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Cu(II), Mn(II), Ni(II) Complexes of Mixed Amodiaquine and Paraaminobenzoic acid: Synthesis, Characterization, Antimicrobial and Toxicological Activities in Wister rats

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ABSTRACT

Four novel metal complexes of mixed Amodiaquine and Paraaminobenzoic acid have been synthesized and confirmed by results of some physicochemical and spectroscopic techniques. Antimicrobial activities have been carried out on the complexes against some selected organisms:(bacterial organisms: *K. pneumonia, B. subtilis, E. coli, S. aureus, P. aeruginosa*, and *S. faecalis*) and (fungal organisms: *C. albicans, A. niger,* and *P. chrysogenum*) to determine their effectiveness. The complexes were evaluated for their toxicity level in Wister rats. About thirty Wister rats were grouped into six of 5 rats each.The Amodiaquine and Paraaminobenzoic acid produce complexes in ratio 1:1:1 in coordination with the metal ion. Octahedral geometry has been proposed for all the complexes. The complexes were found to be non-electrolytic in nature. The complexes were observed to be more active than their free ligands as determined by their zone of inhibition (mm). The metal complexes have shown characteristics to be less toxic to the body.

1. Introduction

Malaria is one of the major threats to human health in the developing countries. Presently, all the existing drugs most especially aminoquinoline based drugs are used to treat malaria. However, there is a great improvement in organic synthetic strategies for the production of antimalarial drugs. Researchers have found some easy ways to develop more approaches to the development of more active drugs for the treatment of the diseases [1]. Coordination complexes have been used to treat different form of diseases most especially platinum complex cisplatin for the treatment of cancer [2]. Researchers have created a great interest in carboxylate compounds, most especially derivatives of

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benzoic acid due to their chemical and biological properties. The benzoic acid and their derivatives are very useful structural molecule for some natural products that participate in different physiological processes in plants. Para-amino benzoic acid (PABA) showed great interest in the field of biology, medicine and industries among other compounds. It is also referring to as precursor of folic acid [3] and also known as a coenzyme Q precursor [4, 5] which produce possibilities for its use in medicine. PABA is well known as a building block in production of drugs and as a structure moiety in drugs [6]. It acts as antioxidant agent [7, 8]. PABA is usually mixed with plant hormone in nutrient media by stimulating seed germination [9]. Chelation of new complexes is a significant step in the evolution of complexes which help to offer important properties and new reactivity. Amodiaquine complexes can enhance the relationship of DNA and cytotoxicity [10]. Some chemotherapeutic drugs offer pharmacological, toxicology and physicochemical properties when administered as chelating agent [11]. Solubility and chemical reactivity may help to change upon formation of complexes [12, 13]. Amodiaquine as well as its derivatives has been reported to inhibit the ebola virus *in vivo.* This accounts for its widespread usage during the breakdown of the ebola pandemic. Several biological studies have been carried out in support of this claim [14, 15]. PABA and its derived complexes have been reported to have an enhanced antimicrobial activity by some researchers. In some of these works, the bacterial species (*Escherichia coli, Pseudomonas auriginosa* and *Staphylococcus aureus)* and species of fungi (*Fusarium verticilloides, Fusarium chlamydosporum* and *Fusarium oxysporum)* were employed for the assay [16, 17]. If an important biological activity of a chelating agent varnish on coordination with the central metal ion, it will be indicated that one of the groups that is bonded to the metal is very useful for the activity [2]. The aim of inorganic chemists is to discover and develop some active drugs in order to fight against diseases. More efforts have been carried out on mixed analgesic drugs. Presence of fluorine in complexes has a prolonged effect on the biological activities. From previous research, introduction of transition metals into drugs gives a better chance to design novel metal based compounds.

