Abstract:- Mechanochemical synthesis of Co(II) and Cu(II) aspirin complexes was carried out by simple grinding of metal (II) acetates with aspirin without any solvent. Also conventional preparation of the above complexes was carried out for comparison purposes using the solution-based method. The products of mechanochemical synthesis were characterized by comparison of solubility, melting points, conductivity values, magnetic moment and IR analyses with those of ligands and conventional solution-based products. The IR spectral and analytical data of the complexes were similar for both products of the two synthetic routes suggesting the formation of identical compounds. Job’s method analyses suggested 1:2 metal to ligand ratio. The elemental analyses results revealed identical percentage composition of each element found in the products as compared to those of calculated percentages. The complexes have low values of molar conductance (4.24-6.60Ω−1cm²mol⁻¹) implying that they are non-electrolytes in DMSO. The complexes were all soluble in dimethylformamide and dimethylsulfoxide. The complexes were mostly soluble in non-polar solvents. All the products decomposed at a temperature range of 177.0-181.9°C higher than that of their ligand revealing their more stable nature. The magnetic moment values obtained proved the paramagnetic nature of the synthesized complexes. The products and the ligand were screened against three bacteria isolates; Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus and two fungi isolates; Aspergillus fumigatus, Mucus specie for antimicrobial activity. The results shows that the ligand was inactive against all the test organisms; the complexes were active in all test concentration, with only Co(asp)₂ complex inactive against Staphylococcus Aureus at a concentration of 15μg/disc.

**Keywords:** Mechanochemical, Ligand, Complex, Job’s Method, Antimicrobial, Aspirin.

**I. INTRODUCTION**

Innovation involving developing an alternative synthetic route for the syntheses of chemical substances without the use of solvent is an attractive goal in the chemical world. This will of course allow chemist and chemical industries to carry out reactions more efficiently, with less waste, less cost and without using volatile, flammable or toxic solvents. In Solvent-based synthesis, solvent allows the reactant molecules to mix together closely so that they can interact to form a product. Without solvent, the same reactions can sometimes be brought about by grinding the reactants in solid states together manually by using mortar and pestle or using ball mill and this has been used as a solvent free synthetic method for the production of different metal complexes [5]; [20]; [4]; [21].

Mechanochemistry is a branch of chemistry concerned with the transformations of chemical substances in all state of aggregation induced by mechanical energy [9].

Aspirin is derived from salicylic acid which is also referred as to acetyl salicylic acid or 2-(acetyloxy) benzoic acid. It is used as analgesic and antipyretic agent and is also used as NSAID. It has also anti-blood clotting effect which is used in long term at low doses to prevent heart attack and stroke [12].

Reference [14] reported the synthesis of aspirin and paracetamol complexes with Co(II), Ni(II) and Fe(III) and Reference [17] reported the synthesis of Mn(II), Co(II), Fe(II) and Cu(II) paracetamol and ibuprofen complexes all via conventional solution-based synthetic route involving refluxing with ethanol for 3hours as this is time consuming, requires more heat, solvent usage, use of more sophisticated equipment which are sometimes delicate to handle and expensive to buy.

Many drugs and other pharmaceutical agents has metal-binding sites which enable them to act as potential ligands. And this will allow them bind or coordinate with metal ions which potentially influence their bioactivities [17]. Coordination compounds are however gaining interest globally in drug design as drugs are used to coordinate with metals to form complex compounds and this has led to lots of study on metal-drug complexes [14].

It was therefore thought that a new synthetic approach should be employed in the synthesis of these metal-drug complexes which are known for their chemotherapeutic properties. This research work hereby reports mechanochemical synthesis, characterization and antimicrobial screening of metal (II) complexes of active pharmaceutical ingredient, aspirin on comparison with complexes synthesized via solution-based synthesis.
II. RESEARCH METHODOLOGY

Analytical grade chemicals were used in the process without any further purification throughout. The active pharmaceutical ingredients, aspirin powder was obtained from Dana Pharmaceutical Company, Minna, Nigeria. Metal salts used include Cobalt acetate and copper acetate.

