

Amodiaquine-Ibuprofen Mixed Metal Complexes: Synthesis, Characterization and Antimicrobial Activities

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Abstract

Mixed Ligand complexes of Amodiaquine and Ibuprofen with Copper(II), Zinc(II), Iron(III) and Cobalt(II) were synthesized. The complexes were synthesised using Reflux method, and the chelates of 1:1:1 stoichiometries were formed and characterized by Melting point, Ultraviolet/ visible and Infrared Spectroscopies. The antimicrobial activities were investigated against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus megaterium*, *Eutrobacter aerogenes*, *Serratia marcescens*. From the data obtained, it was observed that the Zn(II) and Cd(II) complexes exhibited higher activity against the microorganisms when compared with the parent Ligands.

Keywords: Antimicrobial studies, complexes, spectra, anti-inflammatory Drugs.

Introduction

Medicinal Inorganic chemists have risen to the need of synthesising drugs that have high resistance to disease-causing micro-organisms. A lot of breakthrough has been made on complexation of some common known antimalarial drugs with metals [1,2,3,4].

Ibuprofen is a non-steroidal anti-inflammatory drug in the treatment of arthritis[3].

There are different methods in determining Ibuprofen in pharmaceuticals [6]. Much effort has also been made in the combination therapy of synthesizing mixed metal complexes of antimalarial drugs with antiinflammatory, analgesics and also with vitamins such as ascorbic acid. Investigation is being carried out to describe simple, fast and accurate spectrophotometric methods on the reaction between Ibuprofen as donor and chloroquine forming complexes which easily absorb radiation in the visible region[3].

The antimicrobial activity of the synthesised mixed metal complexes has also been carried out to determine those complexes that have high resistance against the disease.

Materials and Methods

Materials

The metal salt Copper(II) Sulphate, Zinc(II) Chloride, Iron(III) Chloride, Cadmium (II) Chloride used in the research work were obtained from Chemistry Department Laboratory, University of Ilorin, Ilorin, Nigeria. The ligands (Amodiaquine and Ibuprofen) were obtained from Sam

Pharmaceutical Industry, Ilorin, Kwara state, Nigeria. The known isolated organisms *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Bacillus substilis*, *Bacillus megaterium*, *Eutorobacter aerogenes*, *Serratua mercescence* were obtained from the Department of Microbiology, University of Ilorin Teaching Hospital, Ilorin, Nigeria.

Synthesis of the complexes

[Cu(Amo)(Ibu)]SO₄

0.36g (1mmol) of Amodiaquine and 0.21g (1mmol) of Ibuprofen were weighed and dissolved in 20ml of methanol separately. 1mmol of Copper sulphate was weighed and dissolved in 20ml of methanol in another beaker. The solutions were mixed together and refluxed for 2 hours at 100°C. The lemon green precipitates formed were washed and recrystallized using methanol and dried in a dessicator.

Yield = 80%; Melting point = 257 – 259°C; Cond.(^Λ) = $2.2 \times 10^{-1} \Omega\text{Cm}^{-1}$;

IR (KBr) ν cm^{-1} : 3300 (O-H), 3387 (N-H), 1543 (C=N)

[Zn(Amo)(Ibu)]Cl₂

Zinc chloride (0.14g, 1mmol) was dissolved in 20ml of distilled water and solution of 0.36g (1mmol) of Amodiaquine and 0.21g (1mmol) of Ibuprofen in 20ml of methanol. The resulting solution was stirred, mixed and stirred for 2 hours. White precipitate was formed, filtered and dried in dessicator. Yield = 65%; Melting point = 261 – 262°C; Cond.($\wedge$) = $1.6 \times 10^{-1} \Omega\text{Cm}^{-1}$; IR (KBr) ν cm^{-1} : 3390 (O-H), 3317 (N-H), 1548 (C=N).

