Chemistry Research Journal, 2016, 1(4):90-96

Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Synthesis, Characterization and Antioxidant Properties of Some Metal(II) Complexes of Mixed Drugs-Vitamin Bx and Aspirin

Adesoji A Olanrewaju[1], Tolulope I Oni[2], Aderoju A Osowole[1,2]

[1]Department of Chemistry and Industrial Chemistry, Bowen University, Iwo, Nigeria
[2]Inorganic Chemistry Unit, Department of Chemistry, University of Ibadan, Nigeria
*Corresponding Author: sojylanrey2009@gmail.com

Abstract Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of mixed drugs, Vitamin Bx and Aspirin were synthesized and characterized by infrared and electronic (solid reflectance) spectroscopies, room temperature magnetic moments, percentage metal, melting points, solubility and conductance measurements. The conductance measurement in DMSO indicated that all the metal(II) complexes were covalent and percentage metal analysis corroborated the formula mass as $[M(HL)(HL^1)X]$, where X = Cl_2/SO_4. Infrared spectra data confirmed that coordination was via the un-deprotonated carboxylate oxygen atoms in the Vitamin Bx, while Aspirin coordinated through its carbonyl oxygen atoms of the carboxylic acid and acetyl groups. In addition, the electronic spectra and room temperature magnetic moment data indicated that Fe(II) and Co(II) complexes were paramagnetic and the Zn(II) complex was diamagnetic.These complexes assumed an octahedral geometry. Fascinatingly, the Ni(II), Mn(II) and Cu(II) complexes were shown by the room temperature magnetic moment to be probably dimeric, and the latter two complexes exhibited antiferromagnetism. Furthermore, antioxidant studies on the complexes revealed that Ni(II) and Cu(II) complexes had the best activity of 89.87 and 87.73 percent inhibition respectively, which were higher than, and comparable with that of the standard, ascorbic acid, with an activity of 87.66 percent inhibition, proving them as potential anti-cancer agents *in-vitro.*

Keywords Vitamin Bx, Aspirin, antiferromagnetism, antioxidant, anti-cancer.

Introduction

Drug metal complexes play an important role in drug action and metabolism [1]. Vitamins are essential for the normal growth and developments of multi-cellular organisms. Once growth and development are completed, vitamins remain essential nutrients for the healthy maintenance of cells, tissues and organ that make up multi-cellular organisms [2]. Vitamin Bx which is also known as *p*-aminobenzoic acid (PABA) is an important co-factor of the Vitamin B complex (folic acid). It is also a non-protein amino acid widely used by nature in the breakdown and utilization of proteins, and in the formation of red blood cells [3]. PABA is necessary for healthy skin, intestinal health, hair pigmentation and may be beneficial in female infertility, arthritis, constipation, dermatitis herpetiformis, and vitiligo [4]. Aspirin is a derivative of salicylic acid (acetylsalicylic acid). It has analgesic, anti-inflammatory and antipyretic actions and inhibits prostaglandins synthetase [2]. It is often used to treat body joint pain, fever and inflammation; and sometimes used to avert or treat strokes, chest pain and heart attacks [5-6].

Detailed literature search showed some works on metal complexes of Vitamin Bx combined with other drugs; and Aspirin mixed with other ligands. However, mixed drug metal complexes of Vitamin Bx and Aspirin have not yet been reported [2,7-10]. Thus, our aims are to synthesis, characterize and investigate the novel metal (II) complexes of mixed drugs, Vitamin Bx and Aspirin for their capability to exhibit magnetic properties such as antiferromagnetism, ferromagnetism and spin cross-over. In addition, the metal (II) complexes potentials as anti-

cancer agents will be verified *in-vitro* by antioxidant studies. This is a continuation of the research activities of our group in the search for novel metallo-drug complexes that are useful as chemotherapeutic agents [8, 10, 11-13].

Materials and Methods

Materials and Reagents

P-aminobenzoic acid (PABA), Aspirin, DPPH (1,1-diphenyl-2-picryl-hydrazyl), ascorbic acid Manganese(II) sulphate monohydrate, Iron(II) sulphate heptahydrate, Cobalt(II) chloride hexahydrate, Nickel(II) chloride hexahydrate, Copper(II) sulphate pentahydrate, Zinc(II) sulphate heptahydrate were obtained from Aldrich and BDH chemicals and were used as received. Ethanol and methanol were purified by distillation.

