RASĀYAN *J. Chem.*
Vol. 17 | No. 1 |78-86| January - March | 2024
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

DESIGN, SYNTHESIS, SPECTRAL ANALYSIS, ANTIMICROBIAL EVALUATION AND TOXICOLOGICAL ASPECTS OF BIVALENT TIN COMPLEXES WITH MACROCYCLIC MOIETY

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ABSTRACT

The novel complexes Sn(II), were synthesized of macrocyclic ligands derived from various diamine and dicarboxylic acids in the ratio of 2:2 and characterized by elemental analysis, molar conductance measurements, mass, NMR, FT-IR, and electronic spectra. The interactions of macrocyclic ligands (ML_n) with $SnCl_2$ in a 1:1 molar ratio in methanol produced the ensuing physiologically active $[Sn(ML_n)Cl_2]$ type complexes, where n = 1 or 2. The complexes were initially identified using conductivity tests, molecular weight calculations, and elemental investigations. The bonding mode was determined using spectral data from the IR, ^{1}H NMR, and ^{119}Sn NMR. The complexes exhibit hexacoordinated octahedral geometry. The positive findings of Brine shrimp lethality of the ligands and their complexes have been discussed. The antimicrobial effects of each complex on several types of harmful fungus and bacteria have been assessed. The research focused on investigating and analyzing various aspects related to male fertility. It specifically investigated cauda epididymal spermatozoa density, sperm motility, testicular sperm density, fertility, and biological constraints of propagative tissues. The findings and discussions about these factors were presented in the study.

Keywords: Macrocyclic, Antimicrobial Activity, Toxicological Aspects, Brine Shrimp Lethality.
RASĀYAN *J. Chem.*, Vol. 17, No.1, 2024

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. In recent years, most individuals have experienced cancer and infectious diseases, leaving mankind with little other alternative than to look for novel therapeutic approaches. 13,800 new instances of cervical cancer are detected each year, according to the American Cancer Society. Therefore, there is a significant need for novel therapeutic drugs with potential therapeutic activity. Thiocarbamide derivatives have a wide range of uses in cancer treatment, as antioxidants, parasites, against HIV, and microbes. As cytotoxic agents, several series of chemical ligands generated from aroylhydrazide thiocarbamide and their metal complexes have been researched. So, Tetraaza macrocyclic ligands can be used as biological models to understand better how metal protein functions[1,2], CO_2 reduction catalysts[3], corrosion inhibitors[4,5], anti-tumour[6], anti-viral[7,8], anti-bacterial, anti-fungal and anti-malarial agents, among other things, due to the variety of metal cations with which they bind.[9-13] Tin templates play a significant role in supramolecular chemistry. In this context, organotin(IV) compounds have been employed as both activating agents and templates.[14] One of the main challenges in achieving the efficient synthesis of macrocyclic compounds is the directing condensation reactions towards ring products rather than polymeric materials. To overcome this obstacle, an alternative approach has been proposed, using metalloid derivatives as ligands. This method involves the synthesis of macrocyclic compounds from cyclic precursors, employing tin templates as covalent templates.[15] Already, some successful reports have demonstrated the synthesis of macrocyclic compounds using Di organotin(IV) dicarboxylates as covalent templates. In the pursuit of efficient and innovative synthetic pathways, the

http://doi.org/10.31788/RJC.2024.1718631

development of novel polythiamacrocycles is valuable attempts that will easier the synthesis of a diverse range of macrocyclic compounds.[16] A long time ago, considerable interest in octahedral complexes of porphyrins and similar aromatic macrocyclic compounds with Tin(IV), primarily due to their potential medical applications. Much of the research has focused on Sn(IV) complexes of protoporphyrin and similar ligands, as they have shown promise in inhibiting the enzyme heme oxygenase, responsible for neonatal hyperbilirubinemia. However, concerns have been raised about their adverse side effects, as these agents also exhibit strong photosensitizing properties.[17] Furthermore, investigations have been conducted on macrocyclic complexes of Tin(II), with studies covering their chemical, biochemical, and toxicological aspects.[14,17-22] 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

The chemicals include malonic acid and glutaric acid, 1,8-Diaminooctane, and $SnCl_2$ (BDH).