All the glass wares used were washed thoroughly with detergent, rinsed with distilled water and dried in an oven at 110°C. All weighing was carried out using College Weighing balance of model B154 METTLER TOLEDO. Molar conductance measurement was done using Jenway conductivity meter of model 4010 in DMSO and Jenway 6305 UV-Visible Spectrophotometer was used for UV-absorbance measurement. Decomposition/melting temperature were recorded using Gallenkamp melting apparatus. Magnetic susceptibility measurement of the complexes was recorded using magnetic susceptibility balance of model MK 1 Sharwood. The bacteria and fungi isolates (bacteria; Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus and fungi isolates; Aspergillus fumigatus, Mucus specie) were obtained and identified at Department of Microbiology, Bayero University Kano.

Infrared spectra of the ligand and the complexes were recorded using Fourier Transform Infrared Spectrophotometer of model Shimadzu FTIR 8400S with the band range of 380 to 4000cm⁻¹. Elemental analyzer of model Eager 300 was used to obtain the elemental analytical data of the synthesized complexes. Assay for purity of the ligand was carried out using High Performance Liquid Chromatography, HPLC Agilent Technologies of model 1100Infinity at the instrument laboratory, Department of Pure and Industrial Chemistry, Bayero University Kano.

- **Synthesis of the Complex**
  - **Mechanochemical Synthesis of Cobalt (II) aspirin Complex**
    3.603g (0.02mol) of aspirin and 2.491g (0.01mol) of Co(CH₃COO)₂·4H₂O were ground in an agate mortar to obtain fine powder as product accompanied with the release of characteristic odour of acetic acid. The product was then dried in desiccator as complex.
  - **Solution Synthesis of Cobalt (II) aspirin Complex**
    An aqueous solution of hydrated salt, Cu(CH₃COO)₂·2H₂O (1.997g, 0.01mol) in 10cm³ ethanol was added to an ethanolic solution of aspirin (3.603g, 0.02mol), the mixture was refluxed for 3hours with constant stirring. The pale blue precipitated complex formed was separated by filtration, washed with ethanol and dried in desiccator over phosphorus (V) oxide for 24hours.

- **Solution Synthesis of Copper (II) aspirin Complex**
  An aqueous solution of hydrated salt, Cu(CH₃COO)₂·2H₂O (1.997g, 0.01mol) in 10cm³ ethanol was added to an ethanolic solution of aspirin (3.603g, 0.02mol), the mixture was refluxed for 3hours with constant stirring. The pale blue precipitated complex formed was separated by filtration, washed with ethanol and dried in desiccator over phosphorus (V) oxide for 24hours.

- **Determination of Metal to Ligand Ratio**
  Job’s method of continuous variation was used to determine the number of the ligand coordinated to the metal ion.

3mmolar solutions of the ligands and metal salts were prepared. The following metal to ligand ratio (in ml); 0:16, 1:15, 3:13, 5:11, 7:9, 9.7, 11:5, 13:3, 15:1 were measured from the ligand solution and each of the metal salt solutions respectively. In that order, a total volume of 16ml was maintained throughout the process. The ligand mole fraction was calculated in each mixture. The wavelength of maximum absorption (λmax) for a particular metal ion was determined after scanning (as blank) the solution of that metal salt. The machine was fixed at λmax (in each case) before taking the absorbance values.

The number of coordinated ligand (coordination number) was determined using the equation below by extrapolating absorbance values against mole fraction of the ligand.

$$\frac{x_i}{(1-x_i)} = \frac{A_i}{A_0}$$

Where n = number of coordinated ligand and x_i = mole fraction at maximum absorbance

- **Antibacterial Activity Test**
  Various test concentrations were prepared in accordance with the dilution method described by reference [22]. A stock solution of the ligand and the metal(II) complexes were prepared by dissolving 0.06g of the ligand or their metal complexes in 1cm³ of DMSO. The stock solution contains 60µg per cm³ of DMSO. 30µg was prepared from the stock solution by taken 0.5cm³ of the stock and added 0.5cm³ of the DMSO. Subsequently 15µg was prepared by taking 0.5cm³ of 30µg and added 0.5cm³ into another bottle. These bottles containing the various concentrations were impregnated with 50pcs of paper disc. The paper discs were used to inoculate the culture plate. The culture media (nutrient agar) was incubated at 37°C for 24hrs and the evaluation of the antibacterial activity of the
ligands, their complexes observed and the diameter of zones of inhibition recorded.

