ANTIMICROBIAL ACTIVITIES OF NOVEL SYNTHESIZED Cu (II) and Co (II) MIXED LIGAND COMPLEXES OF PREDNISOLONE AND PARACETAMOL

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Abstract

Cu (II) and Co (II) mixed ligand complexes of prednisolone and paracetamol were synthesized in water-isopropyl alcohol medium at varying degree of concentrations and characterized on basis of their physical properties such as % yield, colour, melting points and spectroscopic studies as well as anti-microbial evaluations of the metal complexes. Results of this study showed that % yield of the metal complexes were reasonably high. The colour obtained for the metal complexes were different from that of their parent metals and ligands. This indicates that the ligands have dominant effect on the metals. The solubility tests showed that metal complexes were non – polar in nature. The spectroscopic studies as reported by UV –visible confirmed d–d and $\pi \rightarrow \pi^*$ transitions in the metal complexes while FTIR results showed that the metals possibly coordinated through OH and C=O group of prednisolone and – OH group of the paracetamol. The antimicrobial activities of the metal complexes and the ligands were screened against the bacteria such as *Collectotrichum falcatrum, Phythophthora Palmivora, Ceratocystis Parndoxa, Pericularia Oryzal, Helminthosporium Toxicum, Xanthomonas axonopodix, Pseudomonas aeruginosa, Chromobacterium liusdium, Erwinia Carotovora.* The results obtained revealed that metal complexes were more proactive than the free ligands.

Key words: *Prednisolone; paracetamol; mixed ligand; complex and Antimicrobial activities.*

1 INTRODUCTION

The synthesis and study of inorganic compounds containing biologically important ligands is made easier because certain metal ions are active in many biological processes; species of low molecular weight are hence sought to reproduce the structural properties and reactivity of naturally occurring complexes [1].

Synthesized mixed metal complexes have been reported to exhibit antimicrobial propertied and shown to be potent against certain microorganisms. For instance, mixed drug metal (II) complexes of Trimethoprin – sulfamethoxazole were synthesized and characterized

and the antimicrobial activities on the selected organisms like *Bacillius spp, Escherichia spp, Proteus mirabilis and Pseudomonas spp* including their ligands were reported to be active within the inhibitory zones of 6.0 – 32.0 mm [2]. One of the major applications of the transition metal complexes is its medical testing as antibacterial and antitumor agents targeting towards the discovery of an effective and safe therapeutic regimen for the treatment of bacterial infections. More so, mixed ligand complexes are observed in biological systems or in the intermediate chemical reactions with metal ions, which are perquisite for the understanding of the chemistry of reaction in the biological system [3].

Prednisolone is a synthetic steroid that is used to treat a wide variety of acute and chronic disorders such as arthritis, asthma, allergic diseases [4]. Prednisolone which has not been shown to exhibit antimicrobial properties is widely used in the management of a variety of diseases including congential adrenal hyperplasia, severe asthma, certain hematological disorder, and rheumatic, gastrointestinal and malignant diseases [5]. On the other hand, prednisolone therapy are associated with a pronounced side effect profile which include diabetes, weight gain, rise in blood cholesterol, and increased blood pressure etc., [6], [7]. The nature of the interaction between prednisolone and serum proteins has been intensively studied [8], [9]. It has been shown that prednisolone binds to two plasma proteins, albumin and the α1–glycoprotein transcortin (Corticosteroid binding globulin, CBG) [10].

