SOME METAL-ANTIMALARIAL DRUG COMPLEXES: SYNTHESIS, CHARACTERIZATION AND THEIR EFFECT AGAINST MALARIA PARASITES

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Abstract

A series of metal complexes of Sulfadoxine-Pyrimethamine (SP) have been synthesized and characterized. The crystal structures have been determined by spectroscopic techniques using Infra Red (IR), and UV – visible spectrophotometer along side physical and micro analytical methods .The prymethamine ligand functions as a bidentate donors through (C-Cl) and (N-H) while sulfadoxine through (N-H) and O=S=O making it a chelate compound in 1:2 stoichiometry resulting in octahedral and tetrahedral geometry compounds. The standard drug (chloroquine), parent drug (Primethamine-sulfadoxine) and the complexes were screened against malaria parasites (*Plasmodium beighei, NK65*) for their antimalarial activity using in-vivo method with inhibition level of 91.03%, 93.10% , and 95.17%, 100% respectively. The antimalarial activity of Fe-complex was found to have highest therapeutic value (potency), among the chemotherapeutic agents compared.

Keywords: antimalarial complexes, spectroscopic, malaria, ligands, plasmodium berghei (NK65 clone), *in-vivo*.

Introduction

Fansidar combination therapy that contains pyrimethamine and sulfadoxine as the active components, is the most effective commercially available drug in preventing falciparum malaria in area where chloroquine resistant malaria was already highly prevalent. It is widely used for supperssion. The sulfadoxine-Pyrimethamine (SP) has an entirely different mode of action from that of mefloquine consequently no cross-resistance exists between the two (Balogun and Akanji, 1998). Fansidar allows single-dose treatment. (Roche, 1986). Literatures are mostly on pyrimethanmine-metal complexes and sulfadoxine-metal complexes (Kovala *et al.,* 1986) with no references on their mixed forms. Reports have shown also that sulfadoxine/Pyrimethamine combination does not, however, provide a 100% cure rate even in persons infected with fully sensitive parasites (Wilson and Gisvold, 1984) either as a result of drug loss (vomiting or diarrhoea) or because of individual abnormalities in sulfadoxine metabolism, disposition and elimination. (Obaleye *et al* 1996). Since some of this antimalaria drug is lost as a result of either vomiting or individual abnormalities in metabolism, disposition and elimination of sulfadoxine and the fact that there are no information on the action of mixed ligand complexes, our research effort is therefore intended to carry out a systematic study of a series of metal complexes of sulfadoxine- Pyrimethamine. Herein, we report our results for the reactions of Fe (III), Co (II) and Ni (II) complexes as well as *In vivo* evaluation of the antimalarial activity of these complexes against *Plasmodium bergehi* (NK 65 clonne).

Materials and methods

All the chemicals (metal salts inclusive) used were of analytical grade. The sulfadoxine-Pyrimethamine (ligands) were obtained from SwissPharma Dopemu, Lagos State. All solvents used were purified and dried by vacuum distillation. Vibrations spectral were recorded in KBr/Nujol using NaCl and CsCl cells on Unicam 360 FI infrared spectrophotometer. All other physical measurements and analytical procedures were similar to those described previously by (Obaleye *et al* 1996).

Synthesis of complexes

Each of the complexes was prepared by adding aqueous solution of metal salts to an ethanol solution of the ligand to the drug in a 1:1 or 1:2 mole ratios as preferred by the metal geometry. The solution was refluxed with constant stirring for 2 hours until a colour change is observed or formation of precipitate. The complex formed was recovered from the solution by filtration followed by washing with ethanol and drying in vacuum.

Anti-malarial investigation

Plasmodium berghei (NK 65 Clonne) used in this study was obtained from the Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan. Swiss mice, obtained from the same institute's animal house were inoculated with 0.2 ml x 10^6 parasitized erythrocytes suspended in buffered physiological saline (pH 7.4). After day 4, the degree of parasitaemia was determined from Giemsa stained thin blood smear by examining 1,000 erythrocytes in 4 different fields. This was expressed as a percentage of cells parasitized as described by Sanchez-Delgado *et al* 1996. The concentration of the complexes administered on the mice was based on the standard dose per the animal body weight .The inhibitory values for the drugs and complexes were calculated.