2. Materials and Methods

All chemicals and reagents usedfor this research work are of analytical grade without further purification. The solvents were obtained from Aldrich Sigma. Anthranilic acid and Paraaminobenzoic acid were obtained from Sigma-Aldrich company in the United State of America. All the central metal ions used for this work were collected from Department of Industrial Chemistry, University of Ilorin, Ilorin, Kwara State, Nigeria. The melting point of used was determined and noted by Gallen Kamp melting point apparatus at Chemistry Department, University of Ilorin, Ilorin, Kwara state. The molar conductance for the synthesized complexes was performed and recorded with the use of Hanna instruments and EC 214 Conductometer Bridge at Industrial Chemistry Department, University of Ilorin, Ilorin Kwara state. The FT- Infra-red spectra of the free ligands and the synthesized complexes were reported using FT-IR spectrophotometer in the range of 4000 – 400 cm^{-1} at Redeemer University, Lagos state. Elemental analysis of both the ligands and the complexes was carried out using Perkin Elmer 204C micro-analyser atMedac limited company, Brunnel science centre, Eghan, United Kingdom. The selected organisms used were obtained from the Department of Microbiology, University of Ilorin Teaching Hospital, Ilorin, Kwara State Nigeria.The Wister rats used were collected from the Department of Biochemistry, University of Ilorin, Ilorin, Kwara state Nigeria. The percentage of the metal content was determined and recorded using Atomic Absorption Spectrometer (Thermo S-series) at ObafemiAwolowo University, Ile Ife, Osun state Nigeria.

2.1. Synthesis of the Complexes

Procedure followed by Bamigboye *et al*.,2018 [13] was adopted. About 2 mmol (0.71 g) of Amodiaquine was dissolved in 10 ml of DMSO, 2 mmol(0.27 g) of Paraaminobenzoic acid in 10 ml of ethanol and 2 mmol of the metal ions (Cu(II), Mn(II) and Ni(II)) used were dissolved in 10 ml of distilled water. The solutions were mixed together thoroughly and the pH was adjusted to 8.0 with the use of 0.10 molar sodium hydroxide solution. The mixed solutions were refluxed at 78℃ for 3 hours with continuous stirring. After, it was allowed to cool and left to stand for some days. A form of precipitate was observed, filtered and washed by recrystallization in 50percent v/v water – 50 percent v/v ethanol mixture.

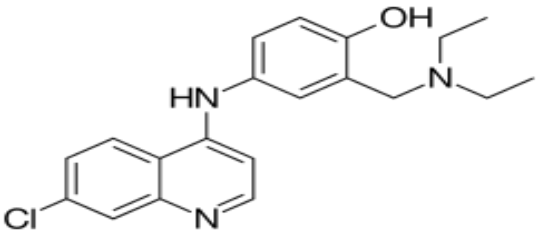


Figure 1- Structure of Amodiaquine

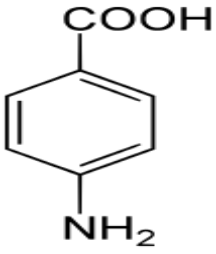


Figure 2- Structure of Paraaminobenzoic acid

2.2 Antimicrobial activity

The prepared complexes and their ligands have been screened *in-vitro* for evaluation of their antibacterial activity against some selected organisms: *Escherichia coli, Staphylococcus aureus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans, Aspergillus niger* and *Penicillium chrysogenum* following broth dilution techniques [18]. About 3 percent of Luria broth solution was prepared and the pH was adjusted at room temperature. The solution was sterilized by autoclaving at 37 ℃ for 1 h. Both the bacterial and fungal organisms were prepared in the broth. They were incubated at 37 ℃ for 24 h. The solution of the synthesized complexes has been prepared in Dimethylsulfoxide at different concentrations 10, 20, 30, 40 µg/ml. The solutions of the parent free ligands (Amodiaquine and Paraaminobenzoic acid) were also prepared in DMSO. Solutions of the complexes were inoculated into 10 ml of Luria broth for each of the concentration respectively. Each of the test-tube containing the solvent acts as the control. The test tubes were inoculated with organisms to be tested. Immediately, it was incubated at the

temperature of 37 ℃ for 24 h. The test tubes were screened for turbidity. The activities were carried out in triplicates.

The zones of inhibition were determined according to the following equation.

Zones of inhibition (%) = $\frac{A - B}{A}$ X 100

A = Average diameter of the growth on the control

B =Average diameter of the growth on the screened plate.

2.3. Biochemical analysis of the complexes

2.3.1. Toxicological activity

The toxicological activity of the complexes and their ligands are carried out following Ogunniran *et al.,* 2008 methods [19]. The level of safety of the complexes was compared with the parent free ligands. About 30 Wister rats were used. They were weighed and grouped into seven. They were fed for seven days and was sacrificed immediately. The tested rats were grouped as follows:

Group 1: Control (2% DMSO)

Group 2: Amodiaquine

Group 3: Paraaminobenzoic acid

Group 4: $Cu(AMD)(SA)Cl_2$

Group 5: $Mn(AMD)(SA)Cl_2$

Group 6: $Ni(AMD)(SA)Cl_2$

2.3.2. **Administration of the complexes and the free parent ligands**

Solution of the synthesized complexes and their parent free ligand in Dimethylsulfoxide (DMSO) were prepared. Body weight of 25 mg/kg and 50 mg/kg per body weight of the complexes and ligands were administered to the Wister ratsfor seven days.

