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# Potentially Biodynamic Tin(II) Complexes derived from Macrocyclic Ligands: Synthesis, Spectral Analysis, *In vitro* Antibacterial, Antifungal and Brine Shrimp Lethality Evaluation

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**ABSTRACT**

Over the past several years, the predominance of biologically active macrocycles in medicinal chemistry has been increasing. Novel macrocyclic complexes of Sn(II) were synthesized by using macrocyclic ligands derived from various diamine and dicarboxylic acids in the ratio of 2:2. The structures of the obtained complexes were identified by various spectrometric methods such as Fourier transformation infra-red (FT-IR), nuclear magnetic resonance (NMR), electron spray ionization mass spectrometry, and powder X-ray diffraction. The spectral data provided evidence that the macrocyclic ligands acted as tetradentate ligands, forming coordination bonds with Sn(II) ions through the nitrogen atom of the imine (>C=N) group. The coordination complexes exhibited an octahedral geometry around the tin ion, with two chloro groups covalently attached. All of the synthesized compounds were evaluated for their biochemical properties, including antibacterial, antifungal, and Brine Shrimp Lethality. The antimicrobial potential of the macrocyclic compounds was examined against a panel of pathogenic microbes, including bacterial strains (*Escherichia coli*, *Xanthomonas campestris*, and *Staphylococcus aureus*) and fungal strains (*Fusarium oxysporum* and *Aspergillus niger*). The result showed that the macrocyclic complexes have remarkable antimicrobial potential as compared to their corresponding macrocyclic ligands. The positive findings of Brine shrimp lethality of the ligands and their complexes have been discussed.

**Keywords:** Antibacterial, Antifungal, Brine shrimp lethality, Macrocyclic, Tin(II).

## INTRODUCTION

The rapid and extensive advancements in the field of coordination compounds, influenced by the unique scientific backgrounds, individual interests, and personal preferences of researchers, have been made accessible because of their widespread relevance in various current areas of interest, particularly in agriculture and medicine. The emergence of microbe's resistance to the marketed drug is a global concern[1,2]. Microbes can easily alter their structure by mutating their genetic material and acquiring resistance to the already reported drugs. So, there is a requirement for new drugs with better

efficacy to control the horrific devastation caused by pathogens. Combating against the virulence of pathogens, metal complexes have gained appreciable consideration over the years because of their relevancy with bioinorganic moieties[3,4]. Among all kinds of metal complexes, organotin(II) complexes concede substantial place based on their potential biological activities such as antimicrobial[5], antidiabetic[6], antioxidant[7], antiinflammatory[8], antitumor[9], antimalarial[10], antiproliferation[11] and antituberculosis[12]. Organotin complexes are widely used in other areas also, such as they have been used in wood preservatives, antifouling paints, and surface disinfectants[13].

The biochemical action of organotin(II) complexes were influenced by coordination number of metal atom, geometry, oxidation states, thermodynamic and kinetic stability of complexes. It is well known that tin metal form stable bond with the carbon as well as with heteroatoms and also exits in different coordination number from four to eight[14,15]. The design of macrocyclic ligands and organotin complexes represents a relevant and qualified objective in the development of coordination chemistry. Due to synthetic flexibility, ease of synthesis and very good binding ability of amide group, macrocyclic ligands play an important role in inorganic chemistry to form stable complexes with most of the metal ions[16,17]. Organotin compounds have been exploited widely in drug design and development due to their continuous increase in the field of pharmaceuticals, industrials, biological, analytical and medicinal areas[18-22].

Based on previous research on the coordinating properties of tetrazamacrocycles[23-26], this work provides a concise description of new dimensions in the structural and biological activity, highlighting the efficiency of tetraaza macrocyclic ligands and their tin(II) complexes.

## EXPERIMENTAL

### Chemicals

All solvents and chemicals employed in this work were of analytical grade and used without further purification. "Methanol, malonic acid and glutaric acid, 1,8-Napthyridine-2,7-diamine, $SnCl_2$ were procured from Merck.