Paracetamol or acetaminophen is a synthetic known opiate derivative of aminophenone with anti-inflammatory, anti-pyretic and analgesic activity in both animals and humans. It is also envisaged that the relationship between bacteria and acetaminophen is focused on the anti-inflammatory action of this agent on the immune system that stimulated by bacterial infection and not on the bacterial activities. In recent years, metal complexes of paracetamol have been synthesized and found to exhibit antimicrobial properties. Metal (II) (cobalt, nickel, copper, zinc and manganese) complexes of paracetamol and vanillin have been found potent against certain species of microorganisms such as *Escherichia coli, Pseudomonas aeruginosa, Klebsiella oxytoca* and *Bacillus cereus* [11]. Also, Antibacterial screening of the mixed ligand metal complexes of paracetamol against *Bacillus substilis, Serratia species* and *Escherichia coli* was also investigated by [12]. They reported that the metal complexes were found to have varying degree of inhibitory effect against the bacteria [12]. Therefore, it is important to investigate the antimicrobial properties of metal mixed ligand complexes of paracetamol and prednisolone. This research is designed to synthesize novel Cu (II) and Co (II) mixed ligand complexes of prednisolone and paracetamol, and to investigate their antimicrobial activities against selected species of fungi and bacteria.

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2.0 MATERIALS AND METHODS

2.1 Synthesis of copper (II) and cobalt (II) mixed ligand complexes of prednisolone and paracetamol at different ratios

2.1.1 Synthesis of copper (II) mixed ligand complexes of prednisolone and paracetamol at different ratios

Copper (II) mixed ligand complex of prednisolone and paracetamol (1:1:1) was prepared using direct method of synthesis by mixing 0.1M of Copper (II) sulphate pentahydrate (blue solution)

and a colourless solution of 0.1M Prednisolone (prepared in distilled water- isopropy alcohol medium) in a 250mL conical flask and stirred for one hour. A colourless solution of 0.1M of Paracetamol was added to a light blue mixture of the copper sulphate and prednisolone and stirring continued for another two hours. The mixture was carefully filtered using sintered glass porosity No4, washed in a mixture of distilled water and isopropyl alcohol and a very light blue residue obtained was kept inside a desiccator for five days to dry and then weighed. The ratio 1: 2: 1for copper (II) mixed ligand complex of prednisolone and paracetamol was also prepared by increasing the mole of the prednisolone ligand to two. The processes of filtration, washing, drying and weighing were followed as stated above.

2.1.2 Synthesis of cobalt (II) mixed ligand complexes of prednisolone and paracetamol at different ratios

Cobalt (II) mixed ligand complex of Prednisolone-paracetamol at different ratio concentrations of 1:1:1 were also prepared by direct mixing method. A pink solution 0.1M cobalt (II) Chloride and a colorless solution of Prednisolone 0.1M prepared in distilled water - isopropyl alcohol medium) were mixed together in an Erlenmeyer flask and stirred for one hour resulting to a pink solution of the mixture. A colourless solution of 0.1M paracetamol was added and stirring continued for another two hours. The reacting mixture was then filtered, washed in a mixture of distilled water and isopropyl alcohol and a primrose residue obtained, which was dried inside a desiccator with silica gel for five days and weighed to constant weight. The ratio 1: 2: 1for cobalt (II) mixed ligand complex of prednisolone and paracetamol was also prepared by increasing the mole of the prednisolone ligand to two. The processes of filtration, washing, drying and weighing were followed as stated above.

2.2 Antibacterial and Antifungal Activity Tests

The ligands and complexes were dissolved separately in DMSO at 0.05gml^{-1}. They were placed on the surface of the culture and incubated at 37 ^{o}C for 24hrs [13], [14]. The vitro antibacterial and antifungal activity tests were carried out by disc diffusion method. The diameter of zone of inhibition produced by the ligand and complex were compared with streptomycin sulphate and mancozeb as bacterial and fungal standards respectively.

3.0 RESULTS AND DISCUSSION.

3.1 Physico-chemical properties of the synthesized complexes

Metal complexes of the mixed ligand were analyzed for their elemental composition, colour change of the complexes, percentage yield, melting point and percentage of metal in the complexes. The results are presented in Table 1. The melting point of paracetamol was in the range 169-170°C, whereas the metal complexes decomposed at higher temperature range confirming coordination [15].

