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Novel Metal Complexes of Mixed Piperaquine-Acetaminophen and Piperaquine-Acetylsalicylic acid: Synthesis, Characterization and Antimicrobial Activities

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Abstract: Synthesis of coordination compounds of zinc(II), copper(II), nickel(II), cobalt(II), and iron(II) with mixed piperaquine-acetaminophen and piperaquine-acetylsalicylic acid has been studied. The complexes were characterized via the following: solubility test, melting point determination, conductivity measurement, atomic absorption spectroscopy, UV-Visible spectrophotometry, FTIR spectroscopy and magnetic susceptibility. The complexes were proposed to have a stoichiometry ratio of 1:1:1 between each metal salt and the ligands with tetrahedral and octahedral geometry following the reaction pattern of $MX.yH_2O + L_1L_{2/3}$ to give $ML_1L_{2/3}X.yH_2O$. Biological activities of the synthesized complexes have been evaluated against *Escherichia coli* and *Staphylococcus aureus*.

Keywords: Antimalarial activity; analgesic compounds; mixed ligands; spectroscopy; biological activities.

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INTRODUCTION

Malaria is one of the major devastating diseases affecting humans since the dawn of history. Over half a billion people are infected with malaria parasite while more than a million die annually from its effect [1]. Children and mostly people with low-income economy are more vulnerable; averagely 3000 children die daily from malaria in Africa [2]. Malaria is caused by an infection of the body by single-cell plasmodia protozoa; though being a very simple organism, it has a complex life cycle with many forms [3]. Since the discovery of the naturally-occurring alkaloids, quinine is an effective therapeutic drug against malaria, numerous antimalarial drugs such as quinacrine, chloroquine, sulfadoxine, *etc* have been in circulation, until the parasites developed resistance against most of them. Currently, pyrimethamine, sulfonamide, artemisinin, and its derivatives, halofantrine, clindamycin, piperaquine, *etc* are mostly in use [4]. The parasites are developing resistance against most of the monotherapy antimalarial drugs, making them less effective; thus, the emergence of combination therapy in forms of Artemisinin Combination Therapies (ACTs) *e. g.* Coartem$^{(R)}$, Artekin$^{(R)}$ *etc*. Fansidar$^{(R)}$ is another combination therapy containing sulfadoxine and pyrimethamine; which possess a better efficacy against the monotherapy-resistant malarial parasites than their respective single forms [5]. Piperaquine is a derivative of quinine, belonging to the 4-aminoquinoline groups. It was replaced for chloroquine in 1978 in China as a first line monotherapy for malaria and metric tons were dispensed for mass prophylaxis until resistant become too high [6]. Recently, piperaquine had become an object of renewed interest as a partner drug in ACTs. Dihydroartemisinin-piperaquine (Artekin) is one of the most common artemisinin combination for effective, short-course, and affordable malaria therapy with limited side effects and lower risks of recurrence of *falciparum* parasite [7]. Synriam$^{(R)}$, containing 150 mg arterolane maleate and 750 mg piperaquine phosphate is an oral fixed-dose combination antimalarial for *Plasmodium falciparum* and *Plasmodium vivax* in children and adults [8]. These and many more justify the aim of this research effort; to develop an antimalarial-analgesic fixed combination therapy against the strains of monotherapy-resistant *plasmodium* parasites especially those associated with fever and severe pain symptoms. Thus, the synthesis of piperaquine-acetaminophen and piperaquine-acetylsalicylic acid becomes a worth-taking approach of antimalarial research.

Materials

All chemicals used are of analytical and reagent grades, used as commercially obtained without further purification. Piperaquine phosphate (antimalarial ligand) was obtained from Zhuhai Runde Pharmaceutical Ltd., Guangzhou province, China, while acetaminophen and acetylsalicylic acid (analgesic ligands) were obtained from Rajrab Pharmeceutical Ltd., Ilorin. Transition metal salts and other solvents were obtained from Aldrich, BDH England.

