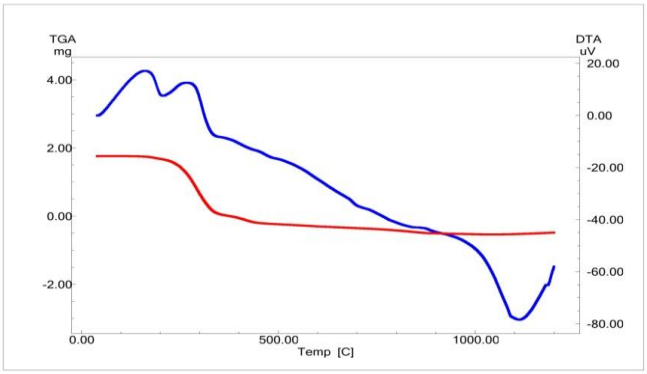


Fig.17 Thermogram of Hg (II)-MOPQIEP

The weight loss evident from TGA curve of Hg (II)-MOPQIEP (Fig.17.) is ascribable to the decomposition of complex majorly up to 1000°C. The DTA curve displayed exothermic peaks at 170 °C and 289 °C indicating release of energy accompanied by the decomposition of complex.

3.3.3. Magnetic Susceptibilities

Magnetic susceptibilities measured for Co (II) and Cu (II) complexes of MOPQIEP showed Magnetic moment values as 2.89 BM and 1.90 BM respectively.

