ANTIMICROBIAL STUDY OF SOME TRANSITION METAL COMPLEXES OF RHODANINE AND SALICYLADIMINE

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ABSTRACT

In this study, complexes of copper and zinc with rhodanine and salicyladimine were examined for their antimicrobial properties against selected bacteria species. The complexes were also characterized using infra-red and ultra-violet spectroscopy for structural elucidation and determination of electronic transitions occurring between the ligands and their complexes. All the complexes showed varied inhibition on the growth of the test organisms at different minimum inhibitory concentrations ranging from 0 – 25 mg/ml. The infra-red spectroscopy showed the presence of different functional groups like O-H stretching vibration at 3441cm^{-1}, C-H bending at 833.28cm^{-1} and 750.33cm^{-1}, C=C stretching vibration at 2360.95cm^{-1} in the salicyladimine ligand and N-H stretching vibration at 3448.84cm^{-1} in the complex formed with copper, whereas Rhodanine shows C=O at 1734cm^{-1} with copper acetate, 1708.99cm^{-1} with Zinc nitrate, C-H stretching at 3086.21cm^{-1}, 3074.63cm^{-1} with copper and 3174.94cm^{-1} with zinc. The ultraviolet spectroscopy showed absorptions assigned to different geometry. The complex of salicylaldimine showed two bands around 26385 cm^{-1} and 42016 cm^{-1} which are assigned to square planar geometry. Rhodanine showed four bands around 48780 cm^{-1}, 33898 cm^{-1}, 39525 cm^{-1} corresponding to n→π* transition and 26809 cm^{-1} corresponding to n→σ* transition. Rhodanine complex with zinc nitrate showed two bands around 23925cm^{-1} and 22411cm^{-1} assigned to charge transfer. Rhodanine complexed with copper acetate showed two bands around 20283 cm^{-1} and 24096 cm^{-1} which are assigned to square planar geometry. From the analysis of variance, there is no significant difference (p-value= 0.05) in the antibacterial activity and the selected pathogen. Based on this study, we recommend that metal complexes should be used to restrict the growth of bacteria in place of Ligands.

Keywords: Rhodanine, Salicyladimine, antimicrobial properties, Infrared and ultraviolet spectroscopy.

1 INTRODUCTION

The global need to overcome the challenge posed by the increasing resistance of bacteria to different pharmaceutical drug treatment is a major concern in the field of human health (Chu, *et al*. 1996). Therefore, the development of several medications to combat this major challenge has

led to the introduction of modified drug samples to address the resistance of bacteria and other microorganisms to previous treatment which is a global challenge in human medicine (Desai, *et al.* 2013). The use of metals in the field of medicine in the treatment and control of various medical complications has gained interest for long. Vessels made with copper and silver were used during the time of Persian kings for purification of water and food preservation. The preservation of water, wine, milk and vinegar by dropping coins made with silver into their containing vessels was adopted by settlers of North America and Japanese soldiers during the Second World War to prevent spread of diseases (Alexandra, 2009; Borkow, and Gabbay, 2009). Certain metals show improved cellular activities that cannot be compared to those shown by organic molecules, this has made their application in biochemistry of life an area of research interest. The structure and participation of most proteins in key cellular processes such as electron transfer and catalysis has been determined to be dependent on metal atom. (Waldron, and Robinson, 2009).