EXPERIMENTAL

Synthesis of mixed piperaquine-acetaminophen metal complexes

The complexes were synthesized following some reported procedure with slight analytical modifications [5], [9], [10]. An aqueous-ethanolic solution of each metal salt (0.01 mol of each) was prepared in a round-bottomed flask. 5.355 g (0.01 mol) of piperaquine phosphate was mixed with 1.512 g (0.01 mol) of acetaminophen in a beaker. The mole ratio of the mixture of piperaquine phosphate, metal salt and acetaminophen was 1:1:1. The mixed ligands were dissolved in 20 mL of 5% lactic acid due to poor solubility of piperaquine in water even when fully ionized [19] and added to each solution of the corresponding metal salt dissolved previously in 10 mL of ethanol in a round-bottomed flask fitted with a condenser. The pH of the mixture was maintained by the addition of 10% methanolic ammonical solution. The mixture was refluxed at 70°C for 4 hours and kept thereafter in a refrigerator for 30 minutes for the metal chelate to crystallize. The crystals were then filtered and washed with dilute lactic acid and then distilled water to remove unreacted ligands and metals. The complexes were then dried in a desiccator for 3 days. The same procedure was applied for all metal salts.

Synthesis of mixed piperaquine-acetylsalicylic acid metal complexes

The procedure as reported above [5], [9], [10] was followed with some slight modifications such as change in analgesic ligands and the reflux time.

Determination of some properties of the complexes

Physical observations of the colors of the synthesized complexes were made and compared with those of the free ligands and the metal salts. The percentage yields were calculated and approximated to the nearest whole number. The melting points and conductivities were measured using Gallenkamp melting point apparatus and WTW conductimeter bridge, respectively and the values were recorded to a single whole number without range. Purity of the complexes was confirmed as a single spot on a thin layer chromatography (TLC) plate. Magnetic susceptibilities were deduced from the magnetic moment obtained on Sherwood Scientific Magnetic Susceptibility Balance. Infrared spectra of the synthesized complexes and the free ligands were recorded in KBr pellets using a Shimadzu FTIR-8400s (IR solution model) in the range of 4000 – 500 cm^{-1}. As a UV-Visible spectrometer, Beckman Coulter DU-730 was used to run the electronic transition of the complexes and the free ligands. Atomic Absorption Spectroscopy (AAS) analysis was used to determine the metal content of the complexes (which confirms evidence of coordination) was carried out using the Alpha 4 AAS PM 8251 single pen recorder.

Antimicrobial Screening

Antimicrobial activities of the free ligands and the complexes were deduced from their inhibitory potentials against *Escherichia coli* and *Staphylococcus aureus* on the basis of zones formed around their wells [5], [9].

Results

Table 1: Reaction pattern between ligands and metal salts to form complexes

$MX.yH_2O + L_1L_2 \rightarrow [ML_1L_2]X.yH_2O$
$MX.yH_2O + L_1L_3 \rightarrow [ML_1L_3]X.yH_2O$
Where M = Cu(II); Co(II); Zn(II) and Fe(II)
X = Cl_2, SO_4 and OAc_2
L_1, L_2 and L_3 = Piperaquine, Acetylsalicylic acid, Acetaminophen

Ligands + Metal salt	**Proposed chemical formula**
PQ + PC + $CuCl_2$	$Cu(PQ)(PC)Cl_2$
PQ + PC + $Co(OAc)_2$	$Co(PQ)(PC)(OAc)_2$
PQ + PC + $ZnSO_4$	$Zn(PQ)(PC)SO_4$
PQ + PC + $FeCl_2$	$Fe(PQ)(PC)Cl_2$
PQ + AS + $Cu(OAc)_2$	$Cu(PQ)(AS)(OAc)_2$
PQ + AS + $ZnSO_4$	$Zn(PQ)(AS)SO_4$

(See Fig. 1-3 below)

