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ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY OF SOME TRANSITION METAL COMPLEXES OF TWO LIGANDS DERIVED FROM AMINO ACIDS AND 2 – IMINO – 1 – METHYLIMIDAZOLIDIN – 4 – ONE

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ABSTRACT

Plant extracts are most of the time used for antioxidant and antimicrobial studies. The Present study was designed to evaluate the activity of metal complexes as antioxidant and against some selected bacterial and fungal isolates. The new metal complexes of Cr (III) and Zn (II) containing ligands derived from Tyrosine, Leucine and 2 – imino – 1 – methylimidazolidin – 4 - one were selected. The test compounds were evaluated for their possible antioxidant activity through free radical scavenging activity via using 1,1 – diphenyl – 2 – picryl – hydrazyl (DPPH) method. All the complexes exhibited good to moderate activity with Cr (III) complex (CrL_1) and (CrL_2) as the best radical scavengers having the % inhibition value of 67.74 and 65.33 respectively. The complexes were also screened for their antimicrobial activities against two bacterial isolates and one fungal isolate (*Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Aspergillus* niger). The result showed that all the compounds have the moderate activity against the tested organisms.

Keywords: antioxidant; antimicrobial; amino acids; ligands; metal complexes.

INTRODUCTION

Metal complexes of amino acids are important in the biological system, for both nutritive and catalytic chemical reactions. On the other hand, the pharmaceutical use of metal complexes in general has an excellent Potential (Sangeeta *et al*, 2009). Resistance of wide spectrum antibacterial agents has prompted discovery and modification toward new chemical agents or antibiotics with a potent, wide therapeutic window, broad spectrum activity, and new mode of action (Selvaganapathy and Raman, 2016). Some of the recent studies have shown that metal complexes are reported to possess antitumor and antiviral, they are also used in the treatment for diabetes and anti-HIV (Orel *et al* 2016). One of the most interesting features of metal coordinated systems is the concerted spatial arrangement of the ligands around the metal ion (Keypour et al, 2015).The advantages of complexes are their diverse structural aspects viz. Metal, Ligands, chelating agents having various functional groups and donor atoms capable of exerting selecting toxicity (Islam *et al* 2013).

A series of metal (II) complexes have been synthesized by the reaction of chloride salts of magnesium, calcium, iron, cobalt, copper and zinc with amino acids DL-alanine, L-glutamic acid and leucine. Complex formation occurred at the proximal sites of the carboxyl moiety and the alpha amino nitrogen by 1:2 stoichiometric reactions which were also confirmed by elemental analysis and FTIR data. The metal complexes of DL-alanine and L-glutamic acid are water soluble while metal-leucine complex has solubility in DMSO (Abdul Qadir *et al*, 2014).

Several Schiff base metal complexes derived from salicylaldehyde and amino acid and reduced salicydene amino acid were also synthesized and characterized. Some of them have been proven to be efficient DNA cleavers and as novel tumor chemotherapeutic and tumor radio imaging agent. (Nagyesh and Mruthyunjaswamu, 2015)

Vanadium (IV) complexes of N-Salicylidene-L-methionine and N-Salicylidene-L-tryptophan having phenanthroline bases, synthesized by Chakravarty *et al* (2015) and his co-workers can photocleave DNA in red light. L-arginine and L-lysine derived Schiff base ligands are chosen to chance to enhance the binding of DNA and photocleavage activity since these two amino acids have photoactive pendant cationic guanidinium better selectivity.

Singh *et al.* (2012) have prepared Co (II), Ni (II) and Cu (II) complexes of 2-nitrobenzaldehyde-methionine and studied their coordination properties. They evaluated the antimicrobial potential of these complexes against the growth of bacteria in *vitro*. They are found to be efficient antimicrobial agents.

