SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF MIXED TRIMETHOPRIM-ASPIRIN METAL COMPLEXES

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ABSTRACT

Some mixed ligands metal complexes of Trimethoprim (TMP), and Aspirin (ASP) were synthesized by solvo-thermal method. The complexes were characterized by physico-chemical and spectroscopic techniques. The results of spectroscopic studies revealed that Trimethoprim acts as a mono-dentate ligand coordinating through the nitrogen N (1) of the pyrimidine ring. Aspirin acts a bidentate ligand binding through oxygen of the hydroxyl group and oxygen of the carbonyl group of the acetoxy moiety. The antimicrobial activity assay of the complexes against *Staphylococcus aureus, Pseudomonas aeruginosa, E.coli* and *Candida spp* showed high activity. Thus all the complexes showed good antimicrobial activity and can be used as broad-spectrum antimicrobial [UP1] in microbial chemotherapy.

INTRODUCTION

Significant progress has been made in the utilisation of transition metal complexes as drugs to treat several human diseases. Several metal chelates are known to possess antimicrobial activity (Prafulla *et al.,* 2012), in several cases, the metal chelates are more effective than the chelating agents themselves. The formation of metal chelates increases the lipophilicity of the bioactive compounds and effective permeability of the compounds into the site of action (Zarranz *et al.,* 2003). Trimethoprim (TMP) is a bacteriostatic antibiotic used mainly in the treatment of urinary tract infection (Masur, 2014; Akron, 2009). Aspirin is an analgesic; it is used in the treatment of fever, pain, rheumatic fever and inflammatory diseases such as rheumatoid arthritis. Antibiotics have revolutionized medicine but the rapid appearance of resistant strains remains a challenge. This has prompted the search for novel drugs for bacterial chemotherapy. Metal-ligand (drug) complexation is one of the chemotherapeutic routes to influencing biological activity of medicinal agents. To this end we report the synthesis, characterization and antimicrobial activity studies of mixed ligands metal complexes of trimethoprim and aspirin.

MATERIALS AND METHOD

Synthesis of Mixed Ligands Metal Complexes

All the chemicals were obtained commercially and used as received. The complexes were synthesized by the procedure described by Idemudia *et al.,* (2012) with slight modification. A methanolic solution of the metal salt and the ligands were mixed in a mole ratio of 1:1:1 and refluxed at a constant temperature of 100^0C for 2 hours. The complexes were recovered after two days, washed and dried in a desiccator.

Antimicrobial Studies

The anti-microbial activity of the ligands and the complexes were carried out on *Staphylococcus aureus, Pseudomonas aeruginosa, E.coli* and *Candida* species to determine the percentage inhibition and minimum inhibitory concentration. The agar diffusion method was used (Simo *et al.,* 2002).

RESULTS AND DISCUSSION

Physical properties

All the complexes were air stable and non-hygroscopic. The complexes were all in powder form and of different colours typical of transition metal complexes. The complexes exhibited high melting points and were slightly soluble in the less polar solvents but soluble in hot acetonitrile as presented in Table 1.

Table 1: Physical properties of the complexes

Complexes	[Ni(TMP)(ASP)$(H_2O)_2$]	[Zn(TMP)(ASP)$(H_2O)_2$]	[Fe(TMP)(ASP)$(H_2O)_2$]
% Yield	54	61	61
Colour	Pink	Pink	Brown
Melting point (^{0}C)	260-269	140-145	216-223
Conductance (Ω^{-1})	$6.7x10^{-6}$	$1.6x10^{-6}$	$8.6x^{-6}$
Solubility Test	C H	C W	C H
• Water	SS S	NS S	SS SS
• Ethanol	S S	SS S	SS S
• Acetone	S S	SS S	SS SS
Acetone nitrile	S S	SS S	S S

C= Cold, H = Hot, W = Warm; NS = Not soluble, SS = slightly soluble, S= Soluble

The elemental analysis results revealed that the complexes contain one mole of trimethoprim and aspirin and two moles of aqua ligand per mole formulae unit. The calculated values of elements present in the complexes are in good agreement with the experimentally determined values from CHNSO analysis as shown in Table 2.