Recent study shows that different metals cause discrete and specific injury to microbial cells. Antimicrobial property shown by transition metals has found useful applications in industry, agriculture and healthcare. These were made possible following the findings that certain metals exert antibacterial activity and kills multi drug resistant bacteria. (Wright, *et al*., 1998 and Mikolay, *et al*. 2010). The broad spectrum of pharmaceutical activities of five-membered ring heterocyclic molecules with thiazole nucleus such as 1,4- thiazolidinedone and rodanines as potent antidiabetic agent (used as ciglitazone, englitazone, pioglitazones, glitazones, elpalrestat and troglitazone) for treatment of type 2 *diabetes miletus* and related complications as well as their varied biological activity has been reported (Bhatti, et al. 2013). This has attracted molecular modification as well as pharmaceutical evaluation of these molecules by synthetic chemists as well as pharmacologists respectively (Boyd, 1997). Schiff bases, which are prepared by the replacement of carbonyl group in aldehyde and ketones by an imine or azomethine group and named after Hugo Schiff, has gained reputation as useful intermediates in the synthesis of various biologically active compounds (Adabiardakani. et al., 2012). They have been found to exhibit various biological activity such as antibacterial, antifungal, herbicidal and anticancer activity (Ren, *et al*. 2002; Taggi, *et al*., 2002; Jarrahpour, *et al*., 2004; Jarrahpour, *et al*., 2006 and Chohan, *et al*., 2006). Schiff bases also found their use as dyes and pigments, catalysts, organic synthesis intermediates as well as stabilizers for polymers (Dhar and Taploo, 1982). Salicyladimine has gained reputable interest due to the asymmetrical hydrogen bond existing between its nitrogen and oxygen atoms. Transition metal complexes with salicyladimine gained considerable interest due to their unusual configuration, ability to be structurally labile and sensitivity to molecular environments (You, et al 2004; You and Zhu, 2004 and Golcu, *et al*., 2005). The biological activity of Schiff bases metal complexes has been observed to show enhanced activity when compared to their free ligands (Chakraborty and Patel, 1996). Transition metals such as cobalt, copper, nickel and zinc have been found to be of use against various diseases. This present study investigates the antibacterial efficiency of complex of copper with n, n'- bis (salicyladimine) -1, 4- phenylenediamine as well has that of copper and zinc complexes of rhodanine on *Serratia marcescens, Micrococcus luteus, Proteus vulgaris, Proteus mirabilis, Bacillus cereus, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli, Shigella flexneri, Lactococcus lactis, Enterobacter cloacae, Staphylococcus aureus* and from the result recorded, it confirms that the metal complexes restrict the growth of bacteria compared to ligands.

2 METHODOLOGIES

2.1 Sample Collection

The test organisms were collected from the Department of Microbiology, University of Ibadan, Nigeria. The details of test organisms are presented below.

Table 1: Selected Bacteria Pathogens.

Species	Family	Gram staining
Bacillus cereus	Baccillaceae	Gram-positive bacterium
Bacillus subtilis	Baccillaceae	Gram-positive bacterium
Enterobacter cloacae syn. Bacillus cloacae	Enterobacteriaceae	Gram-negative
Escherichia coli	Enterobacteriaceae	Gram-negative
Klebsiella pneumoniae	Enterbacteriaceae	Gram-negative
Lactococcus lactis	Streptococcaceae	Gram-positive
Micrococcus luteus	Micrococcaceae	Gram-positive, to Gram-variable
Proteus mirabilis	Enterobacteriaceae	Gram-negative bacterium
Proteus vulgaris	Enterobacteriaceae	Gram-negative bacterium
Serratia marcescens	Enterobacteriaceae	Gram -negative bacteria
Shigella flexneri	Enterobacteriaceae	Gram-negative
Staphylococcus aureus	Staphylococcaceae	Gram-positive

Rhodanine was synthesized and obtained from a research collaborator in University of Ilorin, Ilorin, Nigeria. The Schiff base n,n'-bis (salicyladimine) -1, 4- phenylenediamine was synthesized and obtained from a research associate in Indian Institute of Science, India.