Results and discussion

Physical measurements

The general physical properties of the sulfadoxine-pyrimethamine metal complexes were determined and the results are presented in Table 1.

Table 1: Physical properties of the complexes.

Complexes	Fe (III)	Co (II)	Ni (II)
Yield (%)	37.51	75.17	47.30
Colour	Brown	Pink	Green
Melting Point (^{0}C)	222-224	180-186	170-171
Electricalconductance /Ω	1.55 x10^{-4}	1.60 x10^{-4}	1.40 x10^{-4}
M.Wt (g)	721.80	724.80	661.67
%M	7.11 (7.37)	8.12(8.13)	7.56 (8.52)
Solubility Test	C W	C W	C W
• H_2O	NS SS	NS SS	NS NS
• Ethanol	SS SS	NS NS	NS S
• Methanol	NS NS	SS S	SS SS
• Acetone	NS NS	NS NS	NS NS

Means of triplicate data were recorded.
(Sul-Pyr Conductance value = 1.55 x10^{-5}/Ω).
C =cold W = warm, S = Soluble, NS = Not soluble, SS = Sparingly soluble.

The analytical data and other physical properties of the complexes are shown in Table 1. The interaction of each of the ligands [L, L^1]with metal salt resulted in the formation of the complexes with the formula $[MLL^1(H_2O)]Cl_n$ where L is sulfadoxine; L^1 is pyrimethamine and M is either Fe (III), Co (II) or Ni (II) ions. The complexes are stable, non hygroscopic solids with high melting points that are soluble in polar organic solvents such as methanol, ethanol, etc. The electrical properties of the complexes established the presence of the counter ions in which Co (II) has the highest value.

The important IR spectral bands of both the ligand and complex with their functional groups assignment are given in Table 2 (Figures 1-3). The IR absorption bands of each of the complexes are similar to the ligands. Bands at 3466.3 cm^{-1} and 3557.5 cm^{-1} which undergoes a bathochromic shift in the spectra of the metal complexes of Fe (III) and Co (II) have been assigned to (O-H) group. The spectrum of pyrimethamine & sulfadoxine also show absorption bands at 3472.3 cm^{-1} and 3454 cm^{-1} assigned to N-H stretching vibrations. This peak is found in the spectral of the metal complexes with great shift in their intensity and position. This observation suggests that (N-H) group is one of the co-ordination sites. The free pyrimethamine spectrum showed

band attributed to (C=N) stretching vibration at 1630.2 cm^{-1}. This band is also found in the complexes with red shift attributed to complexation.

Table 2: Possible IR bands of the ligand and its metal complexes of sulfadoxine-pyrimethamine.

Functional groups	L	L^1	Fe (III) Complex (Cm^{-1})	Co (II) Complex (Cm^{-1})	Ni (II) Complex (Cm^{-1})
0-H	–	–	3466.3	3557.5	–
N-H	3454.2-3241	3472-3305	3363-3144.1	3466.3-3235.3	3466.3-3168.3
C=N	1654	1630.2	1648.3	1642.4	1648.3
$N\text{-}H_{DEF}$	1579	1580	1380.9	1460.0	1453.8
O=S=O	1374	–	973.6	1326.1	1313.9