### Analytical Methods and Physical Measurements

The Rast Camphor method was utilized to determine the molecular weights. Conductivity measurements were conducted in dry dimethylformamide using a type 305 conductivity bridge. IR spectra were recorded on a Nicolet Magna FT-IR 550 spectrophotometer, employing KBr pellets. For $^1$H NMR spectra, a JEOL FX-90Q spectrometer was used with TMS serving as the internal standard. Tin was estimated gravimetrically as tin oxide. Powder X-ray diffraction data were collected on a Bruker AXS D8 Advance at diffraction angles $2\theta$=10-90°. Additionally, carbon, hydrogen and nitrogen analyses were performed at the Central Drugs Research Institute (CDRI) in Lucknow.

### Synthesis of the ligands ($ML_1$-$ML_2$)

In a 100 mL round bottom flask with a short neck, a measured quantity of 1,8-Napthyridine-2, 7-diamine (1 mmol, 0.160 g) was placed. To this, an equivalent amount of malonic acid (1 mmol, 0.104 g) dissolved in methanol was supplementary. The reaction was carried out in equimolar ratios and animated underneath reflux for 11 hours. After completion, the reaction mixture was cooled, and the resulting off-white compound was purified through recrystallization using MeOH. The same procedure was employed for the synthesis of $ML_2$, but with a different reagent. Instead of malonic acid, glutaric acid (1 mmol, 0.132 g) was used in the reaction.

### Synthetic process of the complexes [Sn($ML_1$)$Cl_2$-Sn($ML_2$)$Cl_2$]

A mixture of $ML_1$ (1 mmol, 0.456 g) and $SnCl_2$ (1 mmol, 0.189 g) in a 1:1 ratio was prepared in MeOH and subjected to reflux heating for 42 hours. After cooling and left undisturbed for some time, resulting in the formation of a coloured complex that unglued out. The product was then washed and dried under $P_2O_4$, followed by recrystallization from a mixture of toluene and n-hexane in a 1:1 ratio. The same procedure was applied to synthesize [Sn($ML_2$)$Cl_2$] using $ML_2$ (1 mmol, 0.484 g) as ligands.

### Antimicrobial activity

### Antibacterial activity

The antibacterial activity of the newly synthesized macrocyclic compounds was assessed by the paper disc method against *Escherichia coli*, *Xanthomonas campestris*, and *Staphylococcus aureus* bacterial strains. For this technique, the

petri-plates were used to pour the agar medium and left to solidify. Once solidified, the plates were stored upside down in the freezer to encourage water condensation on the higher closure. Synthesized complexes and ligands were dissolved in MeOH to create solutions at concentrations of 500 and 1000 ppm. To evaluate bacterial activity, two methods were used: In the first method, the paper discs were dipped in the test sample solution, and then placed on the seeded agar plates. In the second method, the paper discs were first placed on the seeded plates, and then the required amount of the test sample was pipetted onto the disc. The petri plates with the paper discs on the seeded agar were initially kept at a low temperature for two hours to allow for chemical diffusion. After this, the plates were incubated at the suitable optimum temperature (28±2°C) for 24-30 hours. Following the incubation period, the clear zone of inhibition around the treated disc was measured in millimeters. The standard antibiotic, Gentamicin, was used to compare the antibacterial screening results of the compounds.

**Antifungal activity**

The antifungal activity of the macrocyclic compounds was assessed using the spore germination technique against two pathogenic fungi, *Fusarium oxysporum*, and *Aspergillus niger*. Test compound solutions (0.5 mL) were prepared in DMF and applied on the fungus slides. The slides were then incubated for 24-72 h at 37°C. The diameter of the growth of fungi was measured after incubation period to determine the fungus' linear growth, and the percentage inhibition was calculated as 100x(C-T)/C, where C is the diameter of the fungal growth in the control plate after 96 h and T is the diameter of the fungal growth in the test plates after 96 hours. The standard antibiotic, Bavistin, was used to compare the antifungal screening results of the compounds.