Physical Measurement

The solid reflectance spectra of the metal complexes were recorded using 1800/SHIMADZU UV spectrophotometer PC scanning and infrared spectra were recorded on a CARY 630 FTIR in the range 4000-650 cm^{-1}. The room temperature magnetic moment susceptibility measurements were determined using a Sherwood susceptibility balance MSB Mark 1 at 26 ^oC, and diamagnetic corrections were calculated using Pascal's constant. The melting points and decomposition temperature were determined using Stuart SMP 10 machine while molar conductivity measurement of 1x 10^{-3} M solutions of DCM (dichloromethane) were obtained using DDS-307A conductivity meter, and percentage metal was determined by complexometric titration.

Antioxidant Assay

The antioxidant activities of the mixed drug metal complexes were studied spectrophotometrically by DPPH method. DPPH(1,1-diphenyl-2-picryl-hydrazyl) was dissolved in DMSO to give a violet solution, which, upon reduction by an antioxidant, changed to yellow. Briefly, a solution of 0.4 mM DPPH in DMSO was prepared and 1.0 mL of this solution was mixed with 1.0 mL DMSO solutions of the metal(II) complexes with a single concentration of 100 μg mL^{-1}. The reaction mixture was stirred thoroughly and left in the dark at room temperature for 30 minutes. The absorbance of the mixture was then measured spectrophotometrically at 517 nm. Ascorbic acid (vitamin C) was used as the standard drug. The actual decrease in absorption was measured against that of the control. All tests and analyses were run in triplicate and the results obtained were averaged, and percentage scavenging inhibition of DDPH ability was expressed as:

$$\% \text{ scavenging inhibition} = \frac{\text{Absorbance of the control - Absorbance of the test sample(As)}}{\text{Absorbance of the control (Ac)}} \times 100$$

where Ac is the absorbance of DPPH radical + dimethylsulphoxide, and As is the absorbance of DPPH radical + sample [test samples/standard].

Synthesis

Preparation of $[Mn(HL)(HL^1)SO_4]$ and other metal complexes:

0.57 g (4.16 x 10^{-3} moles) of Vitamin Bx, HL and 0.75 g (4.16 x 10^{-3} moles) of Aspirin, HL^1 were dissolved in 20 mL of methanol. To the resulting homogenous solution, 0.70 g (4.16 x 10^{-3} moles) of the Mn(II) sulphate monohydrate was added neat while stirring at room temperature. After stirring for 30 minutes, the solution was buffered from pH 3 with 8-9 drops of concentrated ammonia to a pH 9. The resulting homogenous solution was left on continuous stirring for 3 hours during which the product formed. The dull-white precipitate obtained was filtered, washed with methanol and dried over silica gel. The same procedure was used for the preparation and isolation of Fe(II), Cu(II), Zn(II) complexes from their hydrated sulphate salts, while Co(II) and Ni(II) complexes were obtained from their hydrated chloride salts respectively.

Results and Discussion

Analytical data

The reactions of Vitamin Bx (HL) and Aspirin (HL^1) with metal(II) sulphates (Mn, Fe, Cu, Zn) and chlorides (Co and Ni) were in accordance with equations 1 and 2.

$$MSO_4.xH_2O + HL + HL^1 \rightarrow [M(HL)(HL^1)SO_4] + xH_2O \quad (1)$$

(M = Mn, Fe, Cu, Zn; x = 1,7,5,7 respectively)

$$MCl_2 \cdot 6H_2O + HL + HL^1 \rightarrow [M(HL)(HL^1)Cl_2] + 6H_2O \quad (2)$$

(M = Co and Ni)

The ligands, Vitamin Bx (HL) and Aspirin (HL^1) melted at 187-189^oC and 134-136^oC respectively, whereas their metal complexes all decomposed in the range 216-258^oC, confirming coordination. All the metal complexes were

coloured due to d-d transitions, with the exceptions of the Zn(II) and Mn(II) complexes which were white. The Zn(II) complex was expectedly white due to its d^{10} configuration, and Mn(II) was white because all its transitions were forbidden. The experimental percentage metal analysis values were very close to theoretical values, corroborating formulated masses. The colours, melting points, molar conductivity, percentage metal and room temperature magnetic moments for the mixed drug metal complexes are presented in Table 1.