Table 1: Physical data of copper (II) and cobalt (II) mixed ligand complexes of Paracetamol and Prednisolone

Compound	Ratio	Colour	% Yield	Melting point (^{o}C)	% Metal (Theoretical/experimental)	Uv-vis (nm)
Cu L L'(H_2O)	1:1:1	Green-blue	64.53	212 – 214	8.95 (8.99)	324, 258
$CuL_2L'(H_2O)$	1:2:1	Light blue	43.09	178 – 180	5.98 (5.91)	356, 300, 293,
Co L L'(H_2O)	1:1:1	Primerose	55.48	220 – 222	8.34 (8.35)	688, 623, 480
$CoL_2L'(H_2O)$	1:2:1	Light Pink	60.00	229 – 230	5.52 (5.50)	700, 626, 455
$C_{12}H_{28}O_5$	---	White	---	238 – 240	---	244
$C_8H_9NO_2$	---	White	---	169 – 170	---	256

L - Prednisolone ($C_{12}H_{28}O_5$) A – Cu ALL'- Cu L L'(H_2O) BLL'- Co L L'(H_2O)

L' - Paracetamol ($C_8H_9NO_2$) B – Co AL_2L' - $CuL_2L'(H_2O)$ BL_2L' – $CoL_2L'(H_2O)$

The theoretical percentage metal and experimental percentage metal of the synthesized complexes are in corroboration. All the synthesized complexes gave colorful yields different from the colours of their parent metals and ligands. The coloured complexes obtained were likely due to charge transfer from ligand to metal and *vice versa* [12]. They have appreciable high melting points which is a good property of metal complexes. The sharp melting point is an indication of a pure metal complex. The low percentage yield for the $CuL_2L'(H_2O)$ may be due to incomplete crystallization. Analytical data of the compounds, together with their physical properties are consistent with proposed molecular formula.

3.2 Solubility test

All the metal complexes are insoluble in chloroform, toluene and n-hexane. They are also insoluble in isopropyl alcohol (IPA), distilled water and distilled water-IPA medium (the medium of synthesis). This result also supports the formation of new compounds (metal complexes) which have physical properties different from their parent metals and ligands.

Table 2: Solubility Tests of Copper (II) and Cobalt (II) Mixed Ligand Complexes of Predni-solone and paracetamol

Solvent	Cu L L'(H_2O)	$CuL_2L'(H_2O)$	Co L L'(H_2O)	$CoL_2L'(H_2O)$
Formaldehyde	Soluble	Soluble	Soluble	Insoluble
Chloroform	Insoluble	Insoluble	Insoluble	Insoluble
Toluene	Insoluble	Insoluble	Insoluble	Insoluble
Isopropyl alcohol (IPA)	Insoluble	Insoluble	Insoluble	Insoluble
Distilled water	Insoluble	Insoluble	Insoluble	Insoluble
n-hexane	Insoluble	Insoluble	Insoluble	Insoluble
Ethyl acetate	Insoluble	Insoluble	Soluble	Soluble
Butan-1-ol	Soluble	Insoluble	Soluble	Soluble
Distilled water-IPA	Insoluble	Insoluble	insoluble	Insoluble

The solubility test also showed that Cu L L'(H_2O), is soluble in formaldehyde, and butan-1-ol; $CuL_2L'(H_2O)$ is soluble only in formaldehyde; Co L L'(H_2O) is soluble in formaldehyde, butan-1-ol and ethyl acetate; while $CoL_2L'(H_2O)$ is soluble in butan-1-ol and ethyl acetate. The solubility of the metal complexes revealed that they are hydrophobic as shown in Table 2.

3.3 IR Spectral Studies

The Fourier Transform Infrared Spectrum of the ligands (paracetamol and prednisolone) showed some characteristic stretching bands at 3360, 3325, 1666, 1711, 1654 and 3164 cm^{-1} (Table 3). In the analysis of the ligands, -NH group showed absorption band at 3164 cm^{-1} [16] in the paracetamol which is seen to be absent in the prednisolone and synthesized complexes. Absence of the N-H stretching vibration indicates that it is deprotonated in complexes [17]; this was confirmed by the bands observed in the C=N stretch of the complexes. The absorption bands at 3325 cm^{-1} and 3360 cm^{-1} are assigned to –OH stretching vibration [11].