[Fe(Amo)(Ibu)]Cl₃

Iron chloride (0.14g, 1mmol) was dissolved in 20ml of distilled water and solution of 0.36g (1mmol) of Amodiaquine and 0.21g (1mmol) of Ibuprofen in 20ml of methanol. The solutions were mixed together to form a brown precipitate. It was washed and dried.

Yield = 65%; Melting point = 173 – 175°C; Cond.($\wedge$) = $3.7 \times 10^{-1} \Omega\text{Cm}^{-1}$; IR (KBr) ν cm^{-1} : 3376 (O-H), 3421 (N-H), 1587 (C=N)

[Cd(Amo)(Ibu)]Cl₂

A solution of 0.36g (1mmol) of Amodiaquine and 0.21g (1mmol) of Ibuprofen in 20ml of methanol and a solution of Cadmium chloride 0.23g (1 mmol) were dissolved in 20ml of distilled water. Immediately, there was formation of a white solid precipitate. It was then filtered, washed, dried and kept for further analysis.

Yield = 70%; Melting point = 262 – 263°C; Cond.($\wedge$) = $2.9 \times 10^{-1} \Omega\text{Cm}^{-1}$; IR (KBr) ν max/ Cm^{-1} : 3348 (O-H), 3321 (N-H), 1546 (C=N)

Antibacterial Activity

The inhibitory action of the metal complexes was tested on eight known isolated bacteria organisms: *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Bacillus substilis*, *Bacillus megaterium*, *Eutorobacter aerogenes*, *Serratua mercescence*.

The zone of inhibitory activity of both the ligands and the mixed metal complexes were determined following the procedure of Adediji et al ¹, Obaleye et al ⁷ and Mohamed and Abdel ⁸. The antibacterial activities of the compounds were determined on the basis of the zone of inhibition formed around the holes on the sensitivity media

About 7 g of nutrient agar was weighed into 250 ml of sterilized water and mixed. The mixture was heated for 15 minutes and placed in an autoclave to sterilize at 121 °C. The agar was reheated and poured into the sterilized petri-dishes and allowed to set. Wells were drilled into the solidified agar by the use of sterilized cork borer. Cotton wool swabs were soaked in the pure culture of the organisms and was used to rub the surface of the solidified agar. Solutions of the complexes were introduced into the well. The incubation of the plates was carried out at 37 °C for 24 hours. Clear zones around the well indicate the antibacterial activity of the complexes on the tested organisms.

Determination of Physical properties of the Complexes.

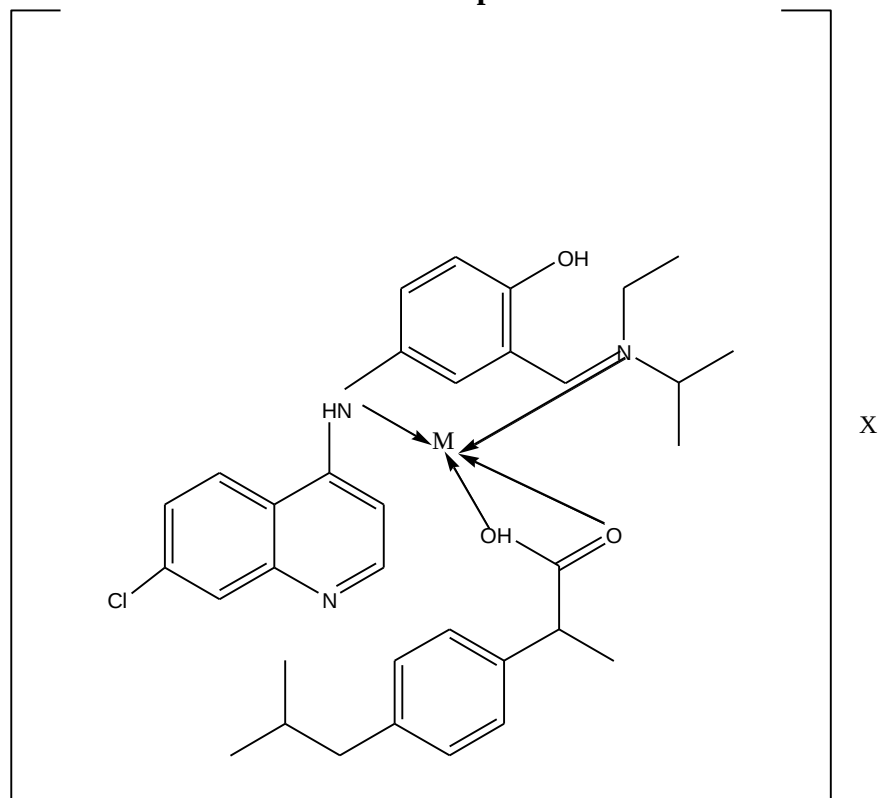
The melting point of the synthesized complexes were recorded on Gallenkamp melting point apparatus (Melting point SMP 10).