Two novel amino acids imine ligands (H_2L_1 and H_2L_2) have been synthesized using green condensation reaction from 2 [3 – Amino - 5 - (2-hydroxy-phenyl) - 5 - methyl -1, 5 - dihydro - 1, 2, 4] triazol - 4 - yl] -3- (1H – indol – 3 - yl) - propionic acid with benzaldehyde/p - flouro benzaldehyde (1:1 molar ratio) in the presence of lemon juice as a natural acidic catalyst in aqueous medium. Their transition metal complexes have been prepared in a molar ratio (1:1). Characterization of the ligands and complexes using elemental analysis, spectroscopic studies, ^{1}HNMR, ^{13}CNMR, and thermal analysis has been reported. E*, ΔH*, ΔS* and ΔG* thermodynamic parameters, were calculated to throw more light on the nature of changes accompanying the thermal decomposition process of these complexes. The molar conductance measurement of metal complexes showed nonelectrolyte behavior. The metal complexes of the two ligands have tetrahedral geometry with a general molecular structure [M $(H_2L)X_n$], where [(M = Mn (II), Co (II), Cu (II) and Zn (II), X = Cl, n = 2]; M = VO (II), X = SO_4, n = 1] for H_2L_1. [M = Co (II), Cu (II), Zn (II)] for H_2L_2. Antibacterial activity of the complexes against (*Bacillis subtilis, Micrococcus luteus, and Escherichia coli*), also antifungal activity against (*Aspergillus Niger, Candida Glabarta,* and *Saccharomyces cerevisiae*) have been screened. The results showed that all complexes have antimicrobial activity higher than free ligands (El - Saghier *et al*, 2018).

Also, Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of mixed ligands, Riboflavin (HL) and 4-aminobenzoic acid (HL1) were synthesized and characterized by percentage metal, infrared and electronic (solid reflectance) **spectroscopies,** room temperature magnetic moments, melting points and conductance measurements. The conductance measurements in DMSO and percentage metal analysis indicated that all the metal (II) complexes were covalent and analyzed as [M (HL) (HL1) X], where X = Cl /SO. Infrared spectra data confirmed that coordination Mn (II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of mixed ligands, Riboflavin (HL) and 4-aminobenzoic acid (HL1) were synthesized and characterized by percentage metal and infrared. In-vitro antimicrobial activities of the metal(II)complexes**,** riboflavin and p-aminobenzoic acid against Escherichia spp, Proteus mirabilis, Streptococcus pyogenes, Candida albicans, Salmonella sp, Streptococcus sp, Bacillus spp, Staphylococcus sp and Pseudomonas spp revealed that all the metal(II) complexes and ligands were active against Pseudomonas sp with inhibitory zones range of was via the 2 4oxygen atoms of two hydroxyl groups in Riboflavin, and the carboxylate oxygen atoms in 4-aminobenzoic acid respectively. Furthermore, electronic spectra data indicated that all the metal (II) complexes adopted octahedral geometry; while room temperature magnetic moment measurements indicated spin-crossover, that is, high spin low spinoctahedral equilibrium for all the complexes with the exceptions of the Cu (II) and Zn (II) complexes. In-vitro antimicrobial activities of the metal(II)complexes**,** riboflavin and p-aminobenzoic acid against *Escherichia spp, Proteus mirabilis, Streptococcus pyogenes, Candida albicans, Salmonella sp, Streptococcus sp, Bacillus spp, Staphylococcus sp* and *Pseudomonas spp* revealed that all the metal(II) complexes and ligands were active against *Pseudomonas sp* with inhibitory zones range of 7.0-11.0 mm. The antioxidant studies on the metal complexes showed that the Zn (II) complex had the best antioxidant activity of about 62 percentage inhibitions, which was about twice the percentage inhibition of the standards, ascorbic acid and D-**tocopherol (**Agbaje *et al*, 2015)**.**

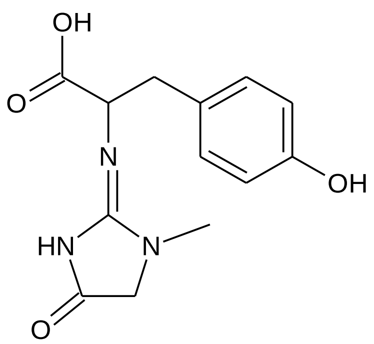
Al – Noor and Abdul Karim (2015) synthesized metal complexes of mixed amino acid L-proline and Trimethoprim antibiotic. The complexes were characterized. The Ligands and their metal complexes were screen for their antimicrobial activity against four bacteria (gram +ve) and (gram –ve) [*Escherichia coli, pseudomonas aeruginosa, staphylococcus aureus* and *bacillus*]. The result revealed that the synthesized compounds were potent as bacteriostatic agents. It also suggested that L-proline is more active than trimethoprim.