Table 3: IR Spectral Studies Copper (II) and Cobalt (II) Mixed Ligand Complexes of Predniso-lone and paracetamol in mm

Compound	Ratio	R-OH	C= O	NH	C=N	M-O	$SO4^{2-}$	Cl^-	Bonded(H_2O)	M-N
$C_{12}H_{28}O_5$		3360	1666, 1711	---	---	---	---	---	656, 746	---

$C_8H_9NO_2$		3325	1654	3164	---	---	---	---	687	---
$CuLL'(H_2O)$	1: 1:1	3563	1655, 1707	---	1596	483	1111	---	721	---
$CuL_2L'(H_2O)$	1: 2:1	3563	1656, 1707	---	1598	483	1090	---	721	---
$CoLL'(H_2O)$	1: 1:1	3424	1708	---	1605	469	----	416	623	---
$CoL_2L'(H_2O)$	1: 2:1	3416	1709	---	1608	472	----	419	622	---

The shift of the O-H stretch to higher wave number is an indicative that the metals are bonded to the hydroxide groups of both ligands. The strong absorption band at 1666, 1664 and 1711 cm^{-1} observed in both ligands' spectra are indicative of a carbonyl group [18]. Insignificant shift in the C=O group of the paracetamol is an indication that the C=O of the paracetamol is not involved in the formation of $CuLL'(H_2O)$ $CuL_2L'(H_2O)$, $CoLL'(H_2O)$ and $CoL_2L'(H_2O)$ while the shift in the C=O stretch of the prednisolone to a lower wave number indicates that the C=O was involved in the formation of all the copper and cobalt complexes. The nitrogen atom was not involved in complex formation with the metal ions and is clearly evident from the non-appearance of new medium intensity band at 560-545 cm^{-1}, assignable to (M-N) in the spectra [17; 11]. This is in accordance with the results obtained by [15] on the synthesis, characterization and evaluation of anti-inflammatory activity of paracetamol complexes of copper (II) and zinc (II) ions. The possible coordination sites are further supported by the appearances of medium bands at 460-490 cm^{-1} which could be attributed to M-O bond.

3.4 Electronic spectra

The electronic spectra of paracetamol and prednisolone in DMSO solvent showed bands at 244 and 256 nm respectively as shown in Table 1. The bands were shifted in the metal complexes due to coordination [14]. The ligands and copper complexes showed bands in UV and visible region (200 - 400nm) which can be attributed to ($n \rightarrow \sigma^*$) transition, ($\pi \rightarrow \pi^*$) transition and ($n \rightarrow \pi^*$) transition [19]. For the copper complexes, the bands below 250 nm are due to the $n \rightarrow \sigma^*$ transitions, the $\pi \rightarrow \pi^*$ transitions of the aromatic rings were observed in the 250–300 nm region whereas the $\pi \rightarrow \pi^*$ transitions confirming the presence of C=N group and the absence of the M-N as discussed in the IR spectra studies are in between 300 and 350 nm [20]. The intensity of these bands in the synthesized copper complexes is consistent with tetrahedral structure that could be possibly proposed for the complexes. The electronic spectra of the Co (II) complexes showed bands in UV and visible region (400 – 700 nm) which are assigned to d-d transitions, ligand-to-metal charge transfer transitions and ligand internal transitions [21]. These bands are consistent with the octahedral geometry of Co (II) complexes.

3.5 Antimicrobial activities

3.5.1. Antibacterial activities

It has been reported that the antibacterial activity of a complex is influenced by its stability. The lower the stability of a metal complex, the greater is the antibacterial activity; this is probably

because they have more free ions in the solution, which can enhance the cooperative interaction between the metal ions and the ligands [22], [23]. This can explain the different antibacterial activity of the copper and cobalt complexes ($CuLL'(H_2O)$, $CuL_2L'(H_2O)$, $CoLL'(H_2O)$ and $CoL_2L'(H_2O)$). As it can be seen from Tab. 4 and 5, the zones of inhibition for the synthesized complexes are higher than for the free ligands. The increased activity of the metal chelates can be explained on the basis of chelation theory [24]. It is known that chelation tends to make the ligand act as more powerful and potent bactericidal agents, thus killing more of the bacteria than the ligand. It was observed that in a complex, the positive charge of the metal is partially shared with the donor atoms present in the ligands, and there may be π-electron delocalization over the whole chelate [24].