Proposed Complex Structures

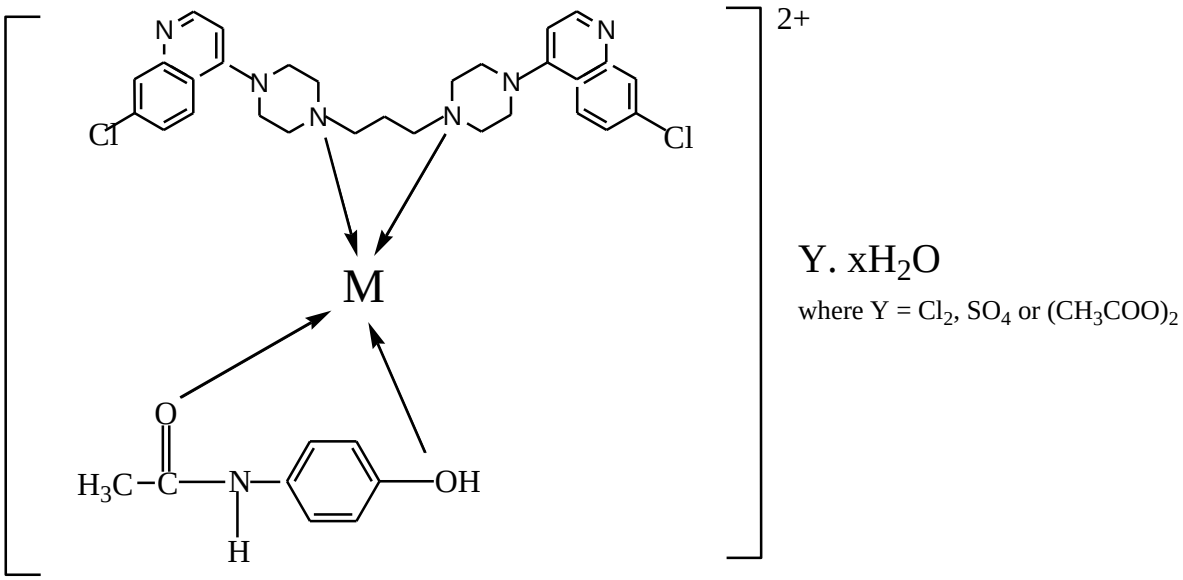

Figure 1: M-(PQ)(PC): Where M = Cu(II), Zn(II), Co(II), and Fe(II) ions.

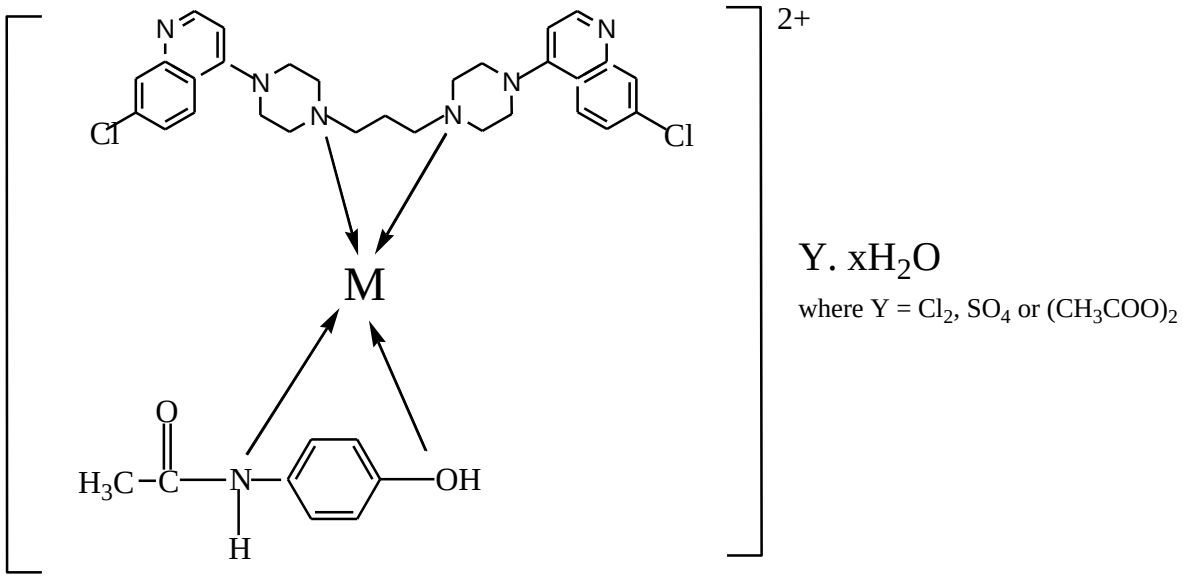

Figure 2: M-(PQ)(PC): Where M = Cu(II), Zn(II), Co(II), and Fe(II) ions.