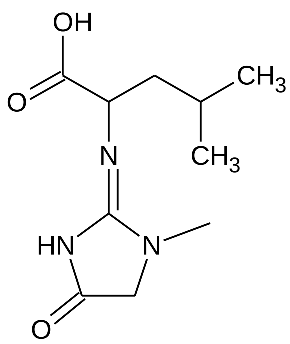
7.0-11.0 mm. The antioxidant studies on the metal complexes showed that the Zn (II) complex had the best antioxidant activity of about 62 percentage inhibition, which was about twice the percentage inhibition of the standards, ascorbic acid and D-tocopherol **(**Agbaje et al 2015**)**.

All the research works reviewed here did not study the antioxidant of their complexes prepared with the exception of the last one. Therefore, this paper aims to evaluate the antioxidant and antimicrobial activities of Cr (III) and Zn (II) metal complexes.

MATERIALS AND METHODS

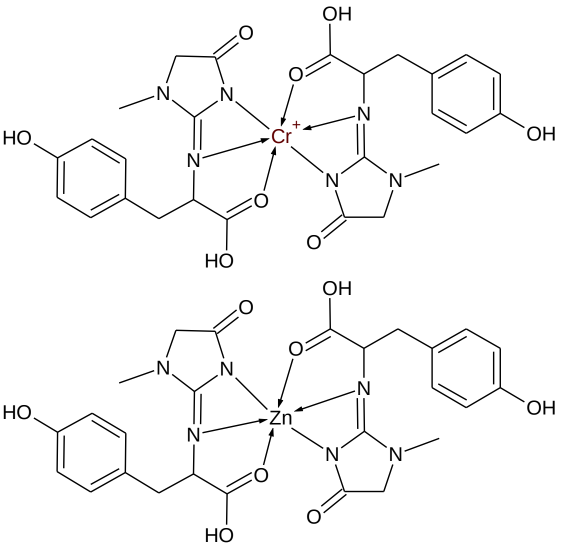
The complexes were synthesized mechanochemically and characterized using various techniques such as FTIR, conductivity measurement Melting point/decomposition temperatures, Molar conductance and magnetic susceptibility measurement to confirm their chemical structures.

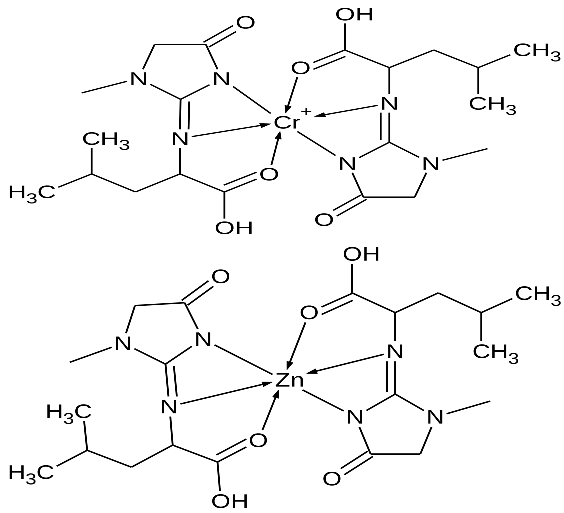




Ligand 1 Ligand 2

COMPLEXES OF LIGAND 1





COMPLEXES OF LIGAND 2

Determination of Antimicrobial Activity

The antimicrobial Activities of the metal complexes and the ligands against two bacterial and one fungal isolates were determined by the paper disc diffusion method (cheesbrough, 2008).

- **Disc preparation**

6mm disc were prepared using filter paper and sterilized before dispersing in to each of the tubes containing different concentrations of the complexes and ligands (CLSI, 2013).

- **Preparation of Ligands and Complexes**

0.2g of each of the complexes was dissolved in 2ml of DMSO to obtain a concentration of 100mg/ml followed by transferring to the next tube containing 1ml of DMSO to obtain another concentration of 50mg/ml, 25mg/ml and 12.5mg/ml.

- **Disc Impregnation**

Disc containing different concentrations of each complex were transferred and dispersed in the Petri-dish containing Nutrient agar and potato dextrose agar with the suspension of strain and allowed to observe for 15-20 minutes, and then incubated at 37^0c for 24 hours, while plates of the Aspergillus niger were incubated for 72 hours.