Table 4: Antibacterial Screening of copper (II) and cobalt (II) mixed ligand complexes of Prednisolone and paracetamol

Compound	Ratio	A	B	C	D	E
$C_{12}H_{28}O_5$		10.00	1.00	6.00	3.50	00.00
$C_8H_9NO_2$		12.00	10.00	5.50	5.00	2.00
$CuLL'(H_2O)$	1: 1:1	15.00	15.00	13.00	10.00	3.50
$CuL_2L'(H_2O)$	1: 2:1	21.00	12.50	15.00	9.00	17.00
$CoLL'(H_2O)$	1: 1:1	20.00	19.00	17.00	17.50	18.5
$CoL_2L'(H_2O)$	1: 2:1	22.00	20.00	18.50	17.00	19.00
Control S. T		27.00	31.00	31.00	33.00	22.00

Where

A – *Xanthomonas axonopodix*

B – *Streptococcus faecadis*

C – *Pseudomonas aeruginosa*

D – *Chromobacterium liusdium*

E – *Erwinia Carotovora*

S. T – *Streptomycine sulphate* (Control).

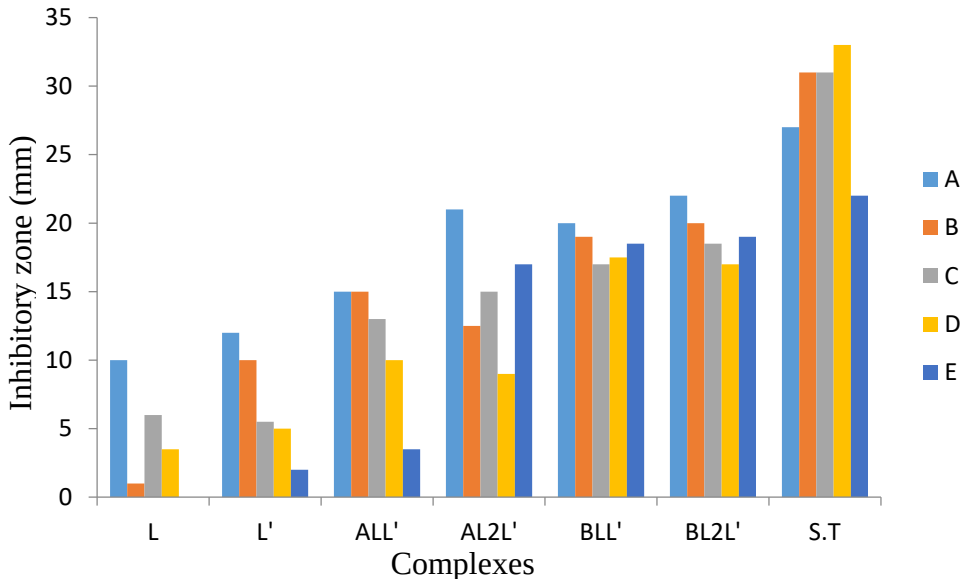

Fig. 1: Activities of the synthesized metal complexes and control against bacteria

This increases the lipophilic character of the metal chelate and favours its permeation through the lipoid layer of the bacterial membranes [25]. The $CoL_2L'(H_2O)$ was found to exhibit higher antibacterial activities than the $CoLL'(H_2O)$ and the free ligands against all the selected bacteria. The higher antibacterial activities may be due to the bulkiness of the $CoL_2L'(H_2O)$ which increases the relative lipophilicity of the molecule. Chelation of a bulky ligand to a metal cation reduces the polarity of the ion due to ligand orbital overlap with the metal orbitals resulting in a delocalization of positive charge. An increase in lipophilicity of a metal complex enhances bacterial cell membrane penetration and blocking of metal binding sites on enzymes [26]. The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or the difference in ribosomes of microbial cells [27]. The antibacterial activities which are also shown in Figure 1 showed that *Streptomycine sulphate* (Control) was more active than the complexes.