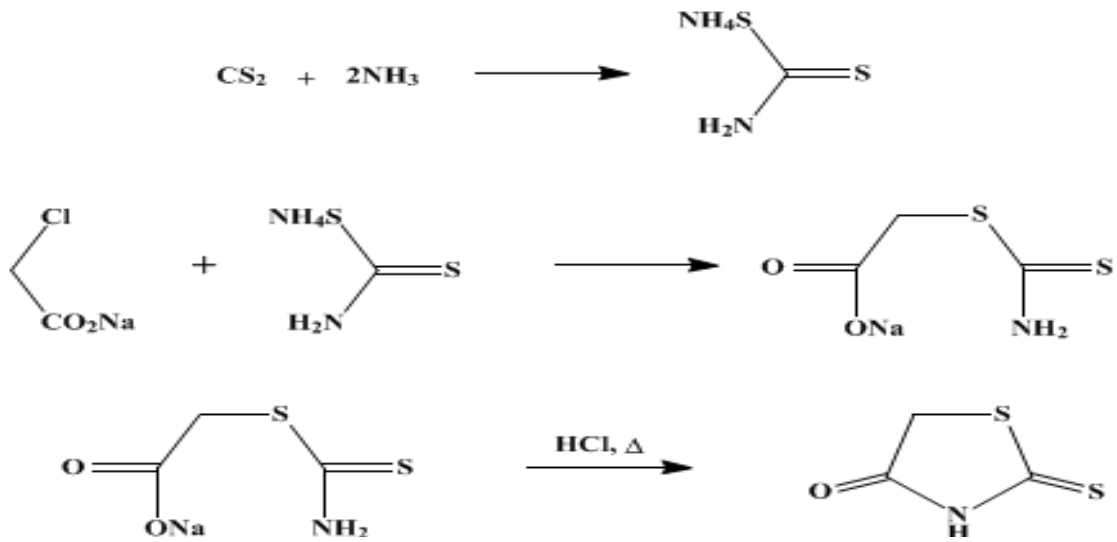


Figure 1: Equation showing the synthesis of rhodanine.

2.2 Synthesis of Complexes: General Procedure

Equivalent amount of metal salts (e.g. $ZnNO_3$, $CuSO_4.5H_2O$, and $CuNO_3$) and 100 mg ligand were dissolved in acetone (20 mL) and the mixture was refluxed for 3 hrs. The resulting mixture was allowed to stand at room temperature for two days and the precipitate formed was filtered and washed with acetone (2 mL) and DMSO (10 mL) and dried at room temperature. All

complexes formed were obtained using the same procedure. The ligands used for the synthesis of the complexes are rhodanine and n, n'-bis (salicyladimine) -1, 4- phenylenediamine.

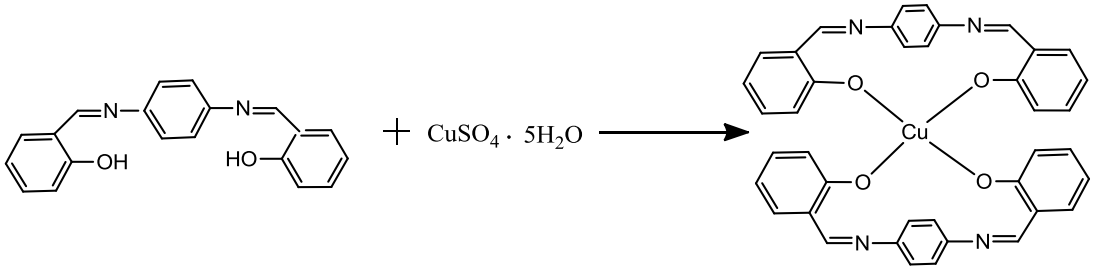


Figure 2: Equation showing the synthesis of complex of $CuSO_4$.$5H_2O$ with n, n' – bis (salicyladimine) -1, 4 –phenylenediamine.

2.3 Determination of Antimicrobial Activity.

2.3.1 Preparation of Solutions

To investigate the antibacterial properties of rhodanine and its complex with copper and zinc as well as that of n, n'-bis (salicyladimine) -1, 4- phenylenediamine and its complex, serial dilution of the complexes was done. A serial dilution is the stepwise dilution of a substance in solution. Usually the dilution factor at each step is constant, resulting in a geometric progression of the concentration in a logarithmic fashion. Serial dilutions were used to obtain required concentrations of the solutions for experiment. Acetone was used for the serial dilution of the rhodanine samples as well as the n, n'-bis (salicyladimine)-1, 4- phenylenediamine complexes. Sterile filter paper discs were placed into each solution.