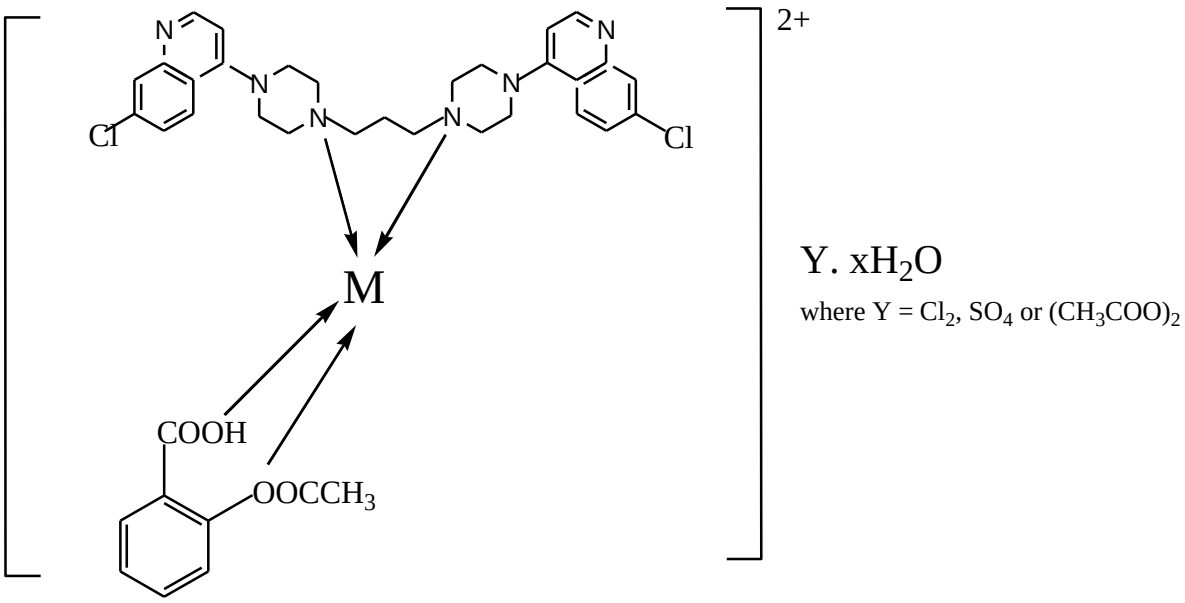

Figure 3: M-(PQ)(AS): Where M = Cu(II), Zn(II), Co(II), and Fe(II) ions.

Table 2: Some physical properties of the ligands and the complexes.

Sample	**Color**	**Yield (%)**	**M. P. (˚C)**	**Metal Content (%) Experimental (Calculated)**	**Conductivity ($\Omega^{-1}cm^{-1}$)**
PQ	White-yellow	-	249	-	6.2×10^{-6}
AS	White	-	138	-	3.3×10^{-4}
PC	White	-	169	-	4.1×10^{-4}
$Cu(PQ)(PC)Cl_2$	Blue	36	155	8.20 (7.93)	8.3×10^{-5}
$Co(PQ)(PC)(OAc)_2$	Faded pink	68	195	7.10 (6.85)	8.2×10^{-5}
$Zn(PQ)(PC)SO_4$	White	76	219	12.30 (14.26)	6.1×10^{-5}
$Fe(PQ)(PC)Cl_2$	Grey	25	205	6.60 (6.58)	6.5×10^{-5}
$Cu(PQ)(AS)(OAc)_2$	Blue	28	206	8.10 (7.57)	3.5×10^{-5}
$Zn(PQ)(AS)SO_4$	White	20	170	7.60 (7.52)	3.2×10^{-6}

Table 3: Solubility of the ligands and the complexes in some selected solvents.

Sample	**H_2O (r.t.p)**	**H_2O (100 °C)**	**Ethanol**	**Dil. Lactic Acid**	**Acetone**	**DMSO**	**Methanol**
PQ	SS	S	IS	S	IS	IS	IS
AS	SS	S	SS	SS	IS	S	S
PC	IS	IS	S	SS	SS	S	S
$Cu(PQ)(PC)Cl_2$	IS	S	IS	S	SS	SS	SS
$Co(PQ)(PC)(OAc)_2$	IS	SS	SS	S	IS	S	SS
$Zn(PQ)(PC)SO_4$	IS	SS	IS	S	IS	S	IS
$Fe(PQ)(PC)Cl_2$	SS	SS	IS	IS	IS	S	SS
$Cu(PQ)(AS)(OAc)_2$	SS	S	IS	S	IS	S	SS
$Zn(PQ)(AS)SO_4$	SS	S	IS	S	IS	S	IS

S = Soluble; SS = Sparingly soluble; IS = Insoluble.