Table 1: Analytical data of the ligands and their metal(II) complexes

Complexes	Formula mass	Colour	M.Pt (^oC)	% yield	%Metal Theo.(Exp)	^m	μeff. (B.M)
HL	137.14	Off-white	187-189	-	-	-	D
HL^1	180.16	White	134-136	-	-	-	D
$[Mn(HL)(HL^1)SO_4]_2$	936.52	White	258*	30.0	11.74(11.87)	21.4	0.7
$[Fe(HL)(HL^1)SO_4]$	469.17	Pinkpearl	237*	30.0	11.90(12.09)	21.2	6.1
$[Co(HL)(HL^1)Cl_2]$	447.23	Brown	216*	20.0	13.18(13.26)	21.4	2.4
$\{[Ni(HL)(HL^1)]_2Cl_2\}.4H_2O$	859.06	Lightgreen	256*	30.0	13.67(13.20)	21.4	5.6
$[Cu(HL)(HL^1)SO_4]_2$	953.72	Armygreen	248*	50.0	13.32(13.72)	21.5	1.0
$[Zn(HL)(HL^1)SO_4]$	478.69	White	252*	40.0	13.66(13.34)	21.4	D

HL = PABA; HL^1 = Aspirin; M.pt = Melting point; * = decomposition temperature; Theo. = Theoretical; Exp. = Experimental; ^m = Molar conductance ($\Omega^{-1}cm^2mol^{-1}$); μeff = effective magnetic moment; B.M = Bohr Magnetron; D = Diamagnetic

Solubility and Molar Conductance Measurements

The complexes were insoluble/slightly soluble in diethyl ether, methanol and ethanol but showed good solubility in dimethylsulphoxide, dichloromethane and water. The metal complexes had molar conductivities values below 22.0 $ohm^{-1}cm^2mol^{-1}$ in DMSO confirming their covalent nature, since values in the range 60 - 118 $ohm^{-1}cm^2mol^{-1}$ is expected for a 1:1 electrolyte [14-15].

Electronic Spectra and Magnetic Moments

The electronic spectra of the compounds are presented in Table 2. The ultraviolet spectra of the HL (PABA) and HL^1 (Aspirin) were characterized by strong absorption maxima in the range 27.32-29.24 kK, 33.33 kK and 41.49 kK respectively, assigned to $n\rightarrow\pi^*$, $\pi\rightarrow\pi^*$ and charge transfer transition. In the metal complexes, these bands shifted to 31.95-32.26 kK and 36.34-40.52 kK respectively due to coordination.

The Mn(II) complex showed two absorption bands typical of low spin octahedral geometry at 16.67 kK and 23.53 kK assigned to $^2T_{2g}\rightarrow{}^2A_{1g}$, and $^2T_{1g}\rightarrow{}^2B_{1g}$ transitions. Low spin octahedral Mn(II) complexes are expected to have moments close to 2.0 B.M. Consequently, a moment of 0.7 B.M was suggestive of strong antiferromagnetism operating through a Mn-Mn bond in a dimeric structure [16, Figure 1.0].

The Fe(II) complex had two absorption bands at 19.25 kK and 24.15 kK and were assigned to $^5T_{2g}\rightarrow{}^5A_{1g}$ and $^5T_{2g}\rightarrow{}^5B_{1g}$ transitions of octahedral geometry. High spin octahedral Fe(II) complexes are expected to have moments in the range 5.0-5.6 B.M and low spin Oh Fe(II) are expected to be diamagnetic, but an observed moment of 6.1 B.M was complimentary of high spin octahedral complex [13, 17].

The Co(II) complex exhibited an absorption band at 18.59 kK, typical of a low spin octahedral geometry, assigned to $^2A_{2g}\rightarrow{}^2T_{1g}$ transition. An observed moment of 2.4 B.M was indicative of low spin octahedral geometry since moments in the range 1.9-2.9 B.M were reported for low spin octahedral Co(II) complexes [12, 16].

The Ni(II) complex showed two absorption bands at 13.52 kK and 15.37 kK typical of a six-coordinate octahedral geometry, assigned to $^3A_{2g}\rightarrow{}^3T_{2g}$ and $^3A_{2g}\rightarrow{}^3T_{1g}(F)$ transitions. An observed moment of 5.6 B.M suggested a dimeric structure with bridging chloride such that each nickel atom had a moment 2.8 B.M. [18, Figure 2.0].