2.3.2 Sterilization

Sterilization is the elimination of microbiological organisms to achieve asepsis (a sterile microbial environment). To avoid unwanted results from this project, sterilization of all apparatus and materials used was done to achieve the desired result.

2.3.3 Preparation of Slant

5.6g of nutrient agar was dissolved homogeneously in 200ml of distilled water in the conical flask and was sterilized in a pressure pot and allowed to cool in water bath at 50˚C. Appropriate volume of the nutrient agar was poured into super bottles and allowed to set. Each individual microorganism was then introduced into the slant and the slants were incubated for 18 hours.

2.3.4 Preparation of Plates

5.6g of nutrient agar was dissolved in 200ml of distilled water in the conical flask and was sterilized in a pressure pot and allowed to cool in water bath at 50˚C. Appropriate volume of the nutrient agar was poured into each plate and allowed to set.

2.3.4 Inoculation and Incubation of Medium

Antibacterial susceptibility test of the isolated organism was done by disc diffusion using the Kirby-Bauer technique (Bauer *et al*., 1966). Inoculums for the minimum inhibitory concentration test was prepared by taking colonies from an overnight culture and inoculated into broth. The broth was prepared by dissolving 2.5g of nutrient broth in 200ml of sterilized distilled water. The resulting solution was then poured into different super bottles and allowed to cool. Microorganisms are being introduced into the broth from the slant using wire loop. The broth

culture was incubated at 35^{o}C for 3 hours until it reaches the desired turbidity. This was then swabbed into the prepared plate. The paper discs soaked into the prepared solutions of rhodanine samples as well as the n, n'-bis (salicyladimine) -1, 4- phenylenediamine complexes were introduced on the surface of the agar plates already swabbed with selected bacteria. Inoculated agar plates were allowed to stand until the soaked paper disc were completely absorbed and was incubated at 35˚C for overnight.

2.3.5 Determination of Minimum Inhibitory Concentration by Agar Plate Dilution Method
Agar plate dilution test was used to determine the minimum inhibitory concentration (MIC) of the metal complexes of rhodanine and n, n'-bis (salicyladimine) -1, 4- phenylenediamine. Minimum inhibitory concentration was determined by taking measurement of zones of inhibition observed from the plates incubated in the oven overnight. Results were recorded and graded as resistant (R) and sensitive (S) according to the reference zone of inhibition at different concentration.

3 RESULTS

3.1 UV-Visible Spectra of the Samples
Salicylaldimine showed three bands around 47393 cm^{-1}(2040 $mol^{-1}dm^3cm^{-1}$), 50251 cm^{-1}(1940 $mol^{-1}dm^3cm^{-1}$) corresponding to $\pi \rightarrow \pi^*$ and 26595 cm^{-1} (270 $mol^{-1}dm^3cm^{-1}$). The $\pi \rightarrow \pi^*$ transitions of the aromatic rings are observed in the 250–300 nm region whereas the $\pi \rightarrow \pi^*$ transitions of the C=N bond are in between 300 and 350 nm. The complex of salicylaldimine showed two bands around 26385 cm^{-1} (161 $mol^{-1}dm^3cm^{-1}$) and 42016 cm^{-1} (123 $mol^{-1}dm^3cm^{-1}$) which are assigned to square planar geometry. Rhodanine showed four bands around 48780 cm^{-1}(105.6 $mol^{-1}dm^3cm^{-1}$), 33898 cm^{-1}(105.5 $mol^{-1}dm^3cm^{-1}$), 39525 cm^{-1}(102.1 $mol^{-1}dm^3cm^{-1}$) corresponding to $n \rightarrow \pi^*$ transition and 26809 cm^{-1}(56.5 $mol^{-1}dm^3cm^{-1}$) corresponding to $n \rightarrow \sigma^*$ transition. Rhodanine complex with zinc nitrate (solvent synthesis) showed two bands around 23925 cm^{-1}(259 $mol^{-1}dm^3cm^{-1}$) and 22411 cm^{-1}(257 $mol^{-1}dm^3cm^{-1}$) assigned to charge transfer. Rhodanine complexed with copper acetate(solvent synthesis) showed two bands around 20283 cm^{-1}(331 $mol^{-1}dm^3cm^{-1}$) and 24096 cm^{-1}(346 $mol^{-1}dm^3cm^{-1}$) which are assigned to square planar geometry.