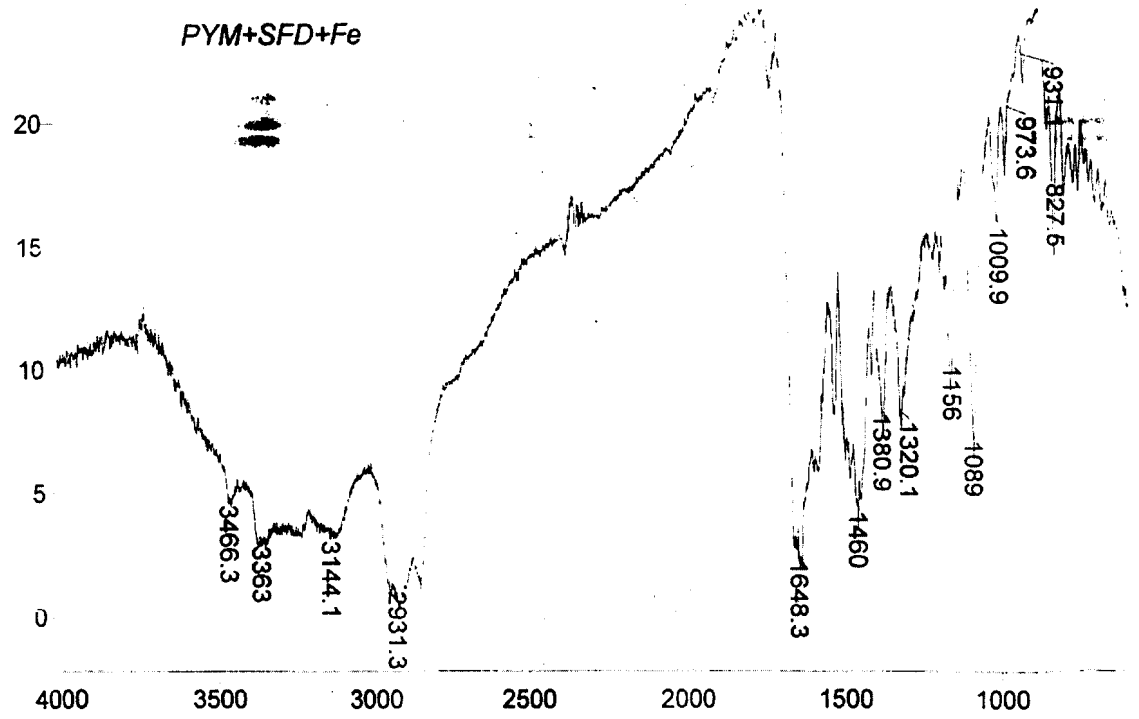

Figure 1: IR spectrum of $[Fe(PYM)(SFD)(H_2O)_2]Cl_2$

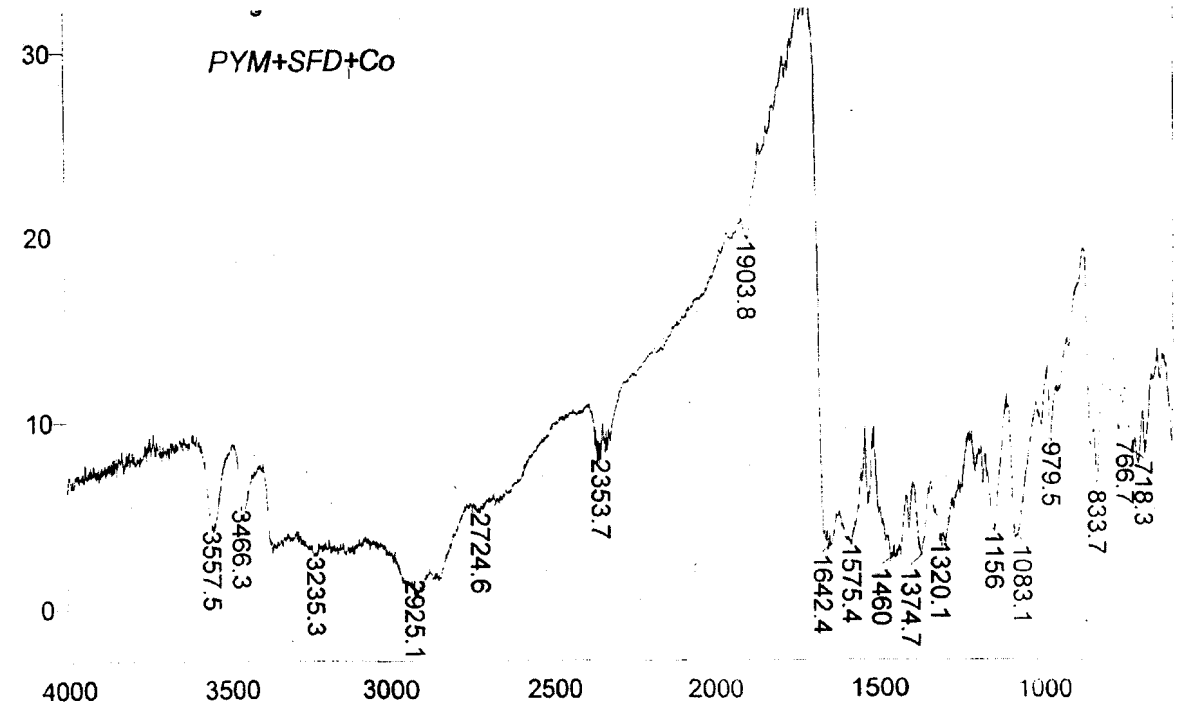

Figure 2: IR spectrum of $[Co(PYM)(SFD)(H_2O)_2]Cl_2$