**Brine Shrimp Lethality**

For Brine shrimp lethality[27], synthesized ligands and complexes have been dissolved in dimethyl sulfoxide and pragmatic at different conc.: 5.0, 10.0, 20.0, 40.0, and 80.0 µg/mL. However, no more than 50 µL of dimethyl sulfoxide have been added vials containing the nauplii. A control group was also included for each concentration, consisting of a vial with the same amount of dimethyl sulfoxide and brine water, but without the test compound. The vials were examined under a microscope after 24 h incubation period, and the quantity of living nauplii in each vials have been noted. The mean % age of nauplii mortality for each concentration was computed using these data.

## RESULTS AND DISCUSSION

All of the complexes were found to be monomeric, as evident from the determination of their molecular weights. The molar conductance values of the tin(II) complexes, measured in $10^{-3}$ M solutions, fall within the range of 11-25 $ohm^{-1}$ $cm^2mol^{-1}$, indicating their non-electrolyte nature. The physio-analytical data of tin(II) complexes are provided in Table 1.

**Table 1: Physio-analytical data of tin(II) complexes**

| Compounds | m.p. (°C) | Analysis, Found (Calcd.) % | | | | | Mol. Wt. Found (Calcd.) |
|---|---|---|---|---|---|---|---|
| | | C | H | N | Cl | Sn | |
| $ML_1$ | 154-156 | 57.85(57.89) | 3.50(3.53) | 24.50(24.55) | - | - | 456.35(456.42) |
| $ML_2$ | 165-167 | 59.45(59.50) | 4.12(4.16) | 23.10(23.13) | - | - | 484.45(484.48) |
| $[Sn(ML_1)Cl_2]$ | 185-187 | 40.01(40.09) | 2.44(2.49) | 17.30(17.34) | 10.91(10.97) | 18.36(18.37) | 646.00(646.02) |
| $[Sn(ML_2)Cl_2]$ | 198-200 | 42.72(42.76) | 2.94(2.99) | 16.60(16.62) | 10.49(10.51) | 17.59(17.61) | 674.02(674.08) |

**IR spectra**

The presence of amide groups at specific wavenumbers (1641–1671, 1431–1465, 1235–1250, and 570–660 $cm^{-1}$) in the complexes strongly indicates the formation of closed cyclic products[28]. Furthermore, strong and sharp absorption bands observed in the regions of 2832–2860 and 1412–1438 $cm^{-1}$ accredited to (C-H) stretching ($\nu$) and bending ($\delta$) vibrations, respectively[29]. The appearance of bands 350 & 370 $cm^{-1}$ and 420 & 440 $cm^{-1}$, corresponding to metal-chloride vibrations[30]. Table 2 provides a summary of the characteristic frequencies of the synthesized Sn(II) complexes.

**Table 2: FT-IR Spectra information ($cm^{-1}$) for the Tin(II) Complexes and the ligands**

| Compounds | Amide | | | | ν(NH) | ν (Sn-Cl) | ν (Sn-N) |
|---|---|---|---|---|---|---|---|
| | I | II | III | IV | | | |
| $ML_1$ | 1641 | 1431 | 1232 | 570 | 3215 | - | - |
| $ML_2$ | 1680 | 1442 | 1265 | 560 | 3250 | - | - |
| $[Sn(ML_1)Cl_2]$ | 1650 | 1450 | 1240 | 550 | 3245 | 350 | 420 |
| $[Sn(ML_2)Cl_2]$ | 1671 | 1465 | 1260 | 660 | 3240 | 370 | 440 |

### $^1$H NMR spectra

The tin(II) complexes were subjected to $^1$H NMR spectroscopy in DMSO-$d_6$, and the conforming chemical shift values (δ) for diverse protons are recorded in Table 3. Several points reinforce the recommended geometry for these tin(II) complexes. The absence of any signals in the $^1$H NMR spectra of the complexes corresponding to amino and hydroxyl groups support the proposed structures. A broad signal detected in all complexes at δ 7.92–8.20ppm can be attributed to the amide protons[31]. The aromatic ring protons of 1,8-Napthyridine-2,7-diamine are represented by the multiplets that appear in the range of 6.63–8.14ppm. Malonic and glutaric acid's methylene protons are attributed to singlets that show at ppm values of 2.86–2.90 and 3.20–3.23, respectively. The chemical shift values of the synthesized tin(II) compounds are presented in Table 3.