3.3.4. Scanning Electron Microscope Images & EDX

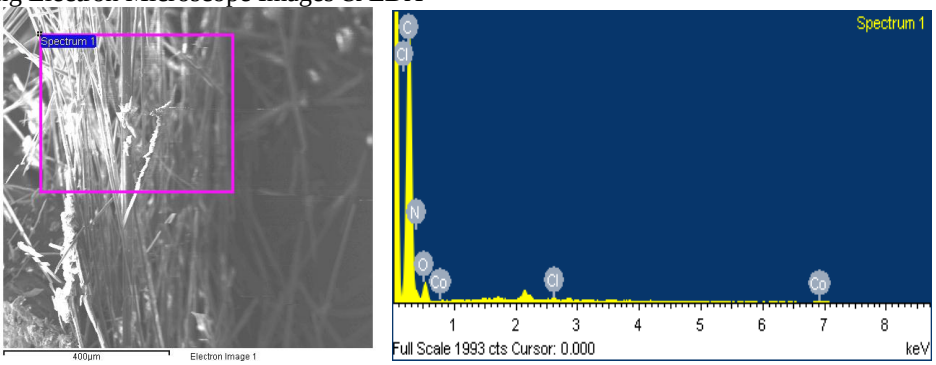


Fig.18 Scanning Electron Microscope Image & EDX Spectrum of Co (II)-MOPQIEP

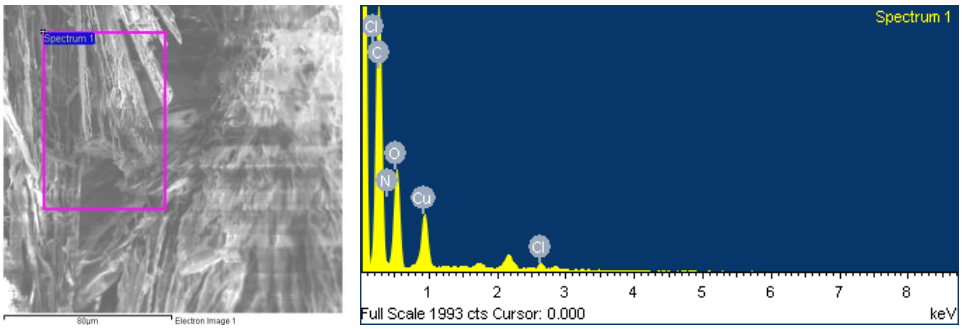


Fig. 19 Scanning electron microscope & EDX images of Cu (II)-MOPQIEP

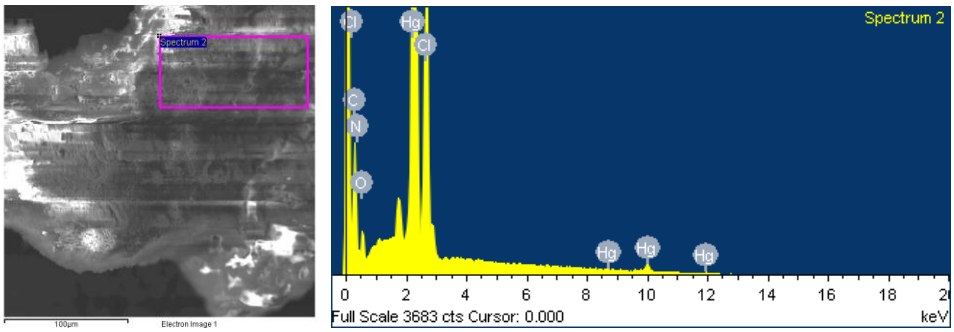


Fig. 20 Scanning electron microscope & EDX images of Hg (II)-MOPQIEP

The SEM images of Co (II)-MOPQIEP, Cu (II)-MOPQIEP and Hg (II)-MOPQIEP) complexes displayed distinct morphology with particle size 40 µm, 80 µm and 100 µm (Fig. 18, 19 & 20) respectively. The EDX spectra of complexes revealed the composition of complexes in accordance with the expected data proposed on the basis of mass spectral results.

The above metal complexes characterized on the basis of spectro-analytical techniques can be assigned tentative structures shown as below (Fig. 21, 22 & 23).

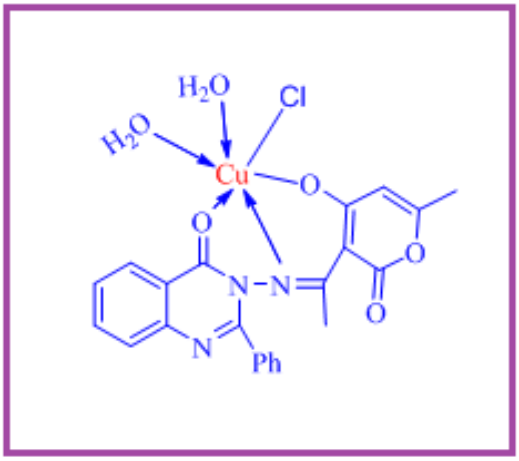


Fig. 21 Tentative structures of Cu (II)-MOPQIEP

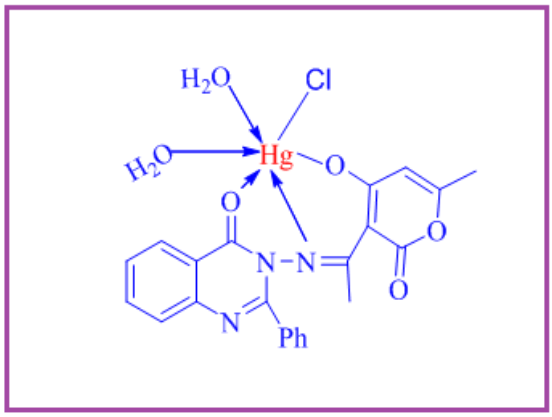


Fig. 22 Tentative structures of Hg (II)-MOPQIEP

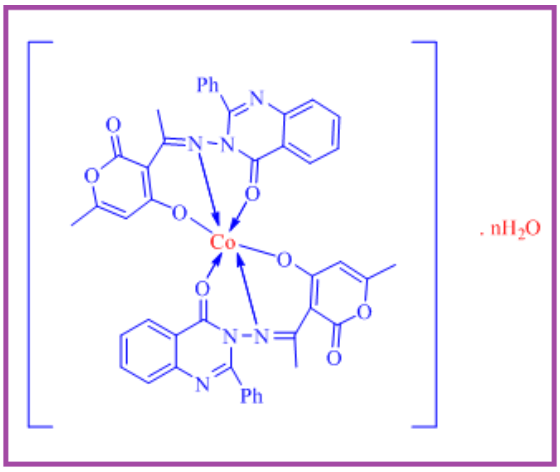


Fig. 23 Tentative structures of Co (II)-MOPQIEP

3.3.5. Biological Studies

The well diffusion assay was used for antimicrobial activity of MOPQIEP and its metal complexes. The compounds were tested in vitro against gram positive Bacillus subtilis, Staphylococcus, gram negative Pseudomonas aeruginosa, Klebsiella and Escherichia coli bacteria and fungi Saccharomyces cerevisiae and Aspergillus niger were spread on nutrient agar, with the help of cork borer, wells were created on agar medium and inoculated with 20 µl of MOPQIEP and its complexes (1mg/ml) in DMSO. After inoculation, plates were kept in refrigerator for diffusion at 10-15minutes in agar medium, plates were transferred to bacteriological incubators and maintained temperatures of 37 °C / 24 hrs, 30 °C / 2-7 days respectively. After incubation, zone

of inhibition was observed. From the table 03, it's clear that the Hg (II)-MOPQIEP complexes were biologically active and shown enhanced antimicrobial activity compared to the ligand.