2.3.3. **Serum Preparation**

Blood samples were obtained immediately the Wister ratswere sacrificed. Serum samples were also collected by centrifuging for 10 min. at 1400 RPM which were carefully pipette out from the blood sample. They were kept in the freezer for further analysis.

2.3.4. **Homogenization of the Kidney**

The kidney was collected from the sacrificing rats which were weighed and homogenized by grinding until smoothly. Sucrose solution (10 ml) were prepared and added to the homogenized kidney. They were transferred into clean sample bottles which were centrifuge for10 minutes at 1400 RPM and left to cool. They were later pipetted out into another sample bottle which was kept in the freezer for further analysis.

2.4. Determination of Stoichiometry of the Complexes

Job's method of continuous variation was used and adopted for determining stoichiometry of the synthesized complexes [36]. Solutions of Amodiaquine, Paraaminobenzoic acid and copper ion were mixed together and stirred for about 3-4 h which were left to equilibrate. Absorbance were determined and noted at the λ-max of each of the compounds.

2.5. Determination of Aqueous Solubility

About 15 ml of each solution of the complexes and their ligands at a determined temperature (20 ºC) were allowed to evaporate to dryness. The weight of the dried residue was determined. The data obtained from the solubility of both the ligands and the complexes were compared. The solubility can be determined using the following equation. S = mass/volume x 100 [20].

2.6. Relative Thermal and Acid Stabilities

Procedure followed by [2] was adopted. Dilute solution of about 0.10 mg/ml of the ligands and their complexes were prepared. Solution of each of the complexes and their ligands were divided into five groups. The temperature was adjusted to10 ºC, 20 ºC, 30 ºC, 40 ºC and 50 ºC respectively for 24 h. The same concentration was also used to prepare the solutions of the compounds at pH 1-6. Absorbance were determined and noted. The differencein absorbance with pH and temperature followed Beer-Lambert law.

3. Results and Discussion

Table 1-Physicochemical properties of the Ligands and their Complexes

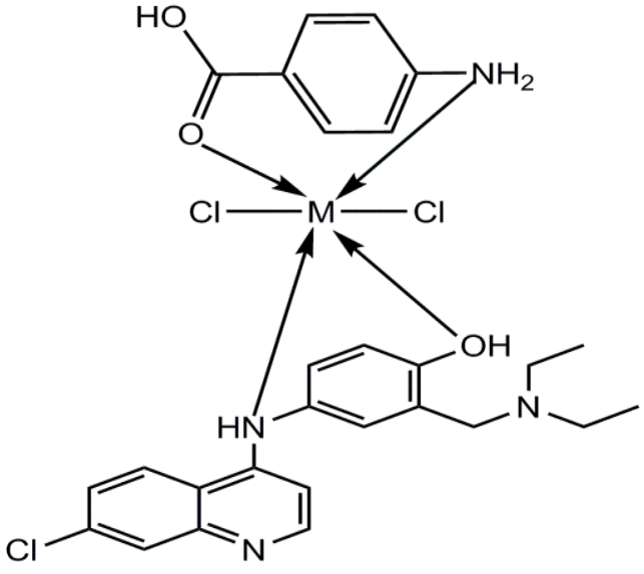
Ligands/ Complexes	Yield (%)	Colour	Melting point (^{o}C)	Conductivity (ohm^{-1}cm^{2}mol^{-1})	μ_{eff} (BM)
[AMO]	70	Yellow	206-208	-	-
[PABA]	65	White	187-189	-	-
Cu(II) Complex	60	Green	256-257	11	1.69
Mn(II) Complex	86	Brown	294-296	7	4.96
Ni(II) Complex	62	Green	244-246	14	1.20

Table 2- Elemental Analysis Data

Ligands/ Complexes	Elemental analysis (Experimental/Theoretical)			
	C	H	N	M
[AMO]				-
[PABA]				-
Cu(II) Complex	48.21/48.98	4.70/4.49	8.31/8.57	12.45/12.96
Mn(II) Complex	48.99/49.85	4.38/4.57	8.76/8.72	11.63/11.40
Ni(II) Complex	49.04/49.46	4.50/4.53	8.43/8.66	12.64/12.10

3.1. Chemistry of the ligands and their complexes

The physicochemical properties of the ligands and their complexes are presented in Table 1. The complexes showed a high percentage yield and were found to be stable in air. The low molar conductance values of the complexes indicated that they are non-electrolytic in nature. The melting points of the complexes were found to be higher than the free ligands when compared. Based on the elemental analysis (Table 2), it was observed that the complexes are in good agreement with each other indicating the mole ratio of 1:1:1 in all the complexes.