- **Antifungal Activity**
  Various test concentrations were prepared in accordance with the dilution method described by reference [8]. A stock solution of the ligand and the metal (II) complexes were prepared by dissolving 0.06g of the ligand or their metal complexes in 1cm³ of DMSO. The stock solution contains 60µg per cm³ of DMSO. 30µg was prepared from the stock solution by taking 0.5cm³ of the stock and added 0.5cm³ of the DMSO. Furthermore, 15µg was prepared by taking 0.5cm³ of 30µg and added 0.5cm³ into another bottle. These bottles containing the various concentrations were impregnated with 50pcs of paper disc. The paper discs were used to inoculate the culture plate. The culture media (sabouraud dextrose agar) was incubated at room temperature for 48hrs and the paper disc technique was used to evaluate the antifungal activity of the ligands, their complexes and the diameter of zones of inhibition recorded after 72hrs.

### III. RESULTS AND DISCUSSION

Reactions were achieved via mechanochemical means and completed within a shorter time of 15 minutes as compared to solution-based method which took hours to obtain the product. The products were generally obtained with neither waste nor further purification processes.

| Compounds | Method          | % Yield | Colour   | Melting temperature(°C) | Decomposition temperature (°C) |
|-----------|----------------|---------|----------|-------------------------|--------------------------------|
| Aspirin   |                 |         | White    | 137                     | -                              |
| Co(Asp)₂  | Mechanochemical | 97.60   | Army green | -                       | 181.0                          |
| Co(Asp)₂  | Solution-based  | 59.59   | Dark green | -                       | 177.3                          |
| Cu(Asp)₂  | Mechanochemical | 99.52   | Pale Blue | -                       | 181.9                          |
| Cu(Asp)₂  | Solution-based  | 75.08   | Turquoise | -                       | 179.0                          |

Table 1: Physical Properties of Aspirin and its Metal (II) Complexes Synthesized by both Methods

- **Solubility**
  Aspirin is soluble in methanol, DMF and DMSO whereas it complexes were all insoluble in ethanol and water, all soluble in DMF, DMSO, while others were soluble in some organic solvents and slightly soluble in other organic solvents as shown in table 2 below.
This is in agreement with the Ω e × 10 or as reported also that this e effective magnetic
geometry. This is in agreement with the complexes tentatively proposes distorted octahedral
mechanochemical and solution
ions. This is in agreement with
5.2BM) for high spin octahedral geometry around Co(II)
correspond to spin
geometry since the values lies within the range that
aspirin
complexes. The values ranges from 4.27BM
moment were similar for both complexes from the two
room temperature for aspirin metal (II) complexes are
of the observed effective magnetic moment measured at
can also be provided by their magnetic moment. The results
of the magnetic properties of aspirin
complexes are paramagnetic. Paramagnetic property is due
to presence of unpaired electrons in the partially filled d
orbital of the central metal ion [15].

The suggestion of the likely geometry of complexes
can also be provided by their magnetic moment. The results
of the observed effective magnetic moment measured at
room temperature for aspirin metal (II) complexes are
presented in Table 3. The values of the effective magnetic
moment were similar for both complexes from the two
different synthetic routes. The values ranges from 4.27BM-
4.88BM and 1.85BM-1.96BM for Co(II) and Cu(II) aspirin
complexes.

The values 4.27BM and 4.88BM obtained for Co(II)
aspirin complexes tentatively proposes high spin octahedral
geometry since the values lies within the range that
correspond to spin-only value magnetic moment (3.87-
5.2BM) for high spin octahedral geometry around Co(II)
ions. This is in agreement with the research conducted by
reference [2].