**Table 3: $^1$H NMR (δ, ppm) Spectral Data of the Ligands and their Tin(II) Complexes**

| Compound | (CO-NH) | CO-$CH_2$-CO | CO-$(CH_2)_3$-CO |
|---|---|---|---|
| $ML_1$ | 7.90 | 1.95 | - |
| $ML_2$ | 8.15 | - | 3.20 |
| $[Sn(ML_1)Cl_2]$ | 8.20 | 2.06 | - |
| $[Sn(ML_2)Cl_2]$ | 8.25 | - | 3.40 |

### Mass spectra

The mass spectrum of the macrocyclic ligand [$ML_1$] is represented in Fig. 1. The molecular formula of the macrocyclic ligand [$ML_2$] is $C_{22}H_{18}N_8O_4$ (m/z=456.35). The mass spectrum of macrocyclic ligand [$ML_1$] displays molecular ion peaks corresponding to molecular ions $[M]^+$ at m/z=456.25. The empirical formula, as revealed by the elemental analysis, and the molecular ion peak $[M]^+$ were in good agreement. The other fragmentation peak observed in the mass spectrum of macrocyclic ligand [$ML_1$] was at 430.12 $[C_{21}H_{18}N_8O_3]^+$, 416.01 $[C_{20}H_{16}N_8O_3]^+$, 388.40 $[C_{19}H_{16}N_8O_2]^+$, and 188.07 $[C_9H_8N_4O]^+$. The mass spectrum of the macrocyclic ligand [$ML_2$] is represented in Fig. 2. The molecular formula of the macrocyclic ligand [$ML_2$] is $C_{24}H_{20}N_8O_4$ (m/z=484.45). The mass spectrum of macrocyclic ligand [$ML_2$] displays molecular ion peaks corresponding to molecular ions $[M]^+$ at m/z=484.30. The empirical formula, as revealed by the elemental analysis, and the molecular ion peak $[M]^+$ were in good agreement. The other fragmentation peak observed in the mass spectrum of macrocyclic ligand [$ML_2$] was at 458.09 $[C_{22}H_{18}N_8O_4]^+$, 444.60 $[C_{21}H_{18}N_8O_4]^+$, 402.59 $[C_{20}H_{18}N_8O_4]^+$, and 188.19 $[C_9H_8N_4O_2]^+$.