Where M = Cu(II), Mn(II), Ni(II)

Figure 3-Proposed structure of the AMO-PABA metal(II) complexes

Table 3- Infrared spectra of the ligands and their complexes

Ligands/ Complex	Wavenumber (cm^{-1})						
	(O-H)	(N-H)	(C=O)	(C=N)	Asy(COOH)	Sym (COOH)	(M-Cl)
[AMO]	3469	3380	-	1540	1791	1706	-
[PABA]	3534	3394	1608	-	1741	1614	-
Cu(II) Complex	3523	3416	1622	1582	1725	1671	652
Mn(II) Complex	3498	3428	1629	1576	1728	1696	677
Ni(II) Complex	3570	3465	1667	1594	1711	1652	591

The IR spectra of the ligands and their complexes are presented in Table 3. It was observed that the broad bands due to OH group of 3469 cm^{-1} is attributed to Amodiaquine [21].Shift to higher frequency (bathochromic shift) were observed in all the metal complexes. This supports coordination through the oxygen of the hydroxyl group from the central metal ions [22]. The IR spectra of the ligands indicate bands which conformto the structure. The strong absorption band at 1760 cm^{-1} which was attributed to COOH of the Amodiaquine was found to be present in all the complexes [23]. The complexes showed two strong absorption bands within the range 1650–1671 $cm^{-1}$and 1711 – 1728 cm^{-1} which are indicative of symmetric and asymmetric COOH respectively [24]. This confirmed corroboratively the deprotonation of COOH group and its coordination through the oxygen of the carboxylic acid [24, 25]. A band at 1608 cm^{-1} is attributed to C=O vibration in the PABA, shifted to higher frequency in the complexes. This proved vibrational changes in the ligand during complexation [26]. The strong absorption bands at 3394 cm^{-1} which was assigned to N-H has been observed to shift to higher frequency in all the complexes which indicate coordination of nitrogen of amine group. The spectra of the complexes showed new bands within 590-680 cm^{-1} which is assigned to (M-Cl) mode [27] which were found to be absent in the spectra of the parent free PABA. Coordination to the central metal ions is through the carboxylic acid due to its acidic nature as observed from previous research [28]. All the complexes have been confirmed to be in octahedral geometry as shown in Figure 3.

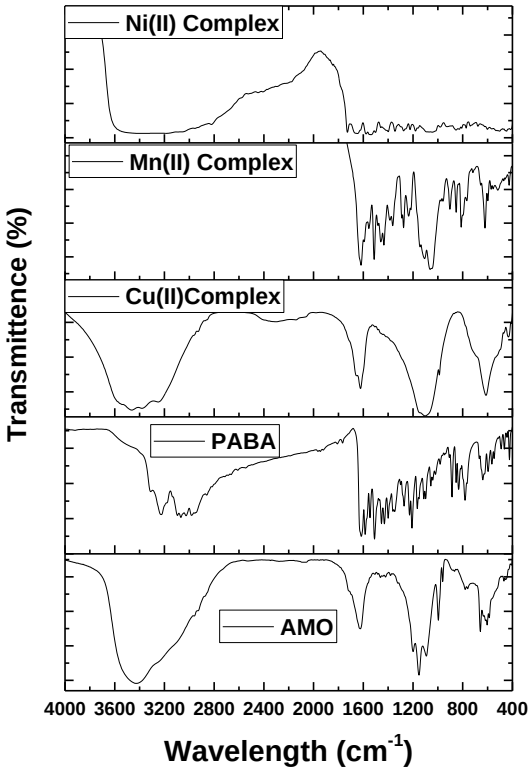


Figure 4-Ultraviolet-visible spectra of the ligands and complexes

Table 4- Electronic spectra of the ligands and their complexes

Ligands/Complexes	Wavelength (cm^{-1})	Assignments
[AMO]	200	$\pi \rightarrow \pi^*$
	319	$n \rightarrow \pi^*$
	362	$n \rightarrow \pi^*$
[PABA]	195	$\pi \rightarrow \pi^*$
	246	$\pi \rightarrow \pi^*$
Cu(II) Complex	273	Intra-ligand
	348	C.T.
	598	$^2T_{1g}(F) \rightarrow {}^2T_{1g}(P)$
Mn(II) Complex	259	Intra-ligand
	376	C.T
	451	MLCT
Ni(II) Complex	360	C.T.
	446	$^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$
	543	$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$