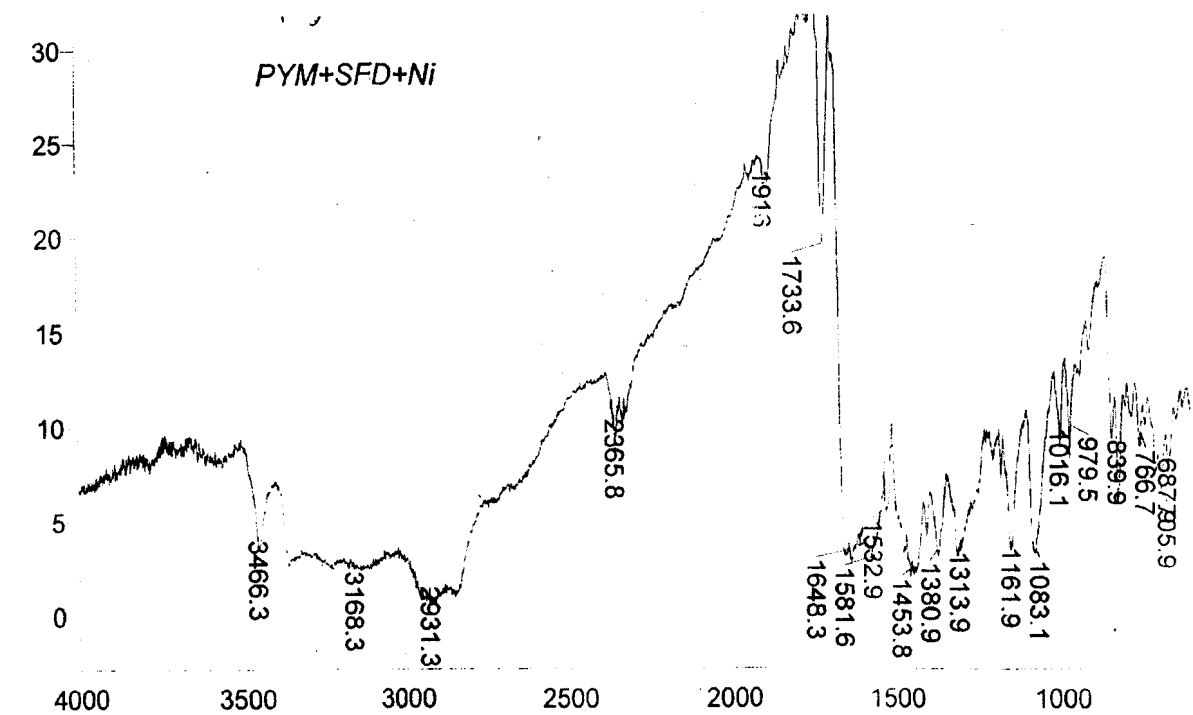

Figure 3: IR spectrum of $[Ni(PYM)(SFD)]Cl_2$

Table 3: Electronic transition absorption bands of the complexes.