The UV spectra were obtained on the BECKMAN COULTER DU 730 UV/VISIBLE Spectrophotometer (using appropriate solvent) in the Chemistry Department instrument room, University of Ilorin, Ilorin, Nigeria. The electronic spectra of the complexes in solution were run within the range of 200-1000nm on the above named spectrophotometer.

Conductivity measurements were carried out using Jenway 4510 conductivity meter in the Chemistry Department instrument room, University of Ilorin, Ilorin, Nigeria..

The IR spectra were recorded in KBr pellets within the range of 4000-400cm⁻¹. The spectra of the ligands and their complexes were recorded on FT-IR Spectrophotometer at the Redeemer University, Sango-ota, Ogun state, Nigeria.

Proposed structure of Mixed metal complexes



X = SO₄, Cl₂, Cl₃, Cl₂

M= Cu, Zn, Fe and Cd

RESULTS

Table 1. Physical properties of the ligands and mixed metal complexes.

Compound	Melting point(°C)	Colour	Conductivity(Ωcm^{-1})
Amodiaquine (Amo)	167-169	Yellow	-
Ibuprofen (Ibu)	79-81	White	-
[Cu(Amo)(Ibu)]SO ₄	257-259	Lemon green Powder	2.2×10^{-1}
[Zn(Amo)(Ibu)]Cl ₂	261-262	White Powder	1.6×10^{-1}
[Fe(Amo)(Ibu)]Cl ₃	173-175	Brown Powder	3.7×10^{-1}
[Cd(Amo)(Ibu)]Cl ₂	262-263	White Powder	2.90×10^{-1}

Table 2. Infra red data of the ligands and metal complexes.

Ligand or Complexes	<u>infra red frequencies</u>			
	$\nu(\text{O-H}) \text{ cm}^{-1}$	$\nu(\text{N-H}) \text{ cm}^{-1}$	$\nu(\text{C=N}) \text{ cm}^{-1}$	$\nu(\text{C=O}) \text{ cm}^{-1}$
Amodiaquine	3500	3350	1610	
Ibuprofen	3450	-	-	1759
[Cu(Amo)(Ibu)]SO ₄	3300	3387	1543	1765
[Zn(Amo)(Ibu)]Cl ₂	3390	3317	1548	1670
[Fe(Amo)(Ibu)]Cl ₃	3376	3421	1587	1740
[Cd(Amo)(Ibu)]Cl ₂	3348	3321	1546	1790

Table 3. Electronic spectral data and configuration of the ligands and metal complexes

Ligand /Complexes	Wavelength(nm)	Energies cm^{-1}	
		Assignment	
Amodiaquine	290	34483	
Ibuprofen	302, 240	3113, 41667	
[Cu(Amo)(Ibu)]SO ₄	454, 700	22026, 14286	MLCT/eg $\rightarrow$ T _{2g}
[Zn(Amo)(Ibu)]Cl ₂	265	3773	n- π^*
[Fe(Amo)(Ibu)]Cl ₃	330, 370	30303, 27027	MLCT
[Cd(Amo)(Ibu)]Cl ₂	270, 294	37037, 34014	π - π^* / n- π^*