The electronic spectra for the parent free ligands and their synthesized complexes are presented in Table 4. The UV spectrum of Cu complex shows three absorption bands at 273, 348 and 598 nm which are attributed to Intra-ligand, charge transfer and $^{2}T_{1g}(F) \rightarrow {}^{2}T_{1g}(P)$ transition. The Ultraviolet-visible spectrum of Mn(II) complex revealed three absorption peaks of 259, 376 and 451 nm which are due to intra ligand, charge transfer and MLCT respectively when compared with the spectra of the ligands. This confirmed an octahedral environment around the Mn(II) complex [21].The ultraviolet-visible absorption band of Ni(II) complex showed three bands of 360, 446 and 543 nm which are assigned to charge transfer, $^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(F)$ and $^{3}A_{2g}(F) \rightarrow {}^{3}T_{2g}(F)$ respectively. This showed an evidence of an octahedral structure around the complex [29]. Bathochromic shift was observed in all the complexes.

Antimicrobial activities of the ligands and their complexes

Table 5- Antibacterial activities

Ligand/ Complexes	*K. pneumonia*	*B. subtilis*	*E. coli*	*S. aureus*	*P. aeruginosa*	*S. faecalis*
			Zone of inhibition (mm)			
[AMO]	5.12 ±0.23[a]	0	4.33 ±0.13[a]	5.24 ±0.29[a]	2.53 ±0.53[b]	6.61 ±0.41[a]
[PABA]	0	0	0	0	0	0
Cu(II) Complex	27.36 ±0.57[b]	35.59 ±0.52[a]	37.35 ±0.28[b]	30.25 ±0.82[a]	35.26 ±0.35[a]	29.71 ±0.62[a]
Mn(II) Complex	22.41 ±0.43[b]	26.32 ±0.47[a]	47.03 ±0.47[a]	32.52 ±0.73[b]	29.33 ±0.45[a]	34.50 ±0.37[a]
Ni(II) Complex	25.36 ±0.71[a]	26.30 ±0.55[b]	37.11 ±0.48[b]	23.06 ±0.47[a]	30.44 ±0.26[b]	34.49 ±0.34[b]

Values are mean ± standard deviation of three replicates. Values in the same column with different superscript from their free parent ligands are significantly different at $P< 0.05$.

Table 6- Antifungal activities

Ligand/ Complexes	*Candida albicans*	*Aspergillusniger*	*Penicilliumchrysogenum*
	Zone of inhibition (mm)		
[AMO]	3.07±0.35[a]	1.04±0.57[a]	6.39±0.76[b]
[PABA]	6.21±0.52[a]	4.03±0.41[b]	4.37±0.96[a]
Cu(II) Complex	20.39±0.51[b]	45.37±0.43[b]	37.63±0.32[a]
Mn(II) Complex	35.80±0.60[a]	30.25±0.74[a]	27.05±0.39[b]
Ni(II) Complex	27.57±0.84[a]	26.34±0.53[a]	31.85±0.47[b]

Values are mean ± standard deviation of three replicates. Values in the same column with different superscript from their free parent ligands are significantly different at $P< 0.05$.

Procedure followed by Bamigboye *et al*., 2017 [18] was adopted. The parent free ligands and their complexes were screened and evaluated as presented in Table 5 and 6. From the result obtained, the complexes were compared with the parent free ligands. It was observed that the complexes have better antibacterial and antifungal activity than the ligands. This suggests that the complexation could help to enhance the ability of the complexes to cross a cell membrane [30]. Mn(II) complex has the highest antibacterial activity with 47.03 mm inhibitory zone against *E. coli* when compared with other complexes. Furthermore, the same complex has the lowest activity at 22.41 mm against *K. pneumonia.* However, all the complexes generally showed higher activities compared to the parent free ligands. Cu(II) complex showed the lowest antifungal activity against *Candida albicans*. From previous research, it has been observed that copper kills organisms due to presence of activated oxygen on the surface of copper. The improvement of the complexes in the activity can be determined based on chelation theory [31]. Chelation processes help to decrease the polarity of the central metal ions as a result of partial sharing of its cation with the donor group. It has been observed that Mn(II) and Ni(II) complexes has the same zone of inhibition of averagely 26 nm and 34 nm against *B. subtilis* and *S. faecalis* respectively. From previous work, it has been observed that complexes in the presence of nitrogen and oxygen atoms could enhance the activity of microbial enzymes. Synthesis of complexes helps to decrease the level of polarity of metal ions as a result of sharing positive charges by donating atom in complex ring systems [32, 33]