The values 1.85BM and 1.96BM for
mechanochemical and solution-based Cu(II) aspirin
complexes tentatively proposes distorted octahedral
geometry. This is in agreement with the research conducted
by reference [7]. Though, it was reported also that this
values lies within the expected range for square pyramidal
too [6].

The µ_eff values which are higher or lower than spin-
only values for the respective metal (II) ion concerned may
be due to spin-orbit coupling.

The observed µ_eff for Co(II) chelate at room
temperature are 4.39BM and 4.10BM for mechanochemical
and solution products which lies within expected range for
high-spin octahedral Co(II) complexes, though slightly
higher than value corresponding to spin-only magnetic
moment, 3.87BM for octahedral Co(II) complexes obtained
may be due to orbital contribution [7].

**Molar Conductivity**
The molar conductance of metal (II) aspirin
complexes measured at room temperature in 1×10^{-3}M
DMSO are presented in Table 3. The molar conductance
values for both mechanochemical and solution-based
synthesized products are low and quite similar. Co(II),
Cu(II) aspirin complexes has molar conductance values of
5.21(4.89Ω cm⁻¹mol⁻¹), 4.58(4.55Ω cm⁻¹mol⁻¹), for
mechanochemical and solution-based products respectively.
The range, 4.24-6.60Ω cm⁻¹mol⁻¹ is low within the
expected values indicating that the complexes are non-
electrolytes in DMSO. This is in agreement with the
research conducted by reference [19]; [16]; [18].

| Complex  | Method        | Magnetic susceptibility(Xg) (g⁻¹) | Xm (mol⁻¹) | Effective magnetic moment (BM) | Molar conductivity (Ω⁻¹cm²mol⁻¹) |
|----------|---------------|----------------------------------|------------|-------------------------------|---------------------------------|
| Co(Asp)₂ | Mechanochemical| 1.835×10⁻⁵                       | 7.656×10⁻³ | 4.27                          | 5.20                            |
| Co(Asp)₂ | Solution-based | 2.403×10⁻⁵                       | 1.003×10⁻² | 4.88                          | 4.89                            |
| Cu(Asp)₂ | Mechanochemical| 3.409×10⁻⁶                       | 1.438×10⁻³ | 1.85                          | 4.58                            |
| Cu(Asp)₂ | Solution-based | 3.858×10⁻⁶                       | 1.627×10⁻³ | 1.96                          | 4.55                            |

Table 3: Effective Magnetic Moment and Molar Conductance of Metal (II) Aspirin Complexes
IR Analysis
The results of the IR analysis are presented in Table 4. The broad absorption band at 3003.27 cm⁻¹ in the spectrum of free aspirin has been attributed to O-H vibration frequency of the carboxylic group. This band disappeared in the spectra of the complexes due to coordination through the oxygen of the O-H of carboxylic group with deprotonation, as observed in both products of mechanochemical and solution-based synthesis respectively. The bands at 1755.28 cm⁻¹ and 1686.81 cm⁻¹ in the spectrum of free aspirin are assigned to v(C=O) of ester and carboxylic acid respectively, as these bands shifted to different frequencies, 1751.28 cm⁻¹(1752.42 cm⁻¹) and 1679.09 cm⁻¹(1627.01 cm⁻¹), 1750.46 cm⁻¹ (1751.42 cm⁻¹) and 1684.88 cm⁻¹(1670.09 cm⁻¹), for Co(Asp)₂ and Cu(Asp)₂ complexes respectively. This shifting also provides evidence that these groups are also coordination sites of aspirin. The bands at 1298.14 cm⁻¹ and 1015.56 cm⁻¹ in free aspirin are attributed to C-O stretching vibrations of carboxylic and ester groups, as these bands shifted to higher and lower frequencies, 1301.99 cm⁻¹(1303.92 cm⁻¹) and 1030.02 cm⁻¹(1034.84 cm⁻¹), 1299.10 cm⁻¹(1301.99 cm⁻¹) and 1024.24 cm⁻¹(1030.02 cm⁻¹), in both mechanochemical and solution aspirin complexes respectively. This supports the formation of new compounds. The similar bands at a range 655.82 cm⁻¹ to 688.82 cm⁻¹ in the spectra of mechanochemical and solution products of Co(II) and Cu(II) aspirin complexes which could not be exactly traced in the spectrum of free aspirin have been tentatively assigned to (M-O) stretching frequencies, supporting coordination of aspirin to respective metal ions.