The Cu(II) complex expectedly showed a single absorption band at 14.73 kK typical of a six-coordinate octahedral geometry. This was assigned assigned to $^2E_g\rightarrow{}^2T_{2g}$ transition, since octahedral Cu(II) complexes usually have lone bands above 10.0 kK. A moment in the range 1.9-2.2 B.M is usually observed for mononuclear copper(II) complexes, regardless of stereochemistry. The Cu(II) complex in this study, had a moment of 1.0 B.M, which was suggestive of a dimeric structure with strong antiferromagnetism operating through a Cu-Cu bond [16, Figure 1.0].

The Zn(II) complex showed only charge transfer transition from metal to ligand at 12.72 kK and 15.43 kK respectively since d-d transition was absent. This complex was expectedly diamagnetic and assumed a six-coordinate octahedral geometry [11].

In conclusion, the drugs, Vitamin Bx and Aspirin, were suitable ligands for formation of low spin complexes with strong antiferromagnetic interactions as seen with Mn(II) complex.

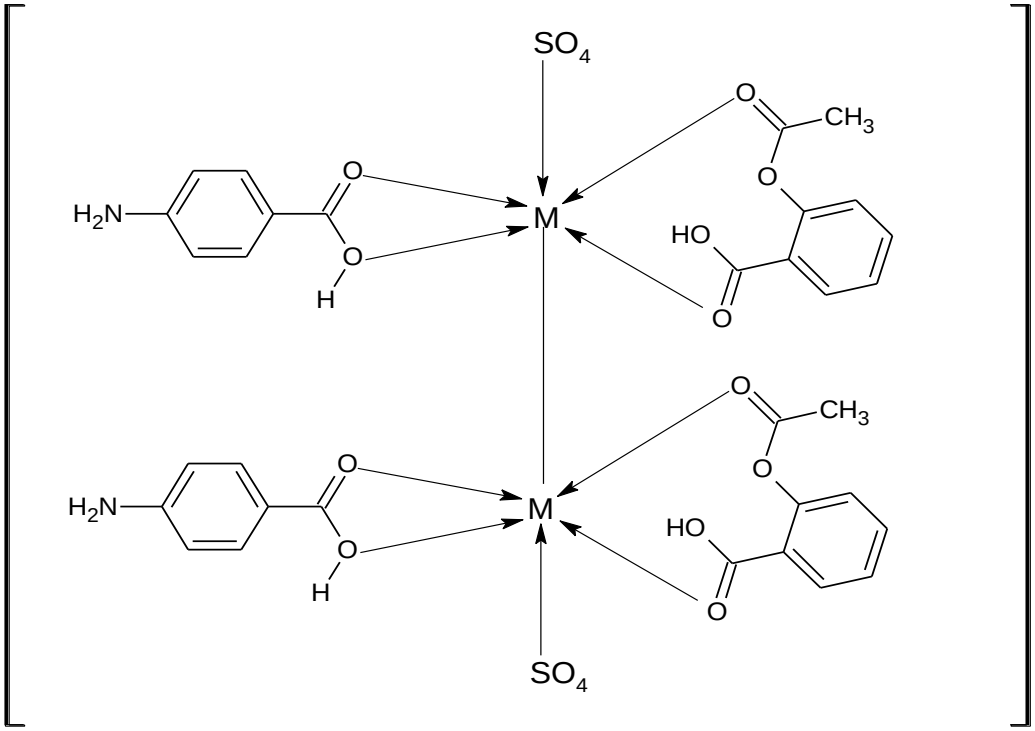

Figure 1: Proposed structure for Mn(II) and Cu(II) complexes

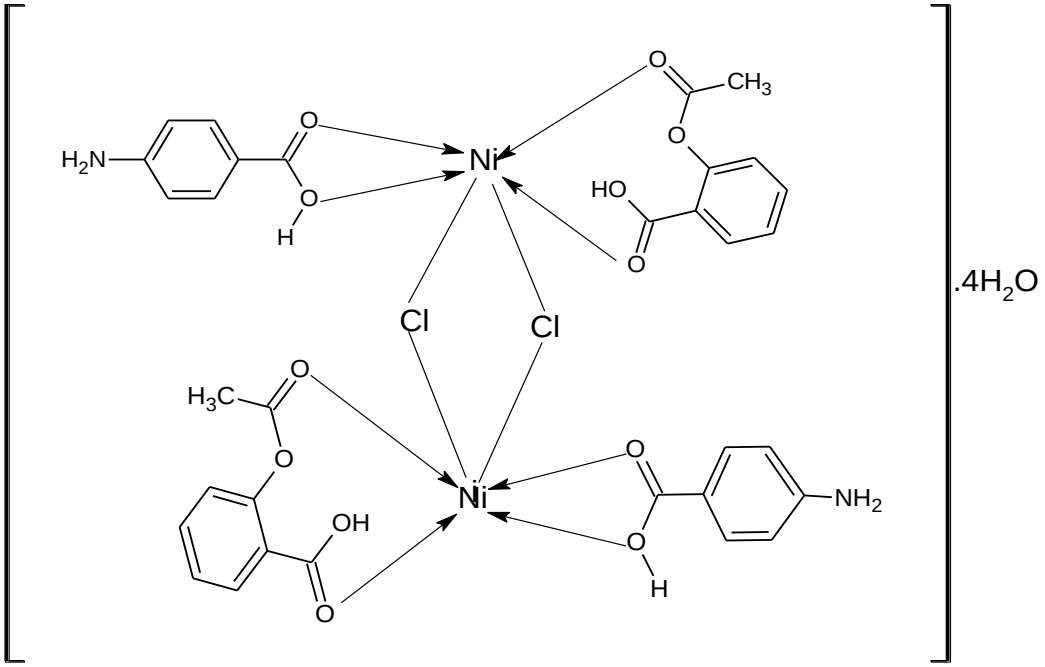

Figure 2: Proposed structure for the Ni(II) complex

Infrared Spectra

The relevant bands of the ligands and the metal complexes are presented in Table 2. The broad and medium bands at 3360 cm^{-1} and 3457 cm^{-1} in Vitamin Bx and Apsirin were assigned as υ(OH) band respectively [7, 8, 12], while Vitamin Bx exhibited strong and medium bands at 3457 cm^{-1} and 3377 cm^{-1} assigned to υ(NH_2). The ν(OH) bands of both ligands, were