3.5.2. Antifungal activities

The copper (II) and cobalt (II) mixed ligand complexes of prednisolone were more active against the selected species of fungi *Collectotrichum falcatrum*, *Phythophthora Palmivora*, *Ceratocystis Parndoxa*, *Pericularia Oryzal*, *Helminthosporium Toxicum*, than the parent ligands as expected.The Co (II) mixed ligand complexes prove to be more active as the concentration of the ligand increases in ratio though less active than the control (mancozeb).

Table 5: Antifungal evaluations of copper (II) and cobalt (II) mixed ligand complexes of prednisolone and paracetamol in %

Compound	Ratio	C.F	P.P	C.P	H.T	P.O
$C_{12}H_{28}O_5$		6.00	4.50	14.00	00.00	14.00
$C_8H_9NO_2$		00.00	3.00	4.00	6.40	14.20
CuLL'(H_2O)	1: 1:1	30.00	20.00	69.00	55.00	58.33
$CuL_2L'(H_2O)$	1: 2:1	28.00	60.50	40.00	60.50	65.20
CoLL'(H_2O)	1: 1:1	58.88	53.00	50.00	40.00	31.00
$CoL_2L'(H_2O)$	1: 2:1	52.64	60.00	56.00	59.30	65.63
Control S. T		85.00	80.00	75.00	95.00	100

C.F = Collectotrichum falcatrum.

P.P = Phythophthora Palmivora.

C.P = Ceratocystis Parndoxa.

H.T = Helminthosporium Toxicum.

P.O = Pericularia Oryzal.

S,T = Mancozeb (Control)

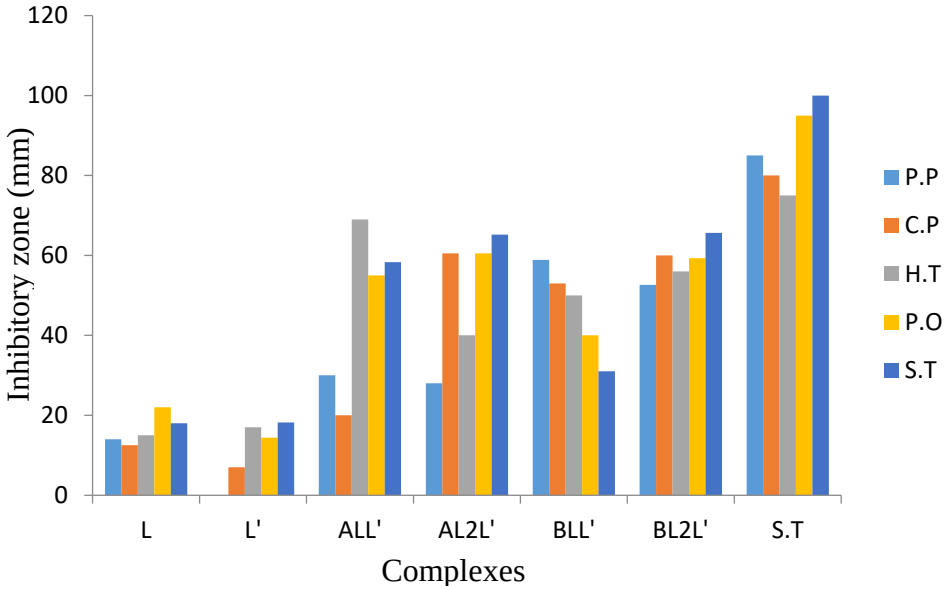

Fig. 2: Activities of the synthesized metal complexes and control against Fungi

4. CONCLUSION

Novel cobalt (II) and Copper (II) mixed ligand complexes of prednisolone and paracetamol which have both chemical and physical properties different from their parent ligands have been synthesized. The results of both the antifungal activities and the antibacterial activities of the metal complexes indicated that the cobalt (II) and Copper (II) mixed ligand complexes of prednisolone were proactive against the selected fungi and bacteria pathogens than the free ligands. The antimicrobial activities of the metal complexes can be better understood by chelation theory.