- **Measurement of Zone of Inhibition**

Prior to the incubation, zone of inhibition produced by each of the complexes and their ligands was measured and recorded in millimetre using a meter ruler.

- **Determination of Minimum Inhibition Concentration** (**MIC**)

Broth micro dilution method was used for the determination of MIC, according to CLSI methodology (2015) by usual inspection of absence of turbidity.

- **Determination of Minimum Bactericidal and Fungicidal Concentration**

Tubes with absence of turbidity were inoculated on the plates containing potato dextrose agar and Nutrient agar to check the growth of the organisms in test.

Antioxidant activity

Methanolic solution of each tested compounds having different concentrations was mixed with methanolic solution of DPPH. The mixture was shaken vigorously and allowed to stand at room temperature in the dark for 30 minutes, and then its absorbance was measured at 517 nm using spectrophotometer (Sofiane et al, 2018). The radical scavenging activities of each of the ligands and complexes were expressed as the % inhibition and were calculated using the formula: %inhibition = Abs of Control – Abs of Sample/Abs of Control x100. Where; **L – Ascorbic acid** was used as control

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Antimicrobial activity

The antimicrobial activities of free ligands and their complexes were evaluated using the micro broth paper disc diffusion method towards two bacteria. The results were compared with that of Augmentin against the two bacteria and ketoconazole against the fungal isolate (Aurora, Stelian, Theodor and Nicolae, 2009). The antibacterial activities of the metal complexes and free ligands were carried out against ***Streptococcus pneumoniae, Klebsiella pneumoniae and Aspergillus niger.*** The results were presented in tables below. The compounds showed high activities at higher concentrations in each case and vice- versa (Mannir et al, 2020). It also revealed that the activities of the free ligands are more pronounced after complexation.

$Zn(L_1)$ complex is effective on the three organisms at concentrations of 100 mg/ml, 50mg/ml and 25mg/ml and also at 12.5mg/ml. This is similar to the findings of Gurbuz et al (2015). On the other hand, the free ligands, $Cr(L_2)$ and the $Zn(L_2)$ complexes have little or no activity on the organisms at the same concentrations as shown in the tables below. However, $Cr(L_1)$ was effective against the organisms which exhibited considerable antimicrobial activity at 100mg/ml, 50mg/ml and 25mg/ml (Al-noor and Abdulkarim, 2015).

The activity increases with increase of concentrations. The mode of action of the complexes may involve formation of hydrogen bond with the active centres of the cell constituents which results an interference with the normal cell process (Sani and Lawal, 2017).

The metal complexes have a higher activity than their ligands against the same organisms under the identical experimental conditions. It is evident that the antimicrobial activity significantly increased on coordination. It has been suggested that the ligands with nitrogen and oxygen donor systems inhibit enzyme activity. Coordination reduces the polarity of the metal ions mainly because of the partial sharing of its positive charge with the donor groups within the chelate ring system (Sarika et al, 2012).

RESULT AND DISCUSSION

Table 1: Zone of inhibitions (mm) of the tested compounds.

Compound	Concentration (mg/ml)	Aspergillus niger	Streptococcus p.	Klebsiella p.
$Zn(L_1)_2$	100	25	20	14.2
	50	20	16	11
	25	9	14	9
	12.5	6	12.5	6
$Cr(L_1)_2$	100	18	14	9.3
	50	8	12.5	8.7
	25	6	7.5	6
	12.5	6	6	6
$Zn(L_2)_2$	100	6	14	6
	50	6	8	6
	25	6	7	6
	12.5	6	6	6
$Cr(L_2)_2$	100	6	6	6
	50	6	6	6
	25	6	6	6
	12.5	6	6	6
Ligand 1	100	6	12	6
	50	6	10	6
	25	6	8.5	6
	12.5	6	6	6
Ligand 2	100	6	14.5	6
	50	6	12	6
	25	6	9.8	6
	12.5	6	6	6
Controls	100	25	19	17

Key: $L_1 = C_{13}H_{15}N_3O_4$ $L_2 = C_{10}H_{17}N_3O_3$

Table 2: Minimum inhibitory concentrations (MIC) of the tested compounds.