observed shifted in the metal complexes to the range 3054-3369 cm^{-1} due to coordination of the carboxylic and acetyl oxygen atoms of Aspirin and carboxylate atoms of Vitamin Bx to the metal ion respectively [8]. In contrast, the υ(NH_2) bands were shifted in the metal complexes to 3312-3588 cm^{-1} due to hydrogen bonding and not coordination since M-N bands were not observed in the range 500- 400 cm^{-1} **[**19]. The sharp bands in the range 1571-1750 cm^{-1} in Vitamin Bx and Aspirin were assigned to υC=O stretching vibrations [2, 8]. These bands shifted to 1541-1707 cm^{-1} in the metal complexes, confirming coordination through the carbonyl oxygen atoms of the Vitamin Bx and Aspirin [12]. The observance of M-O and M-S bands in the metal complexes at 550-580 cm^{-1}, further confirmed coordination sites. However, *ν*(M-Cl) was not observed because it was outside the range of the equipment.

Table 2: Infra-red and electronic spectra data of the metal(II) complexes

Complex	v(OH)	v(NH_2)	v(C=O)	Electronic spectra (kK)
HL	3360m	3457s 3377m	1657s 1597s 1571s	27.32 29.24
HL^1	3457b	--------	1750s 1681s1605s	33.33 41.49
$[Mn(HL)(HL^1)SO_4]_2$	3054b	3735b 3353m	1707s 1541s	19.14 21.25 38.67 47.30
$[Fe(HL)(HL^1)SO_4]$	3369b	3439m	1702s 1614s	19.25 24.15 37.88 40.52
$[Co(HL)(HL^1)Cl_2]$	3340b	3569b	1599s1562s	18.59 32.26 38.58
$\{[Ni(HL)(HL^1)]_2Cl_2\}.4H_2O$	3319b	3588b	1597s 1560s	13.52 15.37 31.95 39.46
$[Cu(HL)(HL^1)SO_4]_2$	3384b	3502b	1687s 1625s 1607s	14.73 32.87 39.75
$[Zn(HL)(HL^1)SO_4]$	3254b	3312b	1702s 1677s 1616s	12.72 15.43 20.70 36.34