Table 4: Magnetic moments, electronic transition and Some FTIR spectra assignment

Sample	**μ_{eff} (BM)**	**Water λ_{max} (nm)**	**V(N-H) cm^{-1}**	**V(O-H)cm^{-1}**	**V(C=O) cm^{-1}**
PQ	-	379	3433.41 m,b	-	-
AS	-	282	-	2999.41 m,b	1691.63 s,S
PC	-	306	3327.32 s,b	3161.43 m,	1654.98 s
$Cu(PQ)(PC)Cl_2$	2.23	392	3327.32 s,b	3163.36 b	1654.98 s,S
$Co(PQ)(PC)(OAc)_2$	4.78	389	3649.14 w	3055.35 m	1606.76 m
$Zn(PQ)(PC)SO_4$	1.89	392	3541.42 s,b	-	1633.76 m,b
$Fe(PQ)(PC)Cl_2$	5.10	250	3381.33 s,b	-	1624.12 m
$Cu(PQ)(AS)(OAc)_2$	2.30	390	3441.12 m,b	3234.73 w	1622.19 m
$Zn(PQ)(AS)SO_4$	1.76	393	3358.18 s,b	3066.92 m,b	-

m = medium; b = broad; s = strong; w = weak; S = sharp

Table 5: Biological activities of the ligands and the complexes

Sample	Concentration (%)	Zone of Inhibition in *Staphylococcus aureus* (mm)	Zone of Inhibition in *Escherichia coli* (mm)
PQ	1.0	3.55	5.60
AS	1.0	2.50	4.00
PC	1.0	2.00	3.50
$Cu(PQ)(PC)Cl_2$	1.0	5.00	5.00
$Co(PQ)(PC)(OAc)_2$	1.0	4.20	5.80
$Zn(PQ)(PC)SO_4$	1.0	4.80	5.00
$Fe(PQ)(PC)Cl_2$	1.0	5.20	5.80
$Cu(PQ)(AS)(OAc)_2$	1.0	3.25	5.00
$Zn(PQ)(AS)SO_4$	1.0	4.60	5.40

DISCUSSIONS

The complexes (Table 2) show different colors due to the presence of transition metal charge transfer to the ligands transition compared to the free ligands [11], [12]. The percentage yield of the complexes varied due to different factors such as the variation in electronic configuration of the metal ion in d-orbital, size of the ion, nature of the electron donation agent (donating atom on the ligand), functional groups of the ligands as Lewis bases and the reaction conditions [12]. The highest percentage yield was observed in $Zn(PQ)(PC)SO_4$ while the lowest was found in $Zn(PQ)(AS)SO_4$. The synthesized complexes were photo- and thermo-stable crystals with varied melting points due to the octahedral and tetrahedral geometry (Figures 1-3) of the transition metal complexes. The melting points of free piperaquine (PQ) ligand are higher than those of the complexes [9]. The percentage metal content as found experimentally is in good agreement with the calculated values as the data in Table 2 reveal. Molar conductivities of the metal complexes in water show non-electrolytic behavior of the free ligands and the complexes in the solvent.

The results of solubility tests (Table 3) show the solubility nature of the free ligands and the complexes in distilled water (at room temperature and at 100 ^{0}C), ethanol, dilute lactic acid, acetone, dimethylsulfoxide (DMSO), and methanol. Most of the complexes dissolved completely

in hot water and dilute lactic acid, some dissolved sparingly in DMSO and methanol, while others are practically insoluble in ethanol and acetone. None of the complexes is soluble in water, $Fe(PQ)(PC)Cl_2$, $Cu(PQ)(AS)(OAc)_2$ and $Zn(PQ)(AS)SO_4$ are sparingly soluble while Cu(PQ)(PC), $Co(PQ)(PC)(OAc)_2$ and $Zn(PQ)(PC)SO_4$ are insoluble. In ethanol, none of them is soluble, $Co(PQ)(PC)(OAc)_2$ is sparingly soluble while others are insoluble. In dilute lactic acid, all the complexes are dissolved well except $Fe(PQ)(PC)Cl_2$ which is sparingly soluble. None is fully dissolved in acetone; only $Cu(PQ)(PC)Cl_2$ is sparingly soluble, others are practically insoluble. In DMSO, only $Cu(PQ)(PC)Cl_2$ is sparingly soluble, others dissolve well and none is insoluble. None of the complexes fully dissolves in methanol, $Zn(PQ)(PC)SO_4$ and $Zn(PQ)(AS)SO_4$ are insoluble while others are sparingly soluble.

