SYNTHESIS AND CHARACTERISATION OF MIXED LIGAND METAL COMPLEXES OF MEFLOQUINE AND CHLOROQUINE

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ABSTRACT:
The basic aim of the study is to find molecules that can be more effective therapeutic substitutes from the available antimalarial drugs. Efforts have also been made on combination of antimalarial drugs for effective control of a large number of diseases. The combination of two short half-life drugs, namely Artesunate and Ladap (Proguanil and Dapsone) has proved the benefits of combination therapy in rapid removal of parasites from the blood stream.

KEYWORDS: basic aim, benefits of combination therapy.

INTRODUCTION
The resistance of these parasites to antimalarial drugs has made an effort to reexamine the pharmacology of alternative antimalarials, which may be effective against resistance strains. The introduction of fluorine can have a prolonged effect on the biological activity and the physico-chemical properties of the aromatic compounds. Niel et al. reported that the presence of fluorine in the aromatic nucleus of amodiaquine and substitution at the 2, 6 position and replacement of the 4-hydroxyl group of the amodiaquine produced analogue drugs that maintain antimalarial efficacy in vitro and are more resistant to oxidation. Since the two ligands in this study (mefloquine and chloroquine) possess active binding sites, it was decided to study their coordination tendencies, characterisation after complexing with metals and their biological activities.[1.2]

SYNTHESIS OF THE METAL COMPLEXES
Ethanol solutions of the metal chlorides were prepared in round bottom flasks. 0.01Mol (4.148 g) of mefloquine was mixed with 0.01 mol (4.179 g) of chloroquine in a beaker. The mixed ligands were dissolved in 20 ml of ethanol and added to the solution of the corresponding metal salt dissolved previously in 10 ml of ethanol at a pH of 8.5. The solution was refluxed for 2 h. The metal chelates crystallized, after leaving the reacting solution for about 30 minutes in a refrigerator. The metal complexes thus separated were filtered and washed with ethanol and then with distilled water to remove unreacted ligand and metal, finally the solid complexes were dried in a desiccator. On the basis of elemental analysis the metal complexes were formulated as[Cu(cq)(mq)Cl2].2H2O, [Zn(cq)(mq)Cl2].2H2O, [Ni(cq)(mq)Cl2].6H2O, and [Fe(cq)(mq)(H2O)Cl3].5H2O

RESULTS AND DISCUSSION
ELEMENAL ANALYSIS
Elemental analysis (Table.1) shows that the ligands (mefloquine and chloroquine) and the metal salts are in the ratio of 1:1:1.
IR spectra

The IR spectra of the ligand shows the stretching frequencies at 3200 cm\(^{-1}\), 1080 cm\(^{-1}\), 3200 cm\(^{-1}\), 1200 cm\(^{-1}\) and 650 cm\(^{-1}\) due to \(-\text{NH}, \text{CN}, \text{-OH}\) group, C-F bond and C-Cl bond, respectively. During complexation (Fig 2), the stretching frequency of NH group gets shifted to 3250 cm\(^{-1}\) indicating the involvement of NH group in metal coordination. The presence of coordinated water in Fe(III) was confirmed by the medium strength bands at 840–850 cm\(^{-1}\) characteristic of \(\nu(\text{H}_2\text{O})\) frequencies. These bands were not observed in the spectra of other metal complexes indicating the absence of coordinated water molecules. The vibrational status of those ligands upon complexation to the metal ion is indicated by the shift in frequencies of the bands of the complexes compared to those of the ligands.[3]

Electronic spectra

There are two absorption bands, assigned to n-\(\pi^*\) and \(\pi-\pi^*\) transitions, in the electronic spectrum of the ligand. These transitions are also found in the spectra of the complexes (Fig 3) but they are shifted towards lower and higher frequencies, confirming the coordination of the ligand to the metallic ions. The electronic spectrum of copper(II) complex exhibits bands at 467 nm and 645 nm which are assigned to \(2B_{1g} \rightarrow 2A_{1g}\) and \(2B_{2g} \rightarrow E_{g}\) transitions [4]. These transitions and the measured value of the magnetic moment (\(\mu_{\text{eff}} = 1.88 \text{ BM}\)) suggest a square-planar geometry of the complex. Since the zinc ion has d\(^{10}\) configuration, the absorption at 371 nm could be assigned to a charge transfer transition. On the basis of spectral data and the configuration of the zinc(II) ion, a tetrahedral geometry could be assumed for its complex. The Ni(II) complex shows a magnetic moment of 3.26 B.M. The electronic spectrum of the Ni(II) complex shows a band at 832 nm which corresponds to the transition \(3T_1(F) \rightarrow 3T_1(P)\) in tetrahedral environment. The magnetic moment for high spin octahedral Fe(III) ion ranges from 5.7 to 6.0 BM. The observed magnetic moment value is well within the accepted range and hence an octahedral geometry is proposed for the Fe(III) complex.