Toxicological activities

Table 7- Toxicology screening of the free ligands and their complexes against serum homogenate

Ligand/Complexes	Enzyme activity (nM/min/mg protein)
[AMO]	48
[PABA]	57
Cu(II) Complex	74
Mn(II) Complex	94
Ni(II) Complex	79

Table 8- Toxicology screening of the free ligands and their complexes against Kidney homogenate

Ligand/Complexes	Enzyme activity (nM/min/mg protein)
[AMO]	26
[PABA]	35
Cu(II) Complex	53
Mn(II) Complex	58
Ni(II) Complex	76

The result obtained from Alkaline phosphate activities in Kidney and serum homogenate of the ligands and its complexes when compared with the control are presented in Table 7 and 8. From the result obtained, it was observed that the serum homogenate indicate significant increase ($P< 0.05$) in the activity when compared with the control. The free ligands showed no significant difference in comparison with the control. The free ligands showed non-significant difference in comparison with

the control. This is because high increase in the enzyme activity might not destroy the plasma membrane of the organ. *In-vitro* administration of the compounds help to increase the enzyme activity more than the level of its tolerance which has no significant value (P<0.05) when compared with the control value. This indicated damage effect of the complexes [34].

Table 9- Aqueous solubility of the compounds

	Solubility (gdm^{-3})	
Compounds	**Pure ligand**	**Cu^{2+} complex**
Amodiaquine [AMO]	Negligible	7.20
Paraaminobenzoic acid [PABA]	> 1	3.51

Table 10- Absorbance of the compounds at different temperature (Relative Thermal Stability)

Temperature /Compounds	**10 (^{o}C)**	**20 (^{o}C)**	**30 (^{o}C)**	**40 (^{o}C)**	**50 (^{o}C)**	**λ max (nm)**
[AMO]	0.532	0.536	0.541	0.530	0.524	376
[PABA]	0.180	0.197	0.216	0.211	0.207	228
[AMO]- Cu^{2+}	0.718	0.739	0.746	0.727	0.723	400
[PABA]- Cu^{2+}	0.325	0.329	0.344	0.337	0.321	324

Table 11- Absorbance of the compounds at different pH (Relative Acid Stability)

Temperature /Compounds	**pH 1**	**pH 2**	**pH 3**	**pH 4**	**pH 5**	**pH 6**	**pH 7**	**λ max (nm)**
AMO	0.312	0.324	0.328	0.336	0.351	0.375	0.393	318
PABA	0.261	0.272	0.277	0.282	0.288	0.294	0.297	323
AMO- Cu^{2+}	0.276	0.280	0.283	0.294	0.297	0.319	0.325	596
PABA- Cu^{2+}	0.523	0.528	0.533	0.567	0.573	0.582	0.591	428

Coordination helps to manipulate redox potentials ligands which depend on reactivity and stability. As the redox potential increase, the higher the reactivity and decrease in stability. Based on the data obtained from the absorbance of the complexes and parent free ligands at different temperature and pH, the change in absorbance were found to be significant in the parent free ligands and non-significant in the complexes at a determined temperature (70℃). This confirmed the concentration of the complexes to be high at that particular temperature. This might also be as a result of high ability of the complexes to hold in an acidic medium. It was also observed that the ligands are not stable in both aqueous and acidic medium which prove that complexes are more stable than their parent free ligands as presented in Table 8 to 10 [35, 36].

4. Conclusions

New alternative mixed complexes of Amodiaquine and Paraaminobenzoic acid have been synthesized. The ligands were found tobe bidentate. The obtained complexes exhibited better physicochemical properties. Octahedral geometry has been proposed for all the complexes. The complexes are envisaged to be promising antimicrobial agents due to their effectiveness when compared with the ligands. The toxicity studies signpost that the complexes are less harmful to the body system.

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