Result of the spectroscopic analysis

The selected IR bands of the ligand and complexes are presented in Table 3. The υ(C=N) band of the quinoline N (1) assigned at 1617cm^{-1} in the free trimethoprim is shifted to a higher wave number in spectra of all the complexes (1664-1653 cm$^{-1)}$, indicating coordination through this atom to the metal centre. In the free aspirin ligand, the O-H stretching frequency which is assigned to the band at 3497 cm^{-1} is however absent in all the complexes. This suggests that aspirin coordinates through the oxygen of the OH group of carboxylic acid. Also, the υ(C=O) of ester which is assigned to the band at 1760 cm^{-1} in the free aspirin has shifted to lower wave number (1595-1584 cm^{-1}) suggesting that aspirin also coordinates through that site. Thus aspirin acts as a bidentate ligand. The N-H stretching frequency of the pyrimidine NH_2 assigned at 3463 cm^{-1} and 3313 cm^{-1} in the free trimethoprim shifted slightly in all the complexes but this is not due to coordination but likely due to hydrogen bonding as reported by Tella and Obaleye (2010), (Tella *et. al* 2016).

Table 2: Elemental Analysis (CHNSO) of some mixed ligands metal complexes

Compounds	Elemental analysis CHNSO % Theoretical and (% Found)				
	C	**H**	**N**	**O**	**S**
$[Ni(TMP)(ASP)(H_2O)_2]$	48.83 (48.86)	4.95 (5.36)	9.91 (9.89)	25.47 (26.51)	- -
$[Zn(TMP)(ASP)(H_2O)_2]$	48.28 (48.22)	4.89 (4.99)	9.79 (10.0)	25.18 (25.24)	- -
$[Fe(TMP)(ASP)(H_2O)_2]$	49.08 (48.99)	4.98 (5.41)	9.96 (9.96)	25.61 (25.55)	- -

Table 3: Selected IR band (cm^{-1}) of ligands and mixed ligand metal complexes of Trimethoprim (TMP) and Aspirin (ASP).

Compounds	**υ(N-H)**	**υ(C=N)**	**υ(C=O)**	**υ(M-N)**	**υ(M-O)**
Trimethoprim	3463, 3313	1617	-	-	-
Aspirin	-	-	1760, 1687	-	-
$[Ni(TMP)(ASP)(H_2O)_2]$	3400, 3325	1663	1595	625	515
$[Zn(TMP)(ASP)(H_2O)_2]$	3400, 3136	1663	1592	620	545
$[Fe(TMP)(ASP)(H_2O)_2]$	3351,3211	1663	1584	652	604

Proposed Structure of mixed Trimethoprim-Aspirin metal complexes

Base on the analytical and spectroscopic data of the metal complexes of mixed ligands, the structure below has been proposed for the complexes formed.

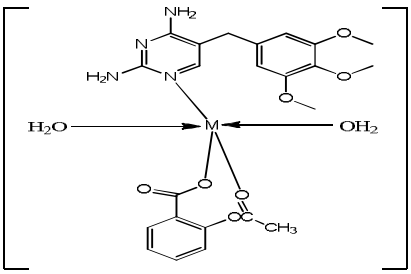

Figure1: Proposed structure of the complexes M= Ni (II), Zn (II) and Fe (II)

Antimicrobial Activity

The result of the susceptibility assay presented in Table 4 revealed that Trimethoprim and Aspirin possess no activity against *Escherichia coli*, but all the metal complexes have greater antibacterial activities than their respective ligands (Lawal *et al.,* 2009). The antifungal activity results revealed that the ligands have no significant activity against Candida sp. Similar finding has previously been reported by Idemudia *et al.,* (2012).