Complex	Electronic confg.	Ground state	(nm)	cm^{-1}	Transition
Fe (III)	d^5	^6S	363	27,548	$\pi \rightarrow \pi^*$(c=c)
			350	28,571	n $\rightarrow \pi^*$ (O=S=O)
			330	30,303	n $\rightarrow \pi^*$(C=N)
			296	33,784	charge transfer
			248	40,323	charge transfer
Co (II)	d^7	^4F	252	28,409	$^4T_{12}$ (F) $\rightarrow ^4T_{2g}$
			344	25,070	$^4T_{1g}$ (F) $\rightarrow ^4A_{2g}$
			325	30,448	$^4T_{1g}$ (F) $\rightarrow ^4T_{2g}$
			300	33,333	
			248	40,323	
Ni (II)	d^8	^4F	352	28,409	$^3A_{2g} \rightarrow ^3T_{2g}$
			341	29,326	$^3A_{2g} \rightarrow ^3T_{1g}$
			326	30,675	$^3A_{1g} \rightarrow ^3T_{1g}$(P)
			292	34,247	charge transfer
			248	40,323	charge transfer

- Means of duplicate results were recorded.

The electronic absorption bands (Table 3) show that the Fe (III), Co (II), Ni (II) gave absorption bands due to either d→d transition charge transfer between metal ligand or transition within the ligand alone. Fe (III) complex band have been assigned to be due charge transfer or intra-ligand transition because Fe (III) is expected not to have d→d transition. The Co (II) transition result into five bands instead of three and this could be due to impurities of organic melting from ligand. This also extends to Ni (II) complex of the mixed ligand.

Table 4: Inhibition of *Plasmodium berghei* with Standard dose of antimalarial drugs and their complexes. (A) Standard dose: 1.25 mg/kg (PYM) and 25 mg/kg (SFD).

TreatmentGroup/Conc /20.44gAnimal weight	% Parasitaemia	% Inhibition
Chloroquine 0.001g/ml	0.13	91.03
Fansidar 0.0027g/ml	0.10	93.10
Fe (III) Complex .0027g/ml	0.00	100.0
Co (III) Complex .0027g/ml	0.07	95.17
Control nil	1.45	–

- Means of triplicate data were recorded.

From the results of the activities of these compounds against malaria parasites as shown in Table 4, it is evident that the addition of the metal to the fansidar did not impede the therapeutic value of the fansidar. Therefore, it can be deduced that fansidar-metal complex, as a drug is as effective as fansidar alone to strains of *P berghei*. However, the results show that the Fe (III) complex of the fansidar has the highest inhibitory value than that of Co (II) with 100% inhibition. However, the Co (II) complex still has an inhibitory value higher than that the chloroquine regimen.

By taking into consideration all the above analytical data, physico-chemical and spectroscopic data, the structure shown in Figure 4 of the mixed ligands complexes is proposed.

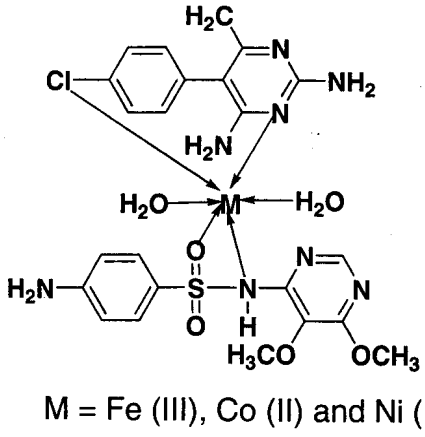

Figure 4: The proposed structure of the mixed ligands complexes.

Acknowledgement

The authors wish to thank SwissPharma Nig. Ltd., Lagos for donating the drugs. The assistance of Prof. Shounmi, A. and his team of IMRAT, University of Ibadan is gratefully acknowledged.

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