ESR spectrum

In square-planar complexes (Fig 4) the unpaired electrons lie in the d\(_{x^2-y^2}\) orbital giving \(2B_{1g}\) as the ground state with \(g_{||} > g_{\perp}\) while the unpaired electron lies in the d\(_{z^2}\) orbital giving \(2A_{1g}\) as the ground state with \(g_{\perp} > g_{||}\). From the observed values, it is clear that \(g_{||} > g_{\perp}\), which indicates that the structure of the complex is square-planar and that the unpaired electron is predominantly in the d\(_{x^2-y^2}\) orbital.

\(^1\text{H}\) NMR spectrum

The signal at \(\delta\ 3.6\) (s, 1H) is assigned to hydroxyl proton (OH) and the signal at \(\delta\ 2.0\) (s, 1H) is assigned to piperidine proton (-NH) in mefloquine ligand. The signals due to (-NH) are shifted to downfield in the spectrum of the zinc complex indicating the coordination of –NH group with metal ions (Fig. 5). The signal due to aromatic protons at \(\delta 6.94 - 7.83\) shifted downfield in the complex. In the same way –NH proton appears at \(\delta 4.0\), CH protons of quinoline appears at \(\delta 8.36\), CH\(_2\) protons appear at \(\delta 1.37\), and CH\(_3\) protons at \(\delta 1.02\) in the chloroquine ligand shifted to downfield in the zinc complexes. Thus \(^1\)H NMR observations are supplemented with the assigned geometry.[5]

TGA study

TGA study of Cu(II) complex (Fig. 6) indicates that it undergoes three stages of decomposition. The complex starts to decompose above 50°C. The initial decomposition temperature was observed at 253.4°C corresponding to 10% weight loss. The second stage of decomposition occurs at \(~340°C\), bringing \(~19%\) weight loss. 50% weight loss occurs at 660°C. 90% decomposition takes place at \(900°C\). The residual weight at 700°C for the Cu(II) complex (47.78%) corresponds to the amount of copper oxide formed at the temperature[6,7].

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DSC studies
The DSC studies of nickel complex (Fig. 7) indicate that it shows the glass transition temperature at 185.1°C. The endothermic peaks observed at 276.3°C and 340°C can be due to decomposition and melting of the complex [8,9].

XRD studies
The XRD pattern of the Cu(II), Ni(II), Fe (III) and Zn(II) complexes (Fig.8) were recorded in the 2θ range 20-80°. The crystalline size of the copper complex calculated from Scherer’s formula was found to be 46 nm indicating its nanocrystalline nature [10].

SEM studies
SEM study of Ni(II)complex (Fig.9) indicates the presence of well defined crystals free from any shadow of the metal ion on their external surface [11].

FAB mass spectrum
The FAB mass spectrum of the mixed ligand copper complex (Fig10) of mefloquine and chloroquines shows the molecular peaks at m/z 868 which confirms the stoichiometry of the metal complexes. Other fragments obtained are (C9H5NCl)+, (C9H19N)+, and (C17H15OF6)+ and their molecular ion peaks are observed at m/z 162, 141, and 343 respectively [12].

Table. 1 Elemental analysis of mixed ligand metal complexes of chloroquine and mefloquine

<table>
<thead>
<tr>
<th>Compound</th>
<th>C% (found)</th>
<th>H% (found)</th>
<th>N% (found)</th>
<th>Metal% (found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cu(cq)(mq)Cl2].2H2O</td>
<td>48.37(48.27)</td>
<td>5.34(5.36)</td>
<td>8.06(8.16)</td>
<td>7.32(7.26)</td>
</tr>
<tr>
<td>[Zn(cq)(mq)Cl2].2H2O</td>
<td>48.27(48.31)</td>
<td>5.33(5.32)</td>
<td>8.05(8.12)</td>
<td>7.52(7.63)</td>
</tr>
<tr>
<td>[Fe(cq)(mq)(H2O)Cl3].5H2O</td>
<td>43.59(42.99)</td>
<td>5.62(5.59)</td>
<td>7.23(7.17)</td>
<td>5.77(5.79)</td>
</tr>
<tr>
<td>[Ni(cq)(mq)Cl2].6H2O</td>
<td>44.9(43.77)</td>
<td>5.82(5.79)</td>
<td>7.48(7.39)</td>
<td>6.27(6.19)</td>
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</table>
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Wave number(cm⁻¹)
Fig 2 IR spectrum of [Fe(cq)(mq)(H₂O)Cl₃].5H₂O