3.2 Infra-red Spectroscopy
The spectra of n, n'-bis (salicyladimine) -1, 4- phenylenediamine shows O-H stretching vibration at 3441 cm^{-1}. The C-H bending vibrations occurs at 833.28 cm^{-1} and 750.33 cm^{-1} while the C=C stretching occurred at 1610.61 cm^{-1}, 1572.04 cm^{-1} and 1492.95 cm^{-1} as well as C≡N stretching vibration at 2360.95 cm^{-1}. The complex of copper with n,n'-bis (salicyladimine) -1, 4-phenylenediamine shows N-H stretching vibration at 3448.84 cm^{-1}, C=C stretching at 1572.04 cm^{-1}, 1492.95 cm^{-1}, 1610.61 cm^{-1} and C≡N stretching vibration at 2359.02 cm^{-1}. Rhodanine spectra shows C=O band at 1734.06 cm^{-1} with copper acetate, 1708.99 cm^{-1} with zinc nitrate. It shows C-H stretching vibration at 3086.21 cm^{-1}, 3074.63 with copper acetate and 3174.94 cm^{-1} with zinc nitrate.

3.3 Biological Activity
Solutions of various concentrations were prepared using serial dilution method and the results are shown in table 1. Rhodanine samples and Schiff bases complexes had antibacterial activity against *Serratia marcescens, Micrococcus luteus, Proteus vulgaris, Proteus mirabilis, Bacillus*

cereus, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli, Shigella flexneri, Lactococcus lactis, Enterobacter cloacae, Staphylococcus aureus at different concentrations and the minimum inhibitory concentrations were recorded. Rhodanine and its complex with copper and zinc as well as n, n'-bis (salicyladimine) -1, 4- phenylenediamine and its complex with copper showed antibacterial activity against the test organisms at different concentrations and the minimum inhibitory concentrations were recorded (fig. 3).

Table 2: Antibacterial Activity against Selected Bacteria Pathogens (Zones of Inhibition).

ORGANISMS	A (mg/ml)	B (mg/ml)	C (mg/ml)	D (mg/ml)	E (mg/ml)
B. cereus	**5**	**2.5**	**2.5**	**R**	**6.25**
B. subtillis	**5**	**2.5**	**2.5**	**25**	**6.25**
E. cloacae	**10**	**2.5**	**2.5**	**6.25**	**3.125**
E. coli	**10**	**2.5**	**5**	**25**	**3.125**
K. pneumonia	**5**	**2.5**	**2.5**	**12.5**	**3.125**
L. lactis	**2.5**	**2.5**	**2.5**	**25**	**6.25**
M. luteus	**10**	**2.5**	**2.5**	**6.25**	**3.125**
P. mirabilis	**10**	**2.5**	**2.5**	**6.25**	**3.125**
P. vulgaris	**5**	**2.5**	**2.5**	**6.25**	**3.125**
S. aureus	**2.5**	**2.5**	**2.5**	**3.125**	**3.125**
S. flexneri	**2.5**	**2.5**	**2.5**	**6.25**	**3.125**
S. marcescens	**5**	**2.5**	**2.5**	**6.25**	**3.125**

A- Rhodanine **B-** Rhodanine ligand + $CuNO_3$ **C-** Rhodanine ligand+$ZnNO_3$ **D-** n, n'-bis (salicyladimine) -1, 4- phenylenediamine. **E-** $CuSO_4$. $5H_2O$ + n, n'-bis (salicyladimine) -1, 4- phenylenediamine