| Ligand/complex | Method          | u(O-H) cm⁻¹ of carboxylic acid | u(C=O) cm⁻¹ of ester/ C=O of carboxylic acid | C-O str. of Carboxylic acid | C-O str. of ester | M-O and M-O=C |
|----------------|----------------|-------------------------------|---------------------------------------------|-----------------------------|------------------|----------------|
| Aspirin        |                | 3003.27                       | 1755.28, 1686.81                            | 1298.14                     | 1015.56          |                |
| Co(Asp)₂       | Mechanochemical| -                             | 1751.42, 1679.09                            | 1301.99                     | 1030.02          | 655.82         |
| Co(Asp)₂       | Solution-based | -                             | 1752.42, 1627.01                            | 1303.92                     | 1034.84          | 658.71         |
| Cu(Asp)₂       | Mechanochemical| -                             | 1750.46, 1684.88                            | 1299.10                     | 1024.24          | 680.89         |
| Cu(Asp)₂       | Solution-based | -                             | 1751.42, 1670.09                            | 1301.99                     | 1030.02          | 688.82         |

Table 4: The IR Spectra Data of Aspirin and its Metal (II) Complexes

Elemental Analysis
The elemental analytical data revealed the percentage of carbon, hydrogen and oxygen to be 8.97%, 42.08% and 1.88% respectively, while the theoretical/calculated percentage was found to be 9.64%, 41.33% and 2.77% for carbon, hydrogen and oxygen revealing similar percentage composition of the elements present in both reactants and products as presented in the table below:

| Complex     | Element: | Percentage (%) |
|-------------|----------|----------------|
|             | Carbon   | Hydrogen       | Oxygen        |
| Cu(Asp)₂    | Calculated: 51.04 | 3.77          | 30.20         |
|             | Found: 49.09 | 2.88          | 30.49         |
| Co(Asp)₂    | Calculated: 51.52 | 3.82          | 30.53         |
|             | Found: 50.32 | 2.78          | 29.99         |

Table 5: Elemental Analytical Data of the Metal (II) Complexes

Biological Activity
Antimicrobial screening results as shown in Table 6 and 7 below revealed that the ligands are inactive towards inhibiting the growth of the bacteria and fungi in all concentrations. Copper complex showed activity against all the isolates in all concentrations except and Co(asp)₂ complex which was inactive at 15µg/disc against *Staphylococcus Aureus* and inactive against *Aspergillus fumigatus* at all concentrations. Cu(asp)₁ showed highest activity against *Mucus specie*. In general, these results revealed that the synthesized complexes have significant antibacterial and antifungal strength even at low concentration of 60µg/disc. However, this inhibitory action increases with increase in concentration of the complexes.
### Table 6: Antibacterial Activity of Aspirin and their Metal (II) Complexes

| Test Organism          | Ligand/Complex | Inhibition Zone (mm) at different Concentration (µg/disc) | Control disk Ampiclox (10µg/disc) |
|------------------------|----------------|----------------------------------------------------------|-----------------------------------|
| *Escherichia coli*     | Aspirin        | NZI, NZI, NZI                                           | 31                                |
|                        | Co(Asp)₂       | 8, 9, 11                                                |                                   |
|                        | Cu(Asp)₂       | 9, 11, 14                                               |                                   |
| *Klebsiella Pneumonia* | Aspirin        | NZI, NZI, NZI                                           | 22                                |
|                        | Co(Asp)₂       | 13, 16, 18                                              |                                   |
|                        | Cu(Asp)₂       | 9, 11, 14                                               |                                   |
| *Staphylococcus Aureus*| Aspirin        | NZI, NZI, NZI                                           | 25                                |
|                        | Co(Asp)₂       | 9, 11, 14                                               |                                   |
|                        | Cu(Asp)₂       | 9, 12, 14                                               |                                   |