Table 4.
Antimicrobial Activity

Lignds/ Complexes	<i>E.</i> <i>coli</i>	<i>B.</i> <i>megateriu</i> <i>m</i>	<i>P.</i> <i>vulgaris</i>	<i>P.</i> <i>aeruginosa</i>	<i>E.</i> <i>aerogenes</i>	<i>S.</i> <i>aureus</i>	<i>B.</i> <i>substilis</i>	<i>S.</i> <i>mercesc</i> <i>enence</i>
	Zone of Inhibition (mm)							
Amodiaquine	14.70	16.80	21.60	13.50	17.10	27.90	24.60	19.80
Ibuprofen	16.90	0	0	24.80	19.70	21.60	23.80	20.20
[Cu(Amo)(Ibu)]SO₄	19.00	16.30	0	0	18.70	0	0	15.50
[Zn(Amo)(Ibu)]Cl₂	16.80	17.70	19.20	26.80	15.80	16.70	17.20	15.60
[Fe(Amo)(Ibu)]Cl₃	19.80	16.70	25.80	17.50	0	0	0	0
[Cd(Amo)(Ibu)]Cl₂	20.90	26.20	22.80	19.50	23.70	25.30	20.70	19.80

Discussions

The analytical data of both the ligands and the complexes are described in Table 1.

The melting points of the metal complexes were found to be higher than those of the ligands indicating formation of complexes [9].

The conductivity results showed that the complexes are electrolytes. Ligands and their complexes are shown in Table 1.

The band of hydroxyl group (O-H) appeared at 3500 cm⁻¹ and 3450 cm⁻¹ in the spectra of Amodiaquine and Ibuprofen respectively [10]. It was observed that these bands shifted to 3300 cm⁻¹, 3390 cm⁻¹, 3390 cm⁻¹, 3376 cm⁻¹ and 3348 cm⁻¹ in Cu(II), Zn(II), Fe(III) and Cd(II) complexes. This is a result of coordination of the metal with the ligands via oxygen of the hydroxyl group. This observation is in agreement with the previous studies carried by Muhammed [11]. The absorbtion was shifted to lower wavenumber and is an evidence of the metal with Amodiaquine.

The amine (N-H) band of Amodiaquine appeared at 3500 cm⁻¹. It was observed that coordination of the ligand occurs through the Nitrogen atom of pyridine and Nitrogen atom of amino group to form a tetrahedral geometry.[12] The band at region of 1759 cm⁻¹ in the free ligand Ibuprofen was assigned to $\nu(\text{C=O})$ stretching mode. This was shifted to 1740–1790 cm⁻¹

¹ in the alternative complexes. This indicates coordination through functional group to the metal ion in the complexes.

The electronic spectra of the ligands and its complexes are presented in Table 3. The spectrum of Amodiaquine and Ibuprofen shows absorption band at 290nm/302nm and 240nm respectively. The bands are assigned to π - π^* and n- π^* / π - π^* respectively. The appearance of the bands confirms the tetrahedral geometry of this complexes.

Antimicrobial activity

The synthesized complexes and their parent ligands were screened against some isolated antimicrobial organisms. From the results, it was observed that Zn(II) and Cd(II) complexes exhibit high antimicrobial activity on some of the organisms when compared with the ligands.

Conclusion

The metal complexes were synthesized using refluxing and mixing methods. They were characterized using Melting point, Conductivity measurements, Infra-red Spectroscopy, Ultraviolet- Visible Spectroscopy. The ligands are bidentate. The proposed geometry of the complexes is Tetrahedral. Zn and Cd complexes showed increased antimicrobial activity compared to the parent drugs. Synthesis of novel metal complexes with effective drugs has become a great interest for inorganic, pharmaceutical and medicinal chemistry. The purpose of the research work is to synthesise new metal complexes which will have better pharmacological profile than their parent ligands [13].

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