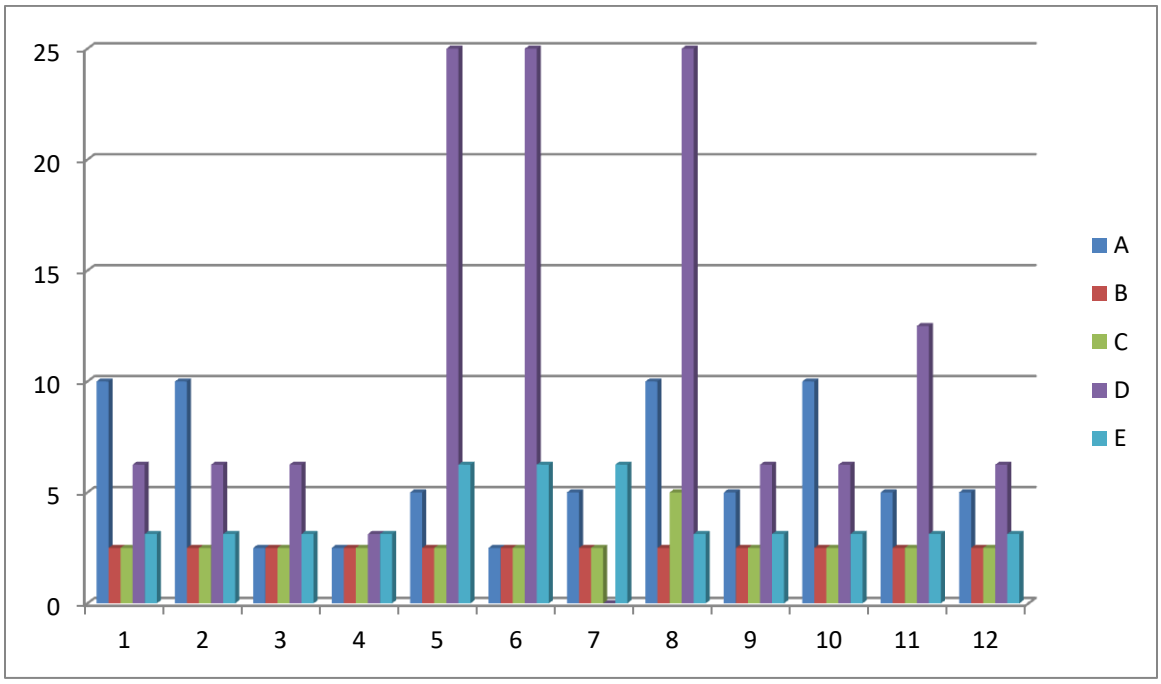


Figure 3: Chart showing the minimum inhibitory concentration (mg/ml) of samples on test organisms

NOTE: 1- *P. mirabilis*, **2-** *E. cloacae*, **3-** *S. flexneri*, **4-** *S. aureus*, **5-** *B. subtillis*, **6-** *L. lactis*,**7-** *B. cereus*, **8-** *E. coli*, **9-** *S. marcescens* **10-** *M. luteus* **11-** *K. pneumonia* **12-** *P. vulgaris*,**A-** Rhodanine **B-** Rhodanine ligand + $CuNO_3$ **C-** Rhodanine ligand+$ZnNO_3$, **D-** n, n'-bis (salicyladimine) -1, 4- phenylenediamine. **E-** $CuSO_4$. $5H_2O$ + n, n'-bis (salicyladimine) -1, 4- phenylenediamine.