Compound	Concentration (mg/ml)	Aspergillus niger	Streptococcus pneumoniae	Klebsiella pneumoniae
$Zn(L_1)_2$	100	+	+	+
	50	+	+	+
	25	+	-	-
	12.5	-	-	-
$Cr(L_1)_2$	100	+	+	+
	50	+	-	-
	25	NA	-	NA
	12.5	NA	-	NA
$Zn(L_2)_2$	100	NA	+	NA
	50	NA	+	NA
	25	NA	+	NA
	12.5	NA	NA	NA
$Cr(L_2)_2$	100	NA	NA	NA
	50	NA	NA	NA
	25	NA	NA	NA
	12.5	NA	NA	NA
Ligand1	100	NA	-	NA
	50	NA	-	NA
	25	NA	-	NA
	12.5	NA	-	NA
Ligand 2	100	NA	-	NA
	50	NA	-	NA
	25	NA	-	NA
	12.5	NA	-	NA
Controls	100	+	+	+

Key: $L_1 = C_{13}H_{15}N_3O_4$ $L_2 = C_{10}H_{17}N_3O_3$
+ =Absence of growth from the plates.
-= Presence of growth from the plates.
NA=Not active against the organisms

Table 3: Minimum bactericidal and fungicidal concentrations (MBC & MFC) of the tested compounds.

Compound	Concentration (mg/ml)	Aspergillus niger	Streptococcus pneumoniae	Klebsiella pneumoniae
Zinc $(L_1)_2$	100	+	+	+
	50	+	+	-
	25	-	-	-
	12.5	-	-	-
$Cr(L_2)_2$	100	+	+	+
	50	-	-	NA
	25	NA	-	NA
	12.5	NA	-	NA
$Zn(L_2)_2$	100	NA	+	NA
	50	NA	+	NA
	25	NA	+	NA
	12.5	NA	NA	NA
$Cr(L_2)_2$	100	NA	NA	NA
	50	NA	NA	NA
	25	NA	NA	NA
	12.5	NA	NA	NA
Ligand 1	100	NA	-	NA
	50	NA	-	NA
	25	NA	-	NA
	12.5	NA	-	NA
Ligand 2	100	NA	-	NA
	50	NA	-	NA
	25	NA	-	NA
	12.5	NA	-	NA
Controls	100	+	+	+

Key L1 = $C_{13}H_{15}N_3O_4$ $L_2 = C_{10}H_{17}N_3O_3$
+ =Absence of growth from the plates.
-= Presence of growth from the plates.
NA=Not active against the organisms

Antioxidant activity

The radical scavenging activities of the ligands and their complexes are summarized below. The percentage inhibition of the free ligands and their complexes was presented in table 4. The % inhibition of the free radical tends to increase as the concentration increases. The metal complexes of chromium showed highest antioxidant activity with 67.74 and 65.33 % for $Cr(L_1)_2$ and $Cr(L_2)_2$ respectively, this is probably because of its ionic nature that makes it to have a greater ability to neutralize free radicals (Sofiane et al, 2018). The Zinc compounds and the two ligands also exhibited good activity.

Table 4: Antioxidant activity of the tested compounds

Compound	**DPPH scavenging Activity:** (Concentration and Inhibition %)						
	0.12 mg/ml	**0.24 mg/ml**	**0.48 mg/ml**	**0.79 mg/ml**	**1.49 mg/ml**	**3.89 mg/ml**	**7.79 mg/ml**
HL_1	7.43	28.44	37.76	41.12	44.76	49.98	57.17
HL_2	8.33	25.78	37.66	39.87	47.24	50.55	55.88
$Zn(L_1)_2$	17.03	31.54	41.55	48.67	53.69	57.77	60.22
$Zn(L_2)_2$	16.23	34.34	40.67	44.51	51.53	55.11	59.12
$Cr(L_1)_2$	18.11	36.98	39.89	48.92	57.35	60.00	67.74
$Cr(L_2)_2$	16.45	32.33	36.97	46.55	55.55	59.76	65.33

Key: $L_1 = C_{13}H_{15}N_3O_4$ $L_2 = C_{10}H_{17}N_3O_3$

CONCLUSION

The antimicrobial and antioxidant activities of Zn(II) and Cr(III) metal complexes were studied and all the compounds showed good activities. The antimicrobial activities may be due to the formation of hydrogen bond with the active centres of the cell constituents of the test organisms which results an interference with the normal cell process

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