REFERENCES

[1] M. Tumer, H. Kolsal, K. Sener and S. Serin, "Antimicrobial activity studies of the binuclear metal complexes derived from tridentate Schiff base ligands". *Transition Met.Chem.*,24. 414 – 420, 1999.

[2] A. A. Osowole, A.S. Wakil, and K .O. Alao, "Synthesis, characterization and antimicrobial activity orsome mixed Trimethoprin- sulfamethoxazole metal drug complexes". *World Applied Science journal* 33 (2): 336 – 242, 2015.

[3] N. Raman and S. Sobha, "Synthesis, characterization and antimicrobial screening of isatin – based polypyridyl mixed ligand Cu (II) and Zn (II)) complexes" .*Journal of Serbian Chemical Society*, 17,1 – 16, 2010.

[4] M. Vogt, H. Derendorf, J. Kramer, H.E. junginger, K.K. Midha, V.P. Shah, S. Stavchansky, J.B. Dressman, and D.M. Barends, "Biowaiver monographs for immediate release solid oral dosage forms: Prednisolone" *Journal of Pharmaceutical Science* Vol. 96, No. 1, pp.27-37, 2006.

[5] M.E. Pickup, J.R. Lowe, P.A. Leatham, V.M. Rhind, V. Wright and W.W. Downie, "Dose dependent pharmacokinetics of prednisolone" *Eur J Clin Pharmacol*,. **12**(3): p. 213-9, 1977.

[6] W.J. Justo, and J.Q. Rose, "Monitoring prednisone and prednisolone" *The Drug Monitoring.* 2(2): 169 -176, 1980.

[7] M.L. Rocci, R. D'Ambrosio, N.F. Johnson and W.J. Jusko, "Prednisolone binding to albumin and transcortin in the presence of cortisol" *Journal of Biochemistry Pharmacology*. 31(3) :289 – 292, 1982.

[8] J.A., Wald, R.M. Law, E.A. Ludwig, R.R. Sloan, E. Middleton, and W.J. Jusko, "Evaluation of dose- related pharmacokinetics and pharmacodynamics of prednisolone and prednisone in man" *Journanl of Pharmacokinet Biopharmac*, 20(6): 317 – 346, 1992.

[9] J .Q. Rose, A. M. Yurchak, and W.J. Jusko, "Dose dependent pharmacokinetics of prednisone and prednisolone in man". *Journal of Pharmacokinetic Biopharmacy*.9 (4): 389 417, 1981.

[10] G. P. Lewis, W. J. Jusko, C. H. Burke, and L. Graves, "Prednisolone sidffects and serum-protein levels.The Lancet", 788- 781, 1971.

[11] A, Osowole, A. Aderoju, B. Aluwatoosin, A. Agbaje and O. Babatope, "Antibacterial properties of some heteroleptic metal(II) complexes of paracetamol and vanillin" *Asian Journal of Pharmaceutical Clinical And Research* Vol 7 ISSN - 0974-2441, 2014.

[12] L. Amudat and A. O. Joshua, "Synthesis, characterization and antibacterial activity of aspirin and paracetamolmetal complexes" *Nigerian Society for Experimental Biology*. 19(1):9-15, 2007.

[13] N. Ramon, V. Motijuraj, S. Rovichandran, and A. Kulandaisamy, "Synthesis, Charactreization and Wlectrochemical Behaviour of Cu (II), Co (II),Ni (II) and Complexes Derived from Acety acetone and p-anisidine and their Antimicrobial Activity". *Pro.Ind.Acad.Sci.*,115 (5), 161 – 16, 2003.