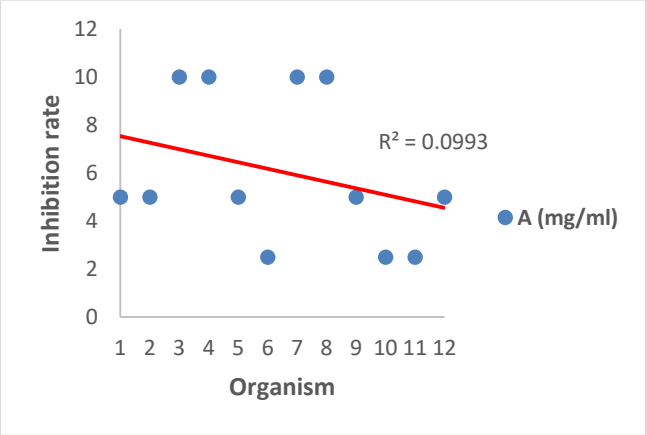
From the analysis of variance, there is no significant difference (p-value= 0.05) in the antibacterial activity and the selected pathogen (table 3).

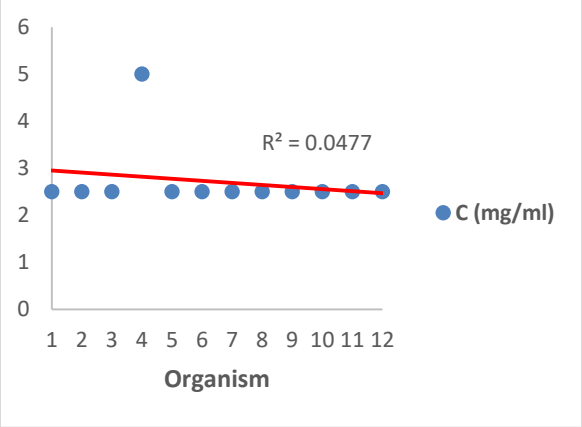
Table 3: ANOVA of zones of inhibition

SV	SS	df	MS	F stat.	P-value	F crit.
Between Groups	550.4818	4	137.6204	7.272268	8.94E-05	2.539689
Within Groups	1040.82	55	18.92401			
Total	**1591.302**	**59**				

***SV**- Source of variance, **SS**-sum of squares, **df**- degree of freedom, **MS**-Mean of squares, **F stat**-Fisher statistics, **F crit.**-Fisher critical*

There was a negative relationship between the organism and inhibition rate of the complexes (Fig. 4). Moreso, there is no significant difference between organism versus Rhodanine ($p< 0.32$, $r= -0.32$), organism vs Rhodanine ligand+$ZnNO_3$ ($p< 0.49$, $r= -0.22$), organism vs n, n'-bis (salicyladimine) -1, 4-phenylenediamine ($p< 0.26$, $r= -0.35$) while there is significant difference between organism vs $CuSO_4.5H_2O$ + n, n'-bis (salicyladimine) -1, 4- phenylenediamine ($p= 0.05$, $r= -0.59$). However, there is perfect relationship between organism vs Rhodanine ligand + $CuNO_3$.