HL = PABA, HL^1 = Aspirin, b = broad, m = medium, s = sharp, 1kK = 1000 cm^{-1}

DPPH Free Radical Scavenging Activity

The antioxidant (free radical scavenging), can be defined as any material or substance when present in low concentration can delay or prevent the oxidation, and inhibit the free radical effect. In the body, they may provide protection against cancers, alzheimer's and Parkinson's diseases **[**20-22]. DPPH acts by accepting an electron from test compounds, and gets converted into a stable molecule. In this study, it was observed that Ni(II) and Cu(II) complexes had highest percentage inhibition of 89.87 % and 87.73 % respectively which were higher than, and comparable to the positive standard, Vitamin C, with an activity of 87.66 %. The scavenging ability of the metal complexes decreases in the order; Ni > Cu > Co > Mn > Fe > Zn. Thus, these compounds had potential as therapeutic agents in treatment of cancer and neurodegenerative diseases.

Table 3: Antioxidant properties of the metal complexes

Complex	**Average±SD**	% inhibition
$[Mn(HL)(HL^1)SO_4]$	0.087±0.0015	69.33
$[Fe(HL)(HL^1)SO_4]$	0.073±0.0029	58.13
$[Co(HL)(HL^1)Cl_2]$	0.090±0.0010	71.99
$[Ni(HL)(HL^1)Cl_2]$	0.112±0.0006	89.87
$[Cu(HL)(HL^1)SO_4]$	0.109±0.0015	87.73
$[Zn(HL)(HL^1)SO_4]$	0.062±0.0015	49.86
Standard (Ascorbic acid)	0.053±0.0026	87.66

HL = PABA , HL^1 = Aspirin, SD = Standard Deviation, % = Percentage

Conclusion

Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of mixed drugs, Vitamin Bx and Aspirin were synthesized and characterized by infrared and electronic(solid reflectance) spectroscopies, room temperature magnetic moments, percentage metal, melting points and conductance measurements. Electronic spectra and room temperature magnetic moments corroborated high spin or low spin octahedral geometry for all the metal(II) complexes. In addition, the Ni(II), Mn(II) and Cu(II) complexes were probably dimeric. The conductance measurements showed that all the metal(II) complexes were covalent in dimethylsulphoxide. Furthermore,

antioxidant studies revealed that Ni(II) and Cu(II) complexes had the best antioxidant activity with percentage inhibition values of 89.87 and 87.73 % respectively.