The results of the magnetic moment (Table 4) show that Co(II) and Zn(II) complexes conform in a stoichiometric manner with tetrahedral geometry while Cu(II) and Fe(II) are proposed within the range of octahedral configuration. It also reveals that some of the $Zn(PQ)(PC)SO_4$ and $Zn(PQ)(AS)SO_4$ complexes are diamagnetic due to unavailable of unpaired electrons on d-orbital of the Zn^{2+} ion, $Fe(PQ)(PC)Cl_2$ are ferromagnetic, while Cu(PQ)(PC), $Co(PQ)(PC)(OAc)_2$ and $Cu(PQ)(AS)(OAc)_2$ are paramagnetic due to the presence of unpaired electron on d-orbital of the Cu^{2+} and Co^{2+} ions. The analytical data obtained provides a supportive evidence for the stoichiometric ratio of 1:1:1 between the metal ion and the ligands [14], [15]. The free piperaquine, acetylsalicylic acid and acetaminophen show a λ_{max} of 379 nm, 282 nm and 306 nm respectively on UV-Visible spectroscopy. The shifting of these bands to a higher wavelength in $Cu(PQ)(PC)Cl_2$, Co(PQ)(PC)(OAc), $Zn(PQ)(PC)SO_4$, $Cu(PQ)(AS)(OAc)_2$ and $Zn(PQ)(PC)SO_4$ confirmed the effective coordination and the formation of complexes between the metal ions and the ligands [9]. Although the λ_{max} values for $Cu(PQ)(PC)Cl_2$, $Cu(PQ)(AS)(OAc)_2$ and $Zn(PQ)(PC)SO_4$ did not really cross the border from UV to Visible region but could be approximated to the visible region and having slight evidences for d-d electron transition – hence the coloration [11]. The selective infrared spectral assignment of free ligands and the complexes have been carried out based on similar compounds [14, 16, 17]. The medium broad absorption band of 3433.41 cm^{-1} found in the spectrum of free piperaquine and the strong broad band of 3327.32 cm^{-1} in free acetaminophen due to N-H stretch have undergone a hyperchromic shifts to 3649.44 cm^{-1} and 3541.42 cm^{-1} in $Co(PQ)(PC)(OAc)_2$ and $Zn(PQ)(PC)SO_4$ respectively. The bands for N-H stretch in free piperaquine and acetaminophen have also undergone a hypsochromic shifts to 3381.33 cm^{-1}, 3441.12 cm^{-1} and 3358.18 cm^{-1} in $Fe(PQ)(PC)Cl_2$, $Cu(PQ)(AS)(OAc)_2$ and $Zn(PQ)(AS)SO_4$ respectively. Infrared spectra which can also probe coordination: The shifting of these N-H bands provides evidence of complex formation which is supported by the disappearance of broad 2999.41 cm^{-1} and 3161.43 cm^{-1} in free acetylsalicylic acid and acetaminophen spectra assigned to O-H in $Zn(PQ)(PC)SO_4$ and $Fe(PQ)(PC)Cl_2$. The strong absorption bands of 1691.63 cm^{-1} and 1654.98 cm^{-1} found in acetylsalicylic acid and acetaminophen respectively have disappeared in $Zn(PQ)(AS)SO_4$ and undergo various shifts in other complexes. The variation in the frequencies of the bands of the free ligands compared to

those of the complexes denotes the change in vibrational pattern of the ligands upon coordination to metal ions (see Figures 1, 2, and 3).

The presence of some anions such as Cl^-, SO_4^{2-} and CH_3COO^- are confirmed by the reaction of the solutions of the metal complexes with aqueous $AgNO_3$, aqueous $BaCl_2$ and neutral $FeCl_3$ [18]. The complexes containing Cl^- and SO_4^{2-} ions produce insoluble white precipitates on testing with aqueous $AgNO_3$ and aqueous $BaCl_2$. Those containing CH_3COO^- produce red color with $FeCl_3$ solution [18]. The formation of single spots on each TLC chromatography plate confirmed the purity of the complexes.