[14] I.H. Bukhari, M. Arif, J. Akbar, and A.H. Khan, "Preparation, Characterization and Biological Evaluation of Schiff base and Transition Metal Complexes with Cephredine.Pakistan" *J.of Biological Sciences*, 84 (4), 614 – 617, 2005.

[15] A. F. John, D. P. Elaoyi, A. D. Yakubu, "Synthesis, Characterization and Evaluation of Anti-Inflammatory Activity of Acetaminophen Complexes with Copper (II) and Zinc (II) Ions" *International Journal of Biomedical Materials Research*. Vol. 5, No. 6, pp. 78-83. doi: 10.11648/j.ijbmr.20170506.13, 2017.

[16] R. M. Silverstein, "Spectrometric Identification of Organic compounds". 4th ed. New York: *John Wiley and Sons*. QD272.S6S55, 1981.

[17] D. Nasrin, A. M. Ashraful, M. M. M. Rahman, H. Banu and M. Nazimuddin. "Synthesis, characterization and antimicrobial activity of some metal complexes with schiff base containing O, N and S as the donor atoms" *Bangladesh international journal of applied and natural sciences (ijans)* issn: 2319-4014, 2013.

[18] W.E. Antholine, J. Knitht and D.H. Petering, *journal of inorganic chemistry* 16: 569, 1977.

[19] R. Roy, P. Paul and K. Nag, "Metal complexes of sulfur-nitrogen chelating agents. Part 12. The chemistry of nickel (II), palladium(II), cobalt(II) and copper(II) complexes of N2S2 and N3S2 donor systems". *Trans. Met. Chem*. 9: 152-155, 1984.

[20] G. Demet, C. Adem, A. Tavman and A. S. Birteksöz. "Synthesis, characterization and antimicrobial activity of some transition metal complexes of *n*-(5-chloro-2-hydroxyphenyl)-3-methoxy-salicylaldimine" *Bull. Chem. Soc. Ethiop.* 29(1), 63-74. ISSN 1011-3924, 2015.

[22] A. Stanila, A. Marcu, D. Rusu, M. Rusu and L. David, “Spectroscopic studies of some copper (II) complexes with amino acids”. *Notulae Botanicae Horti Agrobotanici* 834:364-368, 2007.

[23] A. Marcu, A. Stanila, O. Cozar and L. David, “Structural investigations of some metallic complexes with threonine as ligand” *Journal of Optoelectron Advancement* M 10(4):830-833. 2008.

[24] S.K, Sengupta, O.P. Pandey, B.K. Srivastava and V.K, Sharma, “Synthesis, structural and biochemical aspects of titanocene and zirconocene chelates of acetylferrocenyl thiosemi-carbazones”. *Transition Metal Chemistry* 23(4):349-35, 1998.

[25] S. Chandra, S. Raizada, M. Tyagi and A. Gautam, “Synthesis, spectroscopic, and antimicrobial studies on bivalent nickel and copper complexes of bis (thiosemicrbazone)” *Bioinorgic Chem Appl* (1): 51483, 2007.

[27] S. Andreea, B. Cornelia, S. Sorin, and M. Raluca, “Antibacterial Activity of Copper and Cobalt Amino Acids Complexes”. *Notulae Botanicae Horti Agrobotanici* Cluj-Napoca, Romania ISSN 0255-965X, 2011.

[26] U. El-Ayaan and A.A.M. Abdel-Aziz, “Synthesis, antimicrobial activity and molecular modeling of cobalt and nickel complexes containing the bulky ligand: bis[N-(2,6-diisopropylphenyl)-imino]acenaphthene”. *Eur. J. Med. Chem.*, *40*, 1214–1221, 2005..

[21] A. Adkhis, O. Benali-Baïtich, M.A. Khan and G. Bouet, “Synthesis, Characterization and Thermal Behaviour of Mixed-Ligand Complexes of Cobalt (III) with Dimethylglyoxime and Some Amino Acids”.*Synth. React. Inorg. Met.-Org. and Nano-Met. Chem.* 30(10): 1849-1858 2000.