Key: NZI = No Zones of Inhibition

### Table 7: Antifungal Activity of Aspirin and their Metal (II) Complexes

| Test Organism          | Ligand/Complex | Inhibition Zone (mm) at different Concentration (µg/disc) | Control disk Ketoconazole (250mg/disc) |
|------------------------|----------------|----------------------------------------------------------|---------------------------------------|
| *Aspergillus Fumigatus*| Aspirin        | NZI, NZI, NZI                                           | 25                                    |
|                        | Co(asp)₂       | NZI, NZI, NZI                                           |                                       |
|                        | Cu(asp)₂       | 10, 12, 14                                              |                                       |
| *Mucus specie*         | Aspirin        | NZI, NZI, NZI                                           | 36                                    |
|                        | Co(asp)₂       | 9, 12, 15                                               |                                       |
|                        | Cu(asp)₂       | 12, 15, 18                                              |                                       |

Key: NZI = No Zones of Inhibition

**Job’s Method**

The number of ligand coordinated to the metal in the two complexes synthesized, π was calculated to be 2 using equation (1) above. This however, suggested 1:2 metal to ligand ratio.
On the basis of the analytical data obtained viz: melting point, conductivity measurement, magnetic susceptibility(effective magnetic moment), Job’s method, elemental analysis and FTIR spectroscopic studies, the structures tentatively proposed for the metal (II) complexes are as follows:-

IV. CONCLUSION

This research work has demonstrated the use of mechanochemical synthetic approach for the synthesis of metal (II) complexes of aspirin. It was found out that the solvent free solid-solid state reaction can be used to obtain the same product as that obtained from conventional method. For all complexes, the obtained IR data and effective magnetic moment values suggested the geometry and coordination of molecules of aspirin to their respective metal ions. Aspirin coordinate through carbonyl oxygen of both carboxylic and ester group and also through oxygen of the O-H of carboxylic group after deprotonation giving rise to octahedral geometry. The bands at different frequencies that appeared, shifted and disappeared in the IR spectra of the resulting products in both cases of solvent free technique and solution-based syntheses were similar. Therefore, it can be concluded that structures of the products synthesized mechanochemically are comparable to those obtained via solution syntheses. In contrast to complexes from solution method, mechanochemical products gave high yield, do not require any purification procedure, eco-friendly, low cost, fast, complete solid-solid conversion between metal salts and ligand, stoichiometric and low temperature solid state synthesis, providing possible access to different types of coordination compounds formation. Mechanochemical synthesis, therefore, is the best alternative synthetic route to obtain complexes over conventional method.

REFERENCES

[1]. A. M. Algra, P. M. Rothwell, and L. Oncol, “Effect of Regular Aspirin on Long-term Cancer Incidence and Metastasis: A Systematic Comparason of Evidence from Observational Studies Versus Randomised Trials” 13(5): 2012, pp. 518-527

[2]. T.H. Al Noor, F.H. Ghanim and A.S. Kindeel, “Synthesis, characterization and antibacterial activity of Mn(II), Fe(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) Mixed- Ligand complexes containing fural-2-carboxylic acid and (1,10-Phenanthroline)”, Advances in Physics Theory and Applications. Vol. 29. 2014, pp.1-7
[3]. R. J. Angelici, “Synthesis and techniques in inorganic chemistry”, W.B Savders Company, 2nd ed., 1971, pp. 115-125.

[4]. G. A. Bowmaker, “et al., “Mechanochemical synthesis in copper (II) halide/pyridine systems: single crystal X-ray diffraction and IR spectroscopic studies”, Dalton Trans, Roy. Soc. Chem., 40 (27), pp. 7210-7218, 2011.

[5]. D. Braga, F. Grespion, L. Maini, R. Brescillo and L. Cataraire, “Simple and qualitative mecheanochemical preparation of the first zinc and copper complexes of the neuroleptic drug gabapentin” Cryst. Eng. Comm, 10 (5), Roy. Soc. Chem., pp. 469-471, 2008.