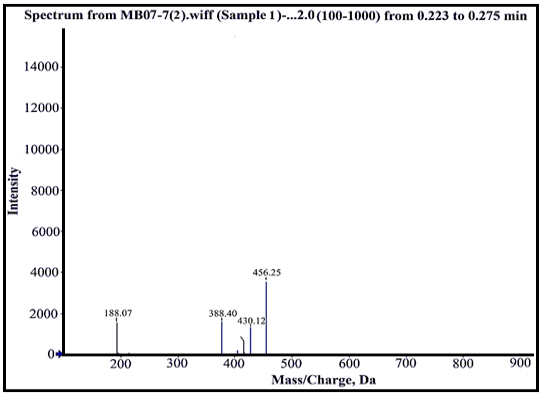


**Fig. 1. Mass spectrum of macrocyclic ligand [$ML_1$]**

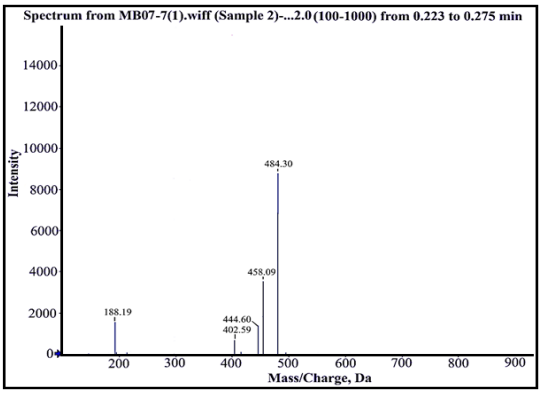


**Fig. 2. Mass spectrum of macrocyclic ligand [$ML_2$]**

### Powder X-ray diffraction studies

The complex $[Sn(ML_2)Cl_2]$ underwent an X-ray powder diffraction analysis to study its lattice dynamics. The recorded inter-planar spacing values (d, Å) and their corresponding Miller-0indices (h, k, l) (Table 4). The data indicate that the metal derivative possesses an orthorhombic lattice structure, with cell dimensions as follows: a=17.8630, b=7.4460, c=15.7480, and α=β=γ=90°.

### $^{119}$Sn NMR spectra

The inferences derived from IR and Proton NMR investigations are corroborated by the

$^{119}$Sn NMR spectra. The complexes $[Sn(ML_1)Cl_2]$ and $[Sn(ML_2)Cl_2]$ exhibit signals at δ 561 and 542ppm, respectively, indicating an octahedral environment around the tin atom in these complexes[32]. Based on the spectral evidence Fig. 3, the proposed structure for the $[Sn(ML_2)Cl_2]$ complex can be suggested.

**Table 4: Powder X-ray diffraction data of $[Sn(ML_2)Cl_2]$**

| Peak No | 2θ(deg.) (obs.) | d-spacing (obs.) Å | h | k | l |
|---|---|---|---|---|---|
| 1 | 10.124 | 8.730 | 0 | 2 | 0 |
| 2 | 12.340 | 7.167 | 1 | 1 | 0 |
| 3 | 15.128 | 5.852 | 1 | 2 | 0 |
| 4 | 16.227 | 5.458 | 0 | 1 | 1 |
| 5 | 18.984 | 4.671 | 1 | 3 | 0 |
| 6 | 19.784 | 4.484 | 1 | 1 | 1 |
| 7 | 21.653 | 4.101 | 1 | 2 | 1 |
| 8 | 21.722 | 4.088 | 0 | 3 | 1 |
| 9 | 22.584 | 3.934 | 2 | 0 | 0 |
| 10 | 23.175 | 3.835 | 2 | 1 | 0 |
| 11 | 23.304 | 3.814 | 1 | 4 | 0 |
| 12 | 24.524 | 3.627 | 1 | 3 | 1 |
| 13 | 24.844 | 3.581 | 2 | 2 | 0 |
| 14 | 27.361 | 3.257 | 2 | 3 | 0 |
| 15 | 27.473 | 3.244 | 2 | 0 | 1 |
| 16 | 27.956 | 3.189 | 2 | 1 | 1 |

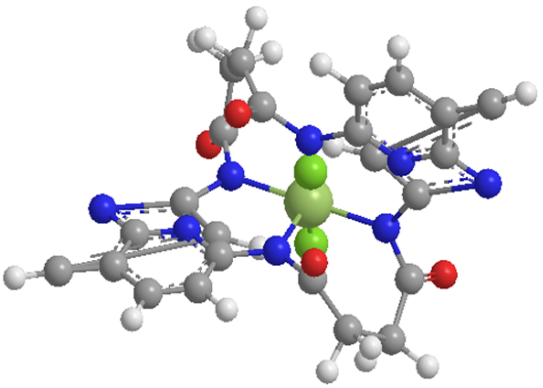

**Fig. 3. Proposed structure of macrocyclic complex $[Sn(ML_2)Cl_2]$**

## Antimicrobial activities

Bacterial activity assessment was conducted using the paper disc method. The bacteria used in these experiments were *Escherichia coli*, *Xanthomonas campestris*, and *Staphylococcus aureus*. The zone of inhibition values for antibacterial activity is given in Table 5. The findings were evaluated in comparison with standard drugs, gentamicin for bacteria. The studied macrocyclic compounds appeared to be effective against all the tested bacterial strains. The macrocyclic complex $[Sn(ML_2)Cl_2]$ showed higher antibacterial activity with zones of inhibition of 24.5mm against *S. aureus*, 26.1mm against *E. coli*, and 27.1mm against *X. campestris* at 1000ppm Figure 4.