Acknowledgements
The authors thanked Bowen University, Iwo and the University of Ibadan, Ibadan, Nigeria for research chemicals/facilities and a sabbatical leave respectively.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Al-Noor, T. H., Mahdi, R. T., & Ismael, A. H. (2014). Preparation, characterization and antibacterial properties of mixed ligand complexes of L-aspargine and sulfamethoxazole (antibiotics) with Mn(II), Co(II), Ni(II) Cu(II), Zn(II) Cd(II) and Hg(II) ions. *J. Chem. Pharm. R*., 6(5): 1286-1294.
2. Lawal, A., & Obaleye, J. A. (2007). Synthesis, characterization and antibacterial activity of aspirin and paracetamol metal complexes. *Biokemistri*, 19(1): 9-15
3. Roberts, S. B., Morrow, F. D., Evans, W. J., Sheppard, D. C., & Dallal, G. E. et al. (1990). Use of p-aminobenzoic acid to monitor compliance with prescribed dietary regimens during metabolic balance studies in man. *Am. J. Clin. Nutr*., 51: 485-488.
4. Zarafonetis, C. J., Dabich, L., Skovronski, J. J., Devol, E. B., Negri, D., Yuan, W., & Wolfe, R. (1998). Retrospective studies in scleroderma: skin response to potassium para-aminobenzoate therapy. *Clin. Exp. Rheumatol*., 6:261-8.
5. Burke, A., Smyth, E., & FitzGerald, G. A. (2006). Analgesic Antipyretic and Anti-inflammatory Agents In: Brunton L.L, Lazo J.S, Parker K (eds.). Goodman & Gilman's the Pharmacological Basis of Therapeutics, New York, McGraw-Hill, 11th Ed., 671–716.
6. Sachs, C. J. (2005). Oral analgesics for acute nonspecific pain. *American family physician*. 71: 913-918.
7. Agbaje, O. B. A., Osowole, A. A., Malumi, E. O., & Wakil, S. M. (2015). Synthesis, spectroscopic characterization, antimicrobial and antioxidant properties of some metal(II) complexes of mixed ligands-Riboflavin and 4-aminobenzoic acid. *Journal of Chemistry*, 4(1): 1-7.
8. Osowole, A. A., Malumi, E. O., & Odutemu, A. E. (2015). Synthesis, magnetic, spectral and antioxidant properties of some metal(II) mixed-drug complexes of Aspirin and Vitamin B3. *Research and Reviews: Journal of Chemistry*, 4(1): 60-65.
9. Weder, J. J. E., Dillon, C. T., Hambley, T. W., Kennedy, B. J., & Lay, P. A. et al. (2002) Copper complexes of non-steroidal anti- inflammatory drugs: an opportunity yet to be realized. *Coordination Chemistry Reviews*, 232: 95-126.
10. Osowole, A. A., Wakil, S. M., & Okediran, E. Q. (2015). Synthesis, characterization and antimicrobial activities of some metal(II) complexes of mixed-ligands- dimethyl dithiocarbamic and para aminobenzoic acids. *Elixir Appl. Chem*., 79: 30375-30378
11. Osowole, A. A., Malumi, O., Wakil, S. M., & Alao, O. K. (2015). Synthesis, Characterization, Antioxidant and Antimicrobial activities of Some Mixed-Drug Metal(II) complexes of Vitamins B2 and B3. *Int. Journal of Applied Medical Sciences*, 1(2): 88-97.
12. Osowole, A. A., Agbaje, O. B. A., & Ojo, B. O. (2014). Synthesis, characterization and antibacterial properties of heteroleptic metal(II) complexes of paracetamol and vanillin. *Asian J. Pharm. Clin Res.*, 7(3): 145-149.
13. Osowole, A. A., & Oni, T. I. (2013). Synthesis, spectroscopic characterization and antibacterial activities of mixed ligand metal(II) complexes of 4-amino-6-chloro-2-methylthiopyrimidine and 1,10-phenanthroline. *Scientific Research Reports*, 1(1): 25-31.
14. Ronald, L. P., Xianli, W. L., & Karen, S. C. (2005). Standardized methods for the determination of antioxidant capacity and phenolic in foods and dietary supplements. *J. Agric Food Chem.*, 53: 4290-4302.
15. Ekennia, A. C., Onwudiwe, D. C., & Osowole, A. A. (2015). Synthesis, Spectral, thermal stability and antibacterial studies of copper, nickel and cobalt complexes of *N*-methyl-*N*-phenyl dithiocarbamate. *Journal of Sulfur Chemistry*, 36(1): 96-104.
16. Sahar, A., Majumdar, P., & Goswami, S. (2000). Low-spin Mn(II) and Co(III) complexes of N-aryl-2-pyridylazophenylamines: new tridentate N,N,N-donors derived from cobalt mediated aromatic ring amination of 2-(phenylazo) pyridine. Crystal structure of a manganese(II) complex. *J. Chem. Soc., Dalton Trans*, 1703-1708.

17. Salmon, L., Molnar, G., Cobo, S., Oulié, P., Etienne, M., Mahfoud, T., Demont, P., Eguchi, A., Watanabe, H., Taaka, K., & Bousseksou, A. (2009). Reinvestigation of the spin crossover phenomenon in the ferrous complex $[Fe(HB(pz)_3)_2]$. *New Journal of Chemistry*, 33(6): 1283-1289.
18. Mohamed, G. G., Omar, M. M., & Hindy, A. M. (2006). Metal complexes of Schiff bases: preparation and biological activity. *Turk. J. Chem.*, 30: 361-382.
19. Sayyed, H., Shaikh, A., & Mazahar, F. (2014). Potentiometric studies of p-amino benzoicacid with transition metal ions. *World journal of pharmacy and pharmaceutical sciences*, 3(5): 632-635.
20. Halliwell, B.; Gutteridge, J.M.C. Oxygen toxicology, oxygen radicals, transition metals and disease. *Biochem. J.* 1984; 219: 1-4.
21. De Souza, R. F., & De Giovani, W. F. (2004). Antioxidant properties of complexes of flavonoids with metal ions. *Redox Report*, 9: 97-104.
22. Fizea, S. M., Musa, F. H., Fidhel, H. A. (2014). Synthesis and spectral studies of metal complexes with 3,4,6,7-0,0,0,0-tetrakis-(Carboxy(chloro)methyl)-L-Ascorbic acid. *Eur. Chem. Bull.*, 3(9): 915-919.