Methods and Methodology

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 ^1H NMR spectra, a JEOL FX-90Q spectrometer was used with TMS serving as the internal standard. Additionally, carbon, hydrogen, and nitrogen analyses were performed by using a CHN analyzer at (CDRI) in Lucknow.

Synthesis of the Ligands (ML_1-ML_2)

The measured quantity of 1,8-diamino octane was placed in a 100 ml round bottom flask. To this, an equivalent amount of malonic acid dissolved in methanol was supplementary. The reaction was conducted in 2:2 molar ratio reflux for 11 hours. After completion, the reaction mixture was cooled, and the resulting off-white compounds were 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 was used in the reaction.

Synthesis of the Complex [$Sn(ML_1)Cl_2$-$Sn(ML_2)Cl_2$]

A mixture of ML_1 and $SnCl_2$ in a 1:1 molar ratio was prepared in methanol and subjected to reflux heating for 42 hours. left undisturbed for some time in the evaporating dish, resulting in the formation of a white compound that filters it out. The product was then washed with ethanol and dried, 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 as ligands.

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 $ohm^{-1}cm^2\ mol^{-1}$, indicating their non-electrolyte nature. The physio-chemical 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	156	62.00 (62.23)	9.28 (9.49)	12.34 (13.19)	16.11 (16.69)	-	392 (424.6)
ML_2	163	66.00 (66.10)	10.09 (10.29)	10.12 (11.01)	13.39 (13.93)	-	482 (508.7)
$[Sn(ML_1)Cl_2]$	182	42.81 (43.02)	6.46 (6.56)	8.23 (9.12)	10.91 (11.54)	18.92 (19.32)	587 (614.2)
$[Sn(ML_2)Cl_2]$	194	47.90 (48.15)	7.30 (7.50)	7.21 (8.02)	9.55 (10.15)	16.48 (16.99)	669 (698.3)

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.[27] Furthermore, strong and sharp absorption bands were observed in the regions of 2832–2860 and 1412–1438 cm^{-1} accredited to (C-H) stretching (ν) and bending (δ) vibrations, respectively.[28] The appearance of bands 361-381 cm^{-1} and 432-448 cm^{-1}, corresponding to metal-chloride vibrations.[29] 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	1631	1431	1235	560	3219	-	-
ML_2	1671	1444	1265	570	3256	-	-
$[Sn(ML_1)Cl_2]$	1655	1455	1240	555	3247	360	430
$[Sn(ML_2)Cl_2]$	1668	1435	1259	567	3238	380	448

^{1}H NMR Spectra

The ^{1}H NMR spectroscopy has been done in DMSO-d_6, and the conforming (δ) values 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 supports the proposed structures. A broad signal detected in all complexes at δ 7.92-8.20 ppm can be attributed to the amide protons.[30] A multiplet in complex spectrums that are present between 1.98 and 2.10 ppm is a sign that the 1,8-diaminoctane moiety's middle methylene protons are present. Malonic and glutaric acid's methylene protons are attributed to singlets that show 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-N-CH_2)	C-CH_2-C	CO-$(CH_2)_x$-CO
ML_1	7.92	3.46	1.98	2.86
ML_2	8.20	3.40	2.10	3.20
$[Sn(ML_1)Cl_2]$	8.09	3.27	2.03	2.90
$[Sn(ML_2)Cl_2]$	8.11	4.49	1.99	3.10

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-0 indices (h, k, l) (Table-4). The data indicate that the metal derivative possesses an orthorhombic lattice structure, with cell dimensions as follows: a = 10.3742 Å, b = 15.5662 Å, c = 17.1274 Å, 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 542 ppm, respectively, indicating an octahedral environment around the tin atom in these complexes.[31] Based on the spectral evidence (Fig.-1), the proposed structure for the Tin(II) complexes can be suggested.