The proposed reaction pathways and chemical formulas as given in Table 4 above are derived from the cumulative characterization results.

Table 5 presents the results of the biological activities as antimicrobial tests of the free ligands and the complexes against a gram-positive *Staphylococcus aureus* and *Escherichia coli*. The inhibition growth effects of the complexes against these bacteria strains show significant differences in metal complex sensitivities as compared to the free ligands [9]. From the results, only $Cu(PQ)(AS)(OAc)_2$ have a lower inhibitory effect against *Staphylococcus aureus*, other complexes have higher effects compared to the free parent drugs. Against *Escherichia coli*, piperaquine was experimentally found to possess a higher inhibitory effect than the complexes while the effects of the free acetylsalicylic acid and acetaminophen are lower compared to the complexes. These provide supportive evidences that the metal complexes of mixed piperaquine-acetylsalicylic acid and piperaquine-acetaminophen have greater medicinal therapeutic potential against microorganism activities than their parent drugs.

CONCLUSION

The complexes were synthesized with the ligands (piperaquine, acetylsalicylic acid and acetaminophen) coordinating through N-H, O-H and C=O to the metal ions in the stoichiometric ratio of 1:1:1 to form both tetrahedral and octahedral complexes. Although some reactions yield low complexes while some are impressive, but solubility behaviors to the tested solvents, the melting point and the magnetic susceptibility of the complexes show distinct results from their parent ligands. The metal-ligand coordination is probed with UV-Vis and FTIR spectroscopy. The synthesized complexes were found to possess better physical and antimicrobial properties when compared to their free ligands. Thus, the complexes show a better therapeutic potential against some target bacteria compared to the free antimalarial piperaquine and free analgesic acetylsalicylic acid and acetaminophen and could also be suggested against malaria strains. This conclusion is also supported by the previous relevant research [5, 9, 10, 14, 16]. However, further characterization and *in vitro* and *in vivo* assessment of the complexes to confirm their therapeutic actions against *plasmodium* strains are needed.

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ABBREVIATIONS

PQ – Piperaquine

PC – Acetaminophen

AS – Acetylsalicylic acid

OAc – CH_3COO^-

TLC – Thin Layer Chromatography

FTIR – Fourier Transformation Infrared

UV – Ultraviolet

AAS – Atomic Absorption Spectroscopy

IUPAC – International Pure and Applied Chemistry

ACTs – Artemisinin Combination Therapies

IC50s – Concentrations for 50% parasite growth inhibition

^{1}H NMR – Proton Nuclear Magnetic Resonance

^{13}C NMR – Carbon-13 Nuclear Magnetic Resonance

XRD – X-ray Diffraction

M(II) – Cu^{2+}, Zn^{2+}, Co^{2+} and Fe^{2+}

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Piperakin-Asetaminofen ve Piperakin-Asetilsalisilik Asit İçeren Yeni Metal Kompleksleri: Sentez, Karakterizasyon ve Antimikrobiyal Aktiviteler

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Öz: Çinko(II), nikel(II), kobalt(II) ve demir(II) komplekseleri, piperakin-asetaminofen ve piperakin-asetilsalisilik asit içeren komplekslerin sentezinde kullanılmıştır. Kompleksler şu yöntemlerle karakterize edilmiştir: Çözünürlük testi, erime noktası tayini, iletkenlik tayini, atomic soğurma spektroskopisi, UV-Görünür spektrofotometri, FTIR spektroskopisi ve manyetik duyarlılık ölçümleri. Komplekslerin her bir metal tuzu ve ligandlar arasında 1:1:1 şeklinde bir stokiyometrik orana sahip olduğu ve tetrahedral ve oktahedral geometrinin tercih edildiği bulunmuştur, kompleksleşme tepkimeleri $MX.yH_2O + L_1L_{2/3}$ tepkimesinden $ML_1L_{2/3}X.yH_2O$ komplekslerinin oluşması şeklindedir. Sentezlenen komplekslerin biyolojik aktiviteleri *Escherichia coli* ve *Staphylococcus aureus*'a karşı değerlendirildi.

Anahtar kelimeler: Antimalaryal aktivite; analjezik bileşikler; karışık ligandlar; spektroskopi; biyolojik aktiviteler.

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