### Table 2 IR spectral data of mixed ligand complexes of chloroquine and mefloquine

<table>
<thead>
<tr>
<th>Compound</th>
<th>v(NH)</th>
<th>v(CN)</th>
<th>v(OH)</th>
<th>v(C-Cl)</th>
<th>v(H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>3200</td>
<td>1080</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[Cu(cq)(mq)Cl₂].2H₂O</td>
<td>3100</td>
<td>1010</td>
<td>3100</td>
<td>650</td>
<td>-</td>
</tr>
<tr>
<td>[Zn(cq)(mq)Cl₂].2H₂O</td>
<td>3150</td>
<td>1020</td>
<td>3120</td>
<td>640</td>
<td>-</td>
</tr>
<tr>
<td>[Fe(cq)(mq)(H₂O)Cl₃].5H₂O</td>
<td>3120</td>
<td>1030</td>
<td>3130</td>
<td>630</td>
<td>840</td>
</tr>
<tr>
<td>[Ni(cq)(mq)Cl₂].6H₂O</td>
<td>3220</td>
<td>1020</td>
<td>3110</td>
<td>635</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig .3 Electronic spectrum of [Cu(cq)(mq)Cl₂].2H₂O

### Table 3 Electronic spectral data of mixed ligand complexes of chloroquine and mefloquine

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transition</th>
<th>Wavelength(nm)</th>
<th>Geometry</th>
<th>μeff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>π→π* and n→π*</td>
<td>Below 250</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[Cu(cq)(mq)Cl₂].2H₂O</td>
<td>2B₁g→2E₁g</td>
<td>467,645</td>
<td>Square planar</td>
<td>1.88</td>
</tr>
<tr>
<td>[Zn(cq)(mq)Cl₂].2H₂O</td>
<td>-</td>
<td>-</td>
<td>tetrahedral</td>
<td>diamagnetic</td>
</tr>
<tr>
<td>[Fe(cq)(mq)(H₂O)Cl₃].5H₂O</td>
<td>6A₁g→3T₂g(G)</td>
<td>477-498</td>
<td>Octahedral</td>
<td>5.7-6.0</td>
</tr>
<tr>
<td>[Ni(cq)(mq)Cl₂].6H₂O</td>
<td>3T₁(F)→3T₁(P)</td>
<td>832-816</td>
<td>tetrahedral</td>
<td>3.26</td>
</tr>
</tbody>
</table>

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Fig. 4 ESR spectrum of \([\text{Cu(cq)(mq)Cl}_2].2\text{H}_2\text{O}\) at 300K

Table 4 ESR spectral data of \([\text{Cu(cq)(mq)Cl}_2].2\text{H}_2\text{O}\)

| Complex                  | \(g_{||}\) | \(g_{\perp}\) | \(g_{iso}\) | \(K_{ll}\) | \(K_{ll}\) | \(\alpha^2\) | \(\beta^2\) | \(\gamma^2\) | \(G\) |
|-------------------------|-----------|--------------|-------------|-----------|-----------|-------------|-----------|-------------|-------|
| \([\text{Cu(cq)(mq)Cl}_2].2\text{H}_2\text{O}\) 77K | 2.212     | 2.202        | -           | 0.78      | 0.526     | 1.246       | 0.7351    | 0.775       | 7.4   |
| \([\text{Cu(cq)(mq)Cl}_2].2\text{H}_2\text{O}\) 300K | -         | -            | 2.10        | -         | -         | -           | -         | -           | -     |

Fig. 5 \(^1\text{H} NMR\) spectrum of \([\text{Zn(cq)(mq)Cl}_2].2\text{H}_2\text{O}\)

Fig. 6 TGA pattern of \([\text{Cu(cq)(mq)Cl}_2].2\text{H}_2\text{O}\)

Fig. 7 DSC pattern of \([\text{Ni(cq)(mq)Cl}_2].6\text{H}_2\text{O}\)
Fig 8 Powder XRD pattern of [Cu(cq)(mq)Cl₂].2H₂O

Fig 9 SEM image of [Ni(cq)(mq)Cl₂].6H₂O

Fig 10 FAB Mass spectrum of [Cu(cq)(mq)Cl₂].2H₂O

[1] Gielen M., Tiekin R.T., Metallotherapeutic Drugs and Metal-Based Diagnostic Agents, the Use of Metals in Medicine, Wiley, Chichester, 2005.
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