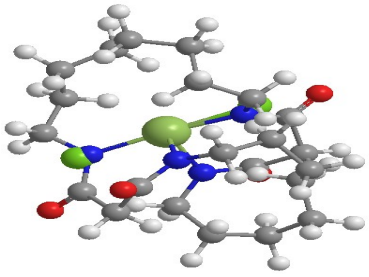

Fig.-1: The Proposed Structure for the Tin(II) Complexes

Antimicrobial Activities

Bacterial activity assessment was conducted using the paper disc method. 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 bacteria used in these experiments were *Escherichia coli*, *Xanthomonas campestris*, and *Staphylococcus aureus* (Table-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. Test compound solutions (0.5 mL) were prepared in DMF and applied to the fungus slides. The slides were then incubated for 24-72 hours at 37 °C. The level of fungal growth inhibition was represented as follows: contamination in the solution indicated 100% growth of the fungus, represented as "+"; 50% growth was denoted by "++"; less than 50% growth was shown as "+++"; and excellent inhibition was designated as "++++" (as shown in Table-5). The results of the antifungal activity, as indicated by the zone of inhibition, are presented in Fig.-2.

Table-4: Bactericidal Activity Data for Synthesized Compounds

Compound	*Escherichia coli*	*Xanthomonas compestris*	*Staphylococcus aureus*
ML_1	-	+	++
ML_2	+	++	++
$[Sn(ML_1)Cl_2]$	++	++	++
$[Sn(ML_2)Cl_2]$	++	++	+++
Gentamicin (Standard)	+ + +	+ + +	+ +

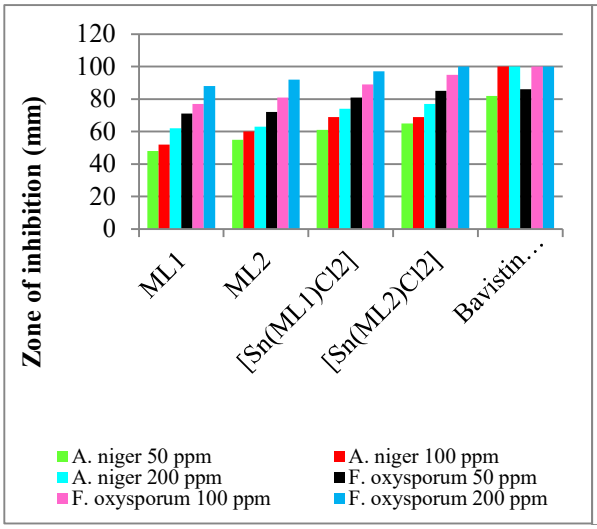

Fig.-2: Antifungal Activity of Compounds

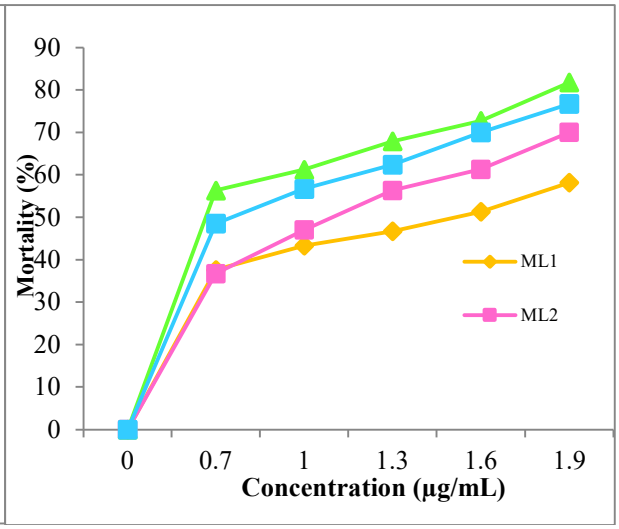

Fig.-3: Mortality Rate of Brine Shrimp of Compounds

Brine Shrimp Lethality

For Brine Shrimp lethality[32], 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 to 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 24-hour incubation period, and the quantity of living nauplii in each vial was noted. The mean %age of nauplii mortality for each concentration was computed using these data. The (B.S.L.) Brine Shrimp Lethality of all the compounds was determined, and the LC_{50} values for each compound have been premeditated. The mortality rate of the nauplii increased as the concentration of each sample increased. When plotting the logarithm of the sample's concentration against %age of mortality, a linear correlation was observed (Fig.-3). From this graph, LC_{50} values for the samples were determined and found to be 29.51, 14.51, 9.12, and 5.75 µg/mL, respectively. 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. 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 $[Sn(ML_2)Cl_2]$. 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, more extensive research on higher animal models is required to investigate its other possible harmful consequences.