The ligands and their corresponding metal complexes were assessed for their potential to inhibit the growth of selected fungi, *Fusarium oxysporum*, and *Aspergillus niger*, using the spore germination technique. The results of the antifungal activity, as indicated by the percentage of inhibition and zone of inhibition, are presented in Table 6. The macrocyclic complex $[Sn(ML_2)Cl_2]$ showed higher antifungal activity with zones of inhibition of 24.1mm against *A. niger* and 25.3mm against *F. oxysporum* at 200ppm Figure 5.

**Table 5: Antibacterial activity of Ligands and theirtin(II) complexes**

| Compounds | Bacterial Inhibition Zone (in mm), Concentration (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | *S. aureus* | | *E. coli* | | *X. campestris* | |
| | 500 | 1000 | 500 | 1000 | 500 | 1000 |
| $ML_1$ | 15.3 | 17.4 | 10.9 | 18.9 | 12.4 | 19.5 |
| $ML_2$ | 17.4 | 20.4 | 12.8 | 21.8 | 15.6 | 22.4 |
| $[Sn(ML_1)Cl_2]$ | 20.8 | 23.8 | 15.9 | 25.4 | 16.4 | 26.7 |
| $[Sn(ML_2)Cl_2]$ | 21.6 | 24.5 | 17.0 | 26.1 | 20.5 | 27.1 |
| *Gentamicin* (Standard) | 22.7 | 25.9 | 17.4 | 26.9 | 21.0 | 27.6 |

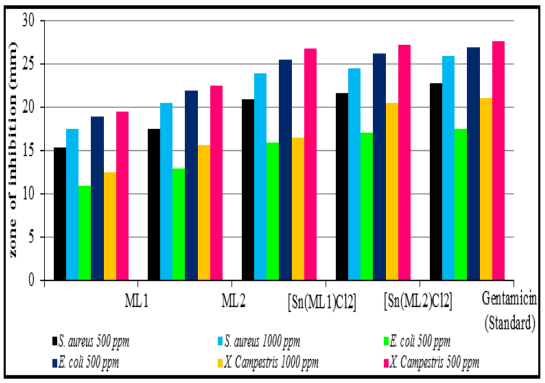


**Fig. 4. Antibacterial activity of Sn(II) compounds (in terms of zone of inhibition)**

**Table 6: Antifungal activity of Ligands and their Sn(II) complexes**

| Compound | Fungal inhibition Zone (in mm), Conc. (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | *A. niger* | | | *F. oxysporum* | | |
| | 50 | 100 | 200 | 50 | 100 | 200 |
| $ML_1$ | 11.5 | 12.8 | 15.4 | 12.1 | 13.0 | 16.0 |
| $ML_2$ | 14.3 | 15.6 | 17.9 | 14.6 | 16.4 | 18.2 |
| $[Sn(ML_1)Cl_2]$ | 16.9 | 20.2 | 22.6 | 17.2 | 21.0 | 22.8 |
| $[Sn(ML_2)Cl_2]$ | 18.0 | 21.2 | 24.1 | 18.9 | 22.1 | 25.3 |
| *Bavistin* (Standard) | 18.4 | 21.8 | 24.3 | 19.5 | 22.4 | 25.9 |