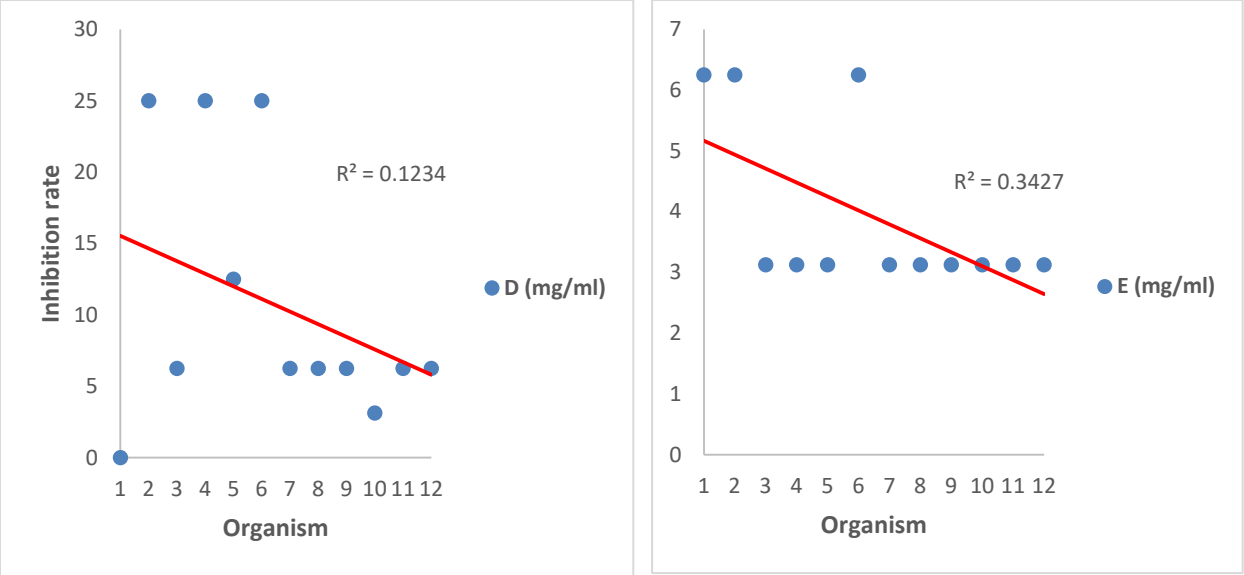


Figure 4:1- *P. mirabilis*, **2**- *E. cloacae*, **3**- *S. flexneri*, **4**- *S. aureus*, **5**- *B. subtillis*, **6**- *L. lactis*,**7**- *B. cereus*, **8**- *E. coli*, **9**- *S. marcescens* **10**- *M. luteus* **11**- *K. pneumonia* **12**- *P. vulgaris*,**A**- Rhodanine ,**C**- Rhodanine ligand+$ZnNO_3$, **D**- n, n'-bis (salicyladimine) -1, 4- phenylenediamine. **E**- $CuSO_4$. $5H_2O$ + n, n'-bis (salicyladimine) -1, 4- phenylenediamine.

4 DISCUSSION

4.1 UV-Visible Spectra of the Samples

The resulted bands of the Salicylaldimine in this study corresponds to n→π* transition reported by Mahmoud, *et al*., (2016); Barwiolek, *et al*., (2013); Cinarli, *et al*., (2012); Habibi, *et al*., (2006) that Schiff base ligands exhibit intense intra-ligand absorption bands in the 250–350 nm region.

4.2 Infra-red Spectroscopy

The study revealed that the spectra occurrence of n, n'-bis (salicyladimine) -1, 4-phenylenediamine with respect to O-H stretching vibration at 3441 cm^{-1}, C-H bending vibrations (833.28 cm^{-1} and 750.33 cm^{-1}), C=C stretching at 1610.61, 1572.04 and 1492.95 cm^{-1} respectively as well as C≡N stretching vibration at 2360.95 cm^{-1} are similar with the IR spectrum of the ligand used by Yildiz, *et al*., (1998) and Schilf, *et al*., (2002). This indicated a medium or strong intensity absorption bands at 1644 and 1495 cm–1 assigned to C=N and C=C stretching modes.

4.3 Biological Activity

The chelating power of the metal ion was enhanced by coordination with Ligand which helps the metal complexes to inhibit the growth of bacteria compared to the ligands alone and this confirms the statement made by Su, *et al*. (2007), that, it is possible that the ligand may be activated by the metal ion.

5 CONCLUSIONS

Transition metals such as cobalt, copper, nickel and zinc have been found to be of use against various diseases, and from the research carried out, which investigated the antibacterial

efficiency of complex of copper with n, n'- bis (salicyladimine) -1, 4- phenylenediamine as well has that of copper and zinc complexes of rhodanine on *Serratia marcescens, Micrococcus luteus, Proteus vulgaris, Proteus mirabilis, Bacillus cereus, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli, Shigella flexneri, Lactococcus lactis, Enterobacter cloacae, Staphylococcus aureus* and from the result recorded, it can be concluded that the metal complexes inhibits the growth of bacteria compared to ligands.

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