Antifertility Activity

We used male rats that we got from the ICMR in New Delhi. Spragge Dawley albino rats (Rattus norvegicus) that were colony-bred and sexually mature were kept in clean wire mesh cages underneath the meticulous lab circumstances of temperature and illumination (12-hour dark and 12-hour bright sequence; 30°C, 35-65% humidity), and they were given a standard pellet diet and water at will. With an equal number of animals in each group, the male rats that had previously been proven to be fertile were separated into groups. One group received a vehicle (olive oil) and was given control treatment. The starting substance, ligand, and their complexes (50 mg/kg BW) were administered orally to other groups for 60 days After the trial, the animals were autopsied to examine histological and biochemical changes and tested for fertility. In order to do biochemical calculations, procreative tissues were cut out, dressed of blood and adherent tissues, weighed, and stored at -20^{o}C. Additionally, the testicles were preserved in Bouin's fluid for histological analysis. Standard laboratory techniques were used to measure the total cholesterol[34], sialic acid[35], fructose[36], sialic acid motility and densities of C.E.S[33], and fructose. The research focused on investigating and analyzing various aspects related to male fertility. Specifically, it explored testicular (Perm-morphology sperm density), sperm mortality, cauda epididymal spermatozoa density, fertility in matings trials, and biological constraints of propagative tissues. The findings and discussions about these factors were presented in the study (Tables-8 to 11). The findings demonstrate that while the ligands were capable of inhibiting fertility on their own, the synergistic effect of leads complexe increased their efficacy.

Evaluations of Male Fertilities Potentials

By the side of the end of the experiment, males from each and all groups were housed separately with proestrus females in a 1:3 ratio. Each time, the vaginal smear revealed copulations of plugs and spermatozoa, indicating that the attempted mating was successful. Day 0 of pregnancy was determined to be the day that spermatozoa were found in the smears. On day 15 post-coitum, these females had laparotomies, and the numeral of embedding places, if any, in the uteri were noted.[37] We examined a variety of male reproductive points in the current investigation. The result has been summarized under:

Body and Genital Organ Weights

When rats in any experimental group were exposed to ligands and their complexes, there was no discernible difference in the body weight when compared to their beginning weights. However, in rats

treated with ligands and metal derivatives, a considerable loss in the weight of the testes was observed, which was likely caused by the degeneration of the spermatogonial cells.

Sperms Motilities & Sperms Densities

Animals treated with the ligands and their compounds showed a considerable reduction in sperm motility in the cauda epididymis.

Biochemicals Parameter of Reproductive Organ

N-acetylneuraminic Acids: The results of synthesized ligands and tin complexes, N-acetylneuraminic acids level in the testes, epididymis, seminal vesicle, and ventral prostate reduced significantly (Table-5). N-acetylneuraminic acid levels have reduced due to the suppression of spermatogenesis in the teste.

Table-5: N-acetylneuraminic Acids Contents Changes in Genital Organs Following Tin(II) Compound Treatment