[6]. B. Cristovoa, “Spectral, thermal and magnetic properties of Cu(II) and Ni(II) complexes with schiff base ligands”, J. Serb. Chem. Soc. 76 (12), 1639-1648, 2011.

[7]. R.A. El-Halawa, “et al., “Synthesis, characterization and antifungal activity of some metal complexes derived from quinoxaloylhydrazone”, World Journal of Organic Chemistry, Vol. 3(1), pp.1-8, 2015.

[8]. S. W. Hassan, R. A. Umar, M. Lawal, L. S. Bilbis and B. Y. Muhammed, “Evaluation of antifungal activity of Ficus sycomorus L. (moraceae)” Best Journal 3(2), pp. 18-25, 2006.

[9]. G. Heinike, ““Triochemistry”, Academie-Verlag, Berlin. Acta Polymorica. 36(7), pp. 400-401, 1984.

[10]. M. A. Kurawa and S. G. Yammama, “Solid state synthesis, characterization and antimicrobial study of 4,4'-bipyridine copper (II) complexes. ChemSearch Journal 5(2), pp. 39 –45, 2014.

[11]. M. A. Kurwa. and S. G. Yammama, “Solid state synthesis, characterisation and biological activity of 4,4'-bipyridiniumtetachloronicelate (II) and 4,4'-bipyridine dichloronickel (II) complexes”, ChemSearch Journal, 5(1), pp. 59 – 65, 2014.

[12]. H.D. Lewis, “et al, “Protective effect of aspirin against acute myocardial infection and death in men with unstable angina. results of the veterans administration cooperative study”, NEng. J. of Med., 309(7), pp. 396-403, 1983.

[13]. F.B. Livingstone, “Frequencies of hemoglobin variant: Hialasemia, the glucose-6- phosphate dehydrogenase deficiency, G6PD variants and ovalocytosis in human population”, Oxford University Press, New York, 1985, pp. 526.

[14]. J.A. Obaleye, and A. Lawal, “Synthesis, characterization and antibacterial activity of aspirin and paracetamol metal complexes”, J. of BIKEMISTRI, 19(1), pp. 9-15, 2007.

[15]. I. A. Odesina, “Essential chemistry for senior secondary schools,” 2nd Ed., TONAD Publishers Limited, Ibafo, Ogun state, pp. 465-466, 2008.

[16]. P.V. Rao, K. Ashwini and S. Ammani, “Synthesis and characterization of transition metal complexes derived from some biologically active furico acid hydrzones” Bull.Chem.Soc. Ethiopia, Vol. 21(1), pp. 63-73, 2007.

[17]. M.S. Refat, S.A. El-korashy and M.A. Hussien, “Ligational, spectroscopic (infrared and electronic) and thermal studies on the Mn(II), Co(II), Fe(II) and Cu(II) complexes with analgesis drugs”, Journal of Canadian Chemical Transactions, Vol. 2, Issue 1, pp. 24-35, 2014.

[18]. B. S. Sekhon, and L. Gandhi, “Synthesis and Characterization of Metal Complexes of Some Antimicrobial Drugs, Intl. J. of Chemtech Research, 2(1), pp. 286-288, 2010.

[19]. A.C. Tella, “Friendly synthesis of metal complexes of antimicrobial drugs”, report from Cent. for supramolecular chemistry research”, Uni. of Capetown, South Africa, 2011, pp.1-4.

[20]. A.C. Tella, U.B. Eke and S.O. Ovalude, “Solvent free mecheanochemical 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”, J. of Saudi Chem. Soc. Elsevier, 20, pp. S376-S381, 2016.

[21]. Y. Vibhute, A. Vibhute, A. S. Zangade and S. Mokle, “An Efficient and Operationally Simple Synthesis of Some New Chalcones by Using Grinding Technique”, Chem. Sci. J., Vol. 2011(13), pp. 1-6, 2011.

[22]. M. Yusha’u and F. U. Salisu, “Inhibition activity of detarium microcarpum extract on Some clinical bacterial isolates, Biol. and Env. Sci. J. for the Tropics, 8(4), pp. 113-117, 2011.