Table.03 Microbiological activity of MOPQIEP
++ Indicates: Inhibition of growth, -- Indicates: No inhibition growth

S. No	Microbial Culture	MOPQIEP	Hg-MOPQIEP
1	*E. Coli*	--	++
2	*Klebsiella*	++	++
3	*Pseudomonas*	--	++
4	*Bacillus*	++	++
5	*Staphylococcus*	++	++
6	*Aspergillus*	--	++
7	*Yeast*	--	++

3.3.6. DNA Cleavage Studies

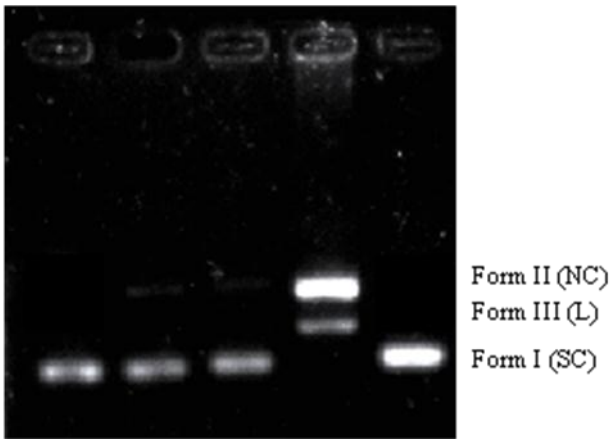


Fig. 24 DNA cleavage activity of MOPQIEP, Co (II)-MOPQIEP, Cu (II)-MOPQIEP and Hg (II)-MOPQIEP

Lane 1: DNA marker (1µl+4 µl Tris – HCl Buffer) Lane 2: DNA (1 µl+4 µl Tris – HCl Buffer) + MOPQIEP (5 µl of 2 mg/ml) Lane 3: DNA (1 µl+4 µl Tris – HCl Buffer) + Co (II)-MOPQIEP (5 µl of 2 mg/ml) Lane 4: DNA (1 µl+4 µl Tris – HCl Buffer) + Cu (II)-MOPQIEP (5 µl of 2 mg/ml) Lane 5: DNA (1 µl+4 µl Tris – HCl Buffer) + Hg (II)-MOPQIEP (5 µl of 2 mg/ml)

Agarose gel electrophoresis is a successful method in studying DNA cleavage by the potential compounds. For the hydrolytic cleavage of DNA, super coiled (SC) plasmid DNA is a central substrate. For the DNA cleavage analysis a potency of compounds are quantitatively evaluated on super coiled plasmid PBR322 in the absence of oxidizing or reducing agents. A variety of the metal complexes along with the ligand (MOPQIEP) have been tested on DNA cleavage studies, Cu (II)-MOPQIEP is found to be most efficient DNA cleaver which has converted super coiled DNA (form I) in to relaxed DNA (form II & form III). The DNA cleavage activity increases with increasing of concentration. There is no significant cleavage activity upon super coiled form for Co (II) and Hg (II) complexes. It is important to note that the Cu (II) complex is proven to act as very efficient nucleases in the hydrolytic cleavage of DNA.

IV. Conclusions

Novel 6-methyl-3-(1-(4-oxo-2-phenylquinazolin-3(4H)-ylimino) ethyl)-2H-pyran-2, 4(3H)-Dione and its Cu (II), Co (II) and Hg (II) metal complexes were prepared and characterized on the basis of Mass, IR, UV-Visible, TGA, DTA, SEM and NMR spectral data. The IR and ^{1}H NMR data computed by using HyperChem.7.5 software were in good agreement with experimental data. FT-IR spectrum suggested that MOPQIEP acts as a tridentate ligand, involving oxygen of carbonyl group from quinazolinone and enol oxygen of pyran through deprotonation and 'N' from azomethine group as donor sites. The title compound and its metal complexes were tested for biological activity. The antimicrobial studies indicated the high potency of mercury complex against the micro organism scanned. The DNA electrophoresis studies carried out on super coiled plasmid PBR322 indicated that only Cu (II) metal complex of MOPQIEP exhibited cleavage property, converting super coiled DNA (Form I) to both circular (Form II) and linear DNA (Form III).

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