Groups	Treatments	N-acetylneuraminic acids (mg/gm)			
		Teste	Epididymis	Seminals Vesiclesa	Ventral Prostate
A	Control	8.9 ± 0.8	7.5 ± 0.9	8.2 ± 0.7	8.4 ± 0.5
B	$SnCl_2$.	6.9 ± 0.9[a]	5.9 ± 0.8[a]	6.6 ± 0.8[a]	6.7 ± 0.6[a]
C	ML_1	7.1 ± 0.8[a]	5.7 ± 0.7[a]	7.0 ± 0.2[a]	6.9 ± 0.5[a]
D	$[Sn(ML_1)Cl_2]$.	4.3 ± 0.5[c]	3.8 ± 0.5[c]	3.5 ± 0.8[c]	4.3 ± 0.6[c]
E	1,8-Diaminooctane	6.0 ± 0.7 [b]	5.4 ± 1.1[b]	6.0 ± 1.0[b]	6.4 ± 0.7[a]
F	ML_2	6.8 ± 0.8[a]	5.3 ± 1.0[b]	6.7 ± 0.6[a]	6.5 ± 0.4[a]
G	$[Sn(ML_2)Cl_2]$.	4.1 ± 0.3[c]	3.3 ± 0.2[c]	3.2 ± 0.9[c]	4.1 ± 0.3

Testicular Cholesterol and Glycogen:

After receiving various substances, testicular total cholesterol and glycogen levels decreased (Table-6). Sugar: All experimental groups' seminal vesicle fructose concentrations considerably decreased.

Table-6: Effects of Ligands and their Corresponding Complexes on Tissue Cholesterol, Glycogen, and Fructose Levels

Group	Treatment	Cholesterol (mg/gm) Testes	Fructose (mg/gm) Seminal Vesicle	Glycogen (mg/gm) Testes
A	Control	8.5 ± 0.7	470 ± 20	5.7 ± 0.5
B	$SnCl_2$.	6.6 ± 0.5[b]	390 ± 25[b]	4.3 ± 0.5[b]
C	ML_1	7.0 ± 0.5[a]	410 ± 25[a]	4.2 ± 0.6[b]
D	$[Sn(ML_1)Cl_2]$.	3.5 ± 0.4[c]	210 ± 20[c]	3.1 ± 0.3[c]
E	1,8-Diaminooctane	6.9 ± 0.5[a]	415 ± 15[a]	4.4 ± 0.4[b]
F	ML_2	6.8 ± 0.6[a]	420 ± 10[a]	4.1 ± 0.8[b]
G	$[Sn(ML_2)Cl_2]$	3.2 ± 0.3	205 ± 18[c]	2.9 ± 0.4[c]

According to the study, weights of the testes, epididymis, seminal vesicle, and ventral prostate were significantly reduced when subjects were treated with $SnCl_2$, 1,8-diamino octane, ligands, and their complexes. This could be a result of the changing level of androgens in the blood, which negatively impacts the shape, size, and structural integrity of the reproductive organs.[38,39] This claim was further substantiated by a resulting decrease in cauda epididymis motility and sperm density in both the testes and cauda epididymis. Male rats given lead acetate were reported to produce less testicular testosterone and have structural changes in the Leyding cell.[40]

In accordance with our findings, the structural integrity of the genital organs has been compromised when there is a decrease in the male reproductive tissues of experimental rats.[41] A substantial reduction in the amount of sialic acid found in male reproductive organs following treatment with $SnCl_2$, 1,8-diamino octane, ligands, and their complexes can also be attributed to the test substance's anti-androgenic properties because the amount of sialic acid is reliant on androgen synthesis. When it comes to controlling fertility, $SnCl_2$, 1,8-diamino octane, and their complexes are superior to their ligands, ML_1 and ML_2, by a wide margin. The fact that seminal vesicles treated with ligands and complexes had less fructose in them

further supports the anti-androgenic properties of these substances. The findings of the present study demonstrate that $SnCl_2$, 1,8-diamino octane, and their complexes are more potent in controlling fertility than their ligands, ML_1 and ML_2.

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, the Sn(II) complex appears to be a strong option, exhibiting concurrent antioxidant and anticancer effects based on comparative studies, and 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. The results of the antifertility study establish that Tin(II) compounds show superior to the synthesized ligands.

ACKNOWLEDGMENTS

The author (Mamta and Subhash) expresses sincere gratitude to the University Grants Commission, New Delhi, India, for the generous financial support received in the form of a Junior Research Fellowship (JRF).

CONFLICT OF INTERESTS

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

AUTHOR CONTRIBUTIONS

All authors contributed significantly to this manuscript, participated in reviewing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs given below:

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