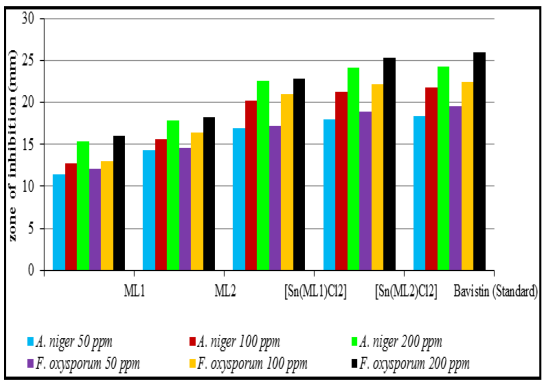


**Fig. 5. Antifungal activity of Sn(II) complexes (in terms of zone of inhibition)**

### Brine Shrimp Lethality

The (B.S.L.) Brine Shrimp Lethality of all the compounds was determined, and the $LC_{50}$ values for each compound have been premediated and are offered. Mortality rate of the nauplii increased as concentration of each sample increased. When plotting the graph of sample's concentration against %age of mortality, a linear correlation was observed Fig. 7. From this graph, $LC_{50}$ values for the samples were determined and found to be 28.91, 15.31, 9.07, and 6.01 µg/mL, respectively.

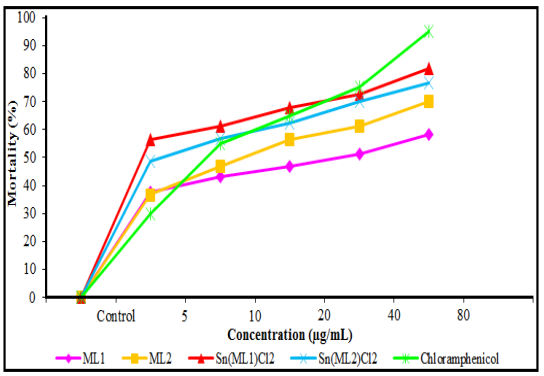


**Fig. 7. Mortality rate of brine shrimp treated with various concentrations of Tin(II) compounds**

The effectiveness of a drug relies on factors such as its size, shape, and degree of ionization. Biological activity is not solely determined by a single functional group; rather, it often depends on multiple functional groups. Therefore, the addition of any (FG) functional group to an inactive organic substance does not usually confer specific biological activity, as potent activity typically requires more than one functional group. The standard drug chloramphenicol has $LC_{50}$ value 18.20 µg/mL. The $LC_{50}$ values are used to infer which concentration is required to show a toxic effect on humans. The lower the $LC_{50}$ value, the more toxic the compound. Based on this observation, it is concluded that compounds $ML_1$ and $ML_2$ have relatively low cytotoxic activity compared to the compounds $[Sn(ML_1)Cl_2]$ and $[Sn(ML_2)Cl_2]$. The macrocyclic compound $ML_1$ is less toxic than standard drug chloramphenicol. Between $ML_1$ and $ML_2$, $ML_1$ exhibited even less activity than $ML_2$. Similarly, a comparison between compounds $[Sn(ML_1)Cl_2]$ and $[Sn(ML_2)Cl_2]$ revealed that $[Sn(ML_2)Cl_2]$ is more active than the former compound. This suggests that the inclusion of glutaric acid in the compound $[Sn(ML_2)Cl_2]$ renders it extremely contaminated for brine shrimp nauplii (B.S.N.). While the compound $[Sn(ML_2)Cl_2]$ displayed significant antimicrobial activity, it exhibited less cytotoxicity, indicating its potential as a safe and effective antibiotic. However, further comprehensive investigations on higher animal models are necessary to study its other potential toxic effects.

## CONCLUSION

In this study, the new ligands and their chelates of Sn(II) metal ions were synthesized. Their structures i.e. octahedral were investigated utilising spectroscopic and elemental studies. The *In vitro* testing of the free ligand and its metal chelates against two different types of bacteria demonstrated their remarkable efficacy. In addition, Sn(II) complex appears to be a strong option, exhibiting concurrent antioxidant and anticancer effects based on comparative studies, providing a reliable substitute for traditional chemotherapy medicines. The compound $[Sn(ML_2)Cl_2]$ has the potential to be a safe and effective antibiotic due to its considerable antibacterial activity and low cytotoxicity.

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### Conflict of interests

The authors declare that they have no conflict of interests regarding the publication of this article

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