Table 4: Result of Antibacterial activity of the ligands and their complexes

Compounds	***E. coli***		***Pseud. aeruginosa***		***Staph. aureus***	
	Zone of Inhibition (mm)					
	100ppm	200ppm	100ppm	200ppm	100ppm	200ppm
Trimethoprim(TMP)	NA	NA	20	NA	NA	30
Aspirin (ASP)	NA	NA	NA	21	50	30
$[Ni(TMP)(ASP)(H_2O)_2]$	54	50	30	17	14	40
$[Zn(TMP)(ASP)(H_2O)_2]$	10	15	21	30	18	24
$[Fe(TMP)(ASP)(H_2O)_2]$	16	21	18	17	19	30

NA= No Activity

Table 5: Result of Antifungal activity of the ligands and their complexes

Compounds	***Candidas spp***	
	Zone of Inhibition (mm)	
	100ppm	200ppm
Trimethoprim(TMP)	NA	NA
Aspirin (ASP)	NA	NA
$[Ni(TMP)(ASP)(H_2O)_2]$	43	50
$[Zn(TMP)(ASP)(H_2O)_2]$	30	47
$[Fe(TMP)(ASP)(H_2O)_2]$	45	21

NA= No Activity

CONCLUSION AND RECOMMENDATION

Mixed ligands complexes of trimethoprim and aspirin are reported. The complexes were synthesized by solvo-thermal method, characterized by elemental analysis and infrared spectroscopy. The antimicrobial activity assay has shown that the complexes are more effective than their parent drugs, thus the metal complexes could be a promising chemotherapeutic agent.

REFERENCES

Akron. (2009).The Chemical Database of the Department of Chemistry at the University of Akron. *http://ull.chemistry.uakron.edu/erd.* Accessed: 11 January 2016.

Idemudia, O.G., Ajibade, P.A. and Okoh, A.I (2012). Synthesis, characterization and antibacterial screening of 2,4-diaminopyrimidine pyrimethamine and trimethoprim silver complexes. *African Journal of Biotechnology*, 11(39): 9323-9329.

Lawal A., Obaleye, J.A., Oyeleke, S.A and Amolegbe, S.A (2009). Synthesis and Antibacterial Studies of Mixed Metronidazole-Vitamin C Metal Complexes Centrepoint (Science Edition). 15(1): 54 -59.

Masur, H., Brooks, J.T.,Benson, C.A., Holmes, K.K., Pau, A.K. and Kaplan, J.E. (2014). Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Updated Guidelines. *An official publication of Infectious Disease Society of America*. 58(9): 1308-11.

Prafulla, M.S., Jahanvi, P., Yogini, P. (2012). Metal complexes: current trends and future potential. *IJPCBS* 2 (3): 251–265.

Simo, B., Perello, L., Ortiz, R., Castineiras, A., Latorre, and Canton, E. (2002). Interaction of metal ions with a 2,4-diaminopyrimidine derivative (trimethoprim) Antibacterial studies. *Journal of Inorganic Biochemistry*, 81:275-283.

Tella, A.C. and Obaleye, J.A (2010). Synthesis and biological studies of Co (II) and Cd (II) 5-(3,4,5-trimethoxybenzyl) pyrimidine-2,4-diamine (Trimethoprim) complexes. *Int. J. Biol. Chem. Sci.* 4(6): 2181-2191.

Tella, A.C., Eke, U.B. and Owalude, S.O (2016). Solvent-free mechanochemical synthesis and X-ray studies of Cu (II) and Ni (II) complexes of 5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) in a ball-mill. *Journal of Saudi Chemical Society* 20:376-381.

Zarranz, B., Jaso, A., Aldana, I., Monge, A. (2003). Synthesis and antimycobacterial activity of new quinoxaline-2-carboxamide-1,4-di-N-oxide derivatives. *Bioorg. Med. Chem.*, 11: 2149–2156