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MOLLUSCICIDAL AND ANTIMICROBIAL ACTIVITY OF BINARY MONONUCLEAR METAL COMPLEXES OF BIDENTATE AZOMETHINE LIGANDS BASED ON ANTHRANILIC ACID

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ABSTRACT

Bidentate azomethine ligands derived from condensation of anthranilic acid with vaniline (SL_1), furfural (SL_2), p-hydroxybenzaldehyde (SL_3) and p-nitrobenzaldehyde (SL_4) were synthesized. These ligands were used to prepare mononuclear metal complexes using Cu(II), Ni(II) and Zn(II) metal ions and formed square planar metal complexes with ligand to metal ratio of (2:1).

Compounds were screened *in vitro* for antimicrobial activity using disc diffusion technique and were tested *in vivo* for molluscicidal activity against *E. vermiculata* l and snails. The ligands SL_1 and SL_3 were inactive (< 10 mm) against both bacterial types. SL_2 and SL_4 showed moderate activity (12.2-12.8 mm) against *S. aureus* and (14.8-15.6 mm) against *S. pneumonia* Gram-positive bacterial strains and were resistance against Gram-negative bacterial strains. SL_2 and SL_4 ligands showed moderate activity (11.6-16.4 mm) against *C. albicans* fungal strains too. While, the synthesized coordination compounds showed noticeable improvement in the activity against the *C. albicans* fungal strains, and the Gram-positive bacterial species *S. pneumoniae* and *S. aureus* strains under the same conditions. $[Zn(SL_2)_2]$ and $[Zn(SL_4)_2]$ were highly active against *S. pneumonia* bacterial species with zones of inhibition 20.4 mm and 30.2 mm respectively. Similarly, $[Zn(SL_2)_2]$ and $[Zn(SL_4)_2]$ were highly active against *C. albicans* with inhibition zones of 22.7 mm and 22.8 mm respectively.

The minimum inhibition concentration (MIC) investigation was carried out and notable susceptibility was indicated for S. *pneumonia* bacterial strains with MIC values of 25μg/disc for the complex $[Zn(SL_4)_2]$.

The molluscicidal activity tests showed highest activity at concentration of 0.45 mg/L for the complex $[Zn(SL_2)_2]$.

Keywords: bidentate Schiffbase ligands, metal complexes, antifungal, antibacterial, molluscicidal activity

1. INTRODUCTION

The metal complexes of Schiff base ligands have been amongst the widely studied compounds in coordination chemistry [1-2]. These compounds found to have applications in many fields and particularly in biological and medicinal areas [3]. Numerous Schiff bases are medicinally important molecules and are utilized to tailor medicinal compounds [4]. Hundreds of research papers and reviews are available in the literature on Schiff bases and their metal complexes. The literature survey of previous studies have highlighted the fact that the biological activity of the Schiff bases as organic materials increases on coordination with metal ions [5-6].

Anthranilic acid is a primary aromatic amine with two adjacent functional groups NH_2 and COOH at *ortho*- position to each other. It is an amino acid analogue and considered as alternative ligand to amino acid contains oxygen and nitrogen atoms with high electronegativity that capable of coordinating to metal ions [7]. Anthranilic acid and its derivatives are important compounds in medicinal field and reported to possess a wide variety of biological activities and are used as intermediates in synthesis of pharmaceutically bioactive compounds and are important pharmacophores in drug discovery [8-11]. The coordination chemistry of anthranilic acid and its derivatives as ligands has attracted the interest of inorganic chemistry researchers and many metal complexes with different metal ions utilizing these ligands with carboxylic group moiety have been synthesized and studied [7, 12-13]. Studies on the metal complexes with Schiff bases derived from anthranilic acid are reported in the literature and showed antibacterial, antifungal, anti-inflammatory and antiviral activities [14-16]. Schiff base ligands derived from anthranilic acid were used in synthesis of oxovanadium complexes of mixed ligands and found to be potent inhibitors against protein tyrosine phosphatase (PTP) [17]. The presence of azomethine (C=N) linkage that have nitrogen as donor atom along with the adjacent carboxylic (-COOH) group in the Schiff bases derived from anthranilic acid

are an advantage for forming stable metal complexes. Moreover, it may constitute a good factor for the biological activity of the metal complexes derived from these ligands [18-19].

In the present paper, we synthesized, characterized and investigated the antibacterial, antifungal and molluscicidal activities of Cu(II) , Ni(II), and Zn(II) complexes of the bidentate ligands derived from the condensation of anthranilic acid as primary amine condensed with vaniline, furfural, p-hydroxybenzaldehyde and p-nitrobenzaldehyde.

2. MATERIALS AND METHODS

2.1. Chemicals

The starting materials 2-aminobenzoic acid, vaniline, furfural, p-hydroxy-benzaldehyde and p-nitrobenzaldehyde, copper, nickel and zinc salts and solvents used in this research project were of analytical grade purchased from the market and were used as received without purification.

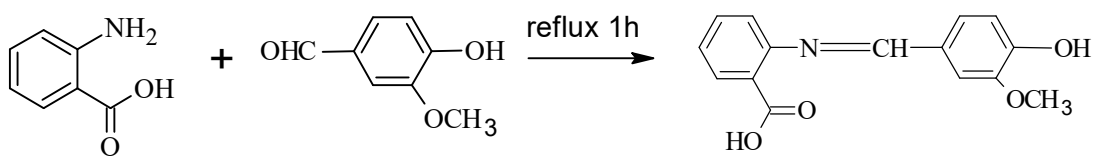
2.2. Synthesis of Ligands

The general method for synthesis of the designed azomethine ligands was adopted as reported in published literature [16, 20]. They were synthesized by condensation reaction between 2-aminobenzoic acid and the aldehyde in (1:1) stoichiometric molar ratio. The details procedures for preparing different designed azomethine compounds are given in the following sub-sections.

2.2.1. *Preparation of 1-(2-carboxyphenylimino)-4-hydroxy-3-methoxybenzene (SL_1)*

4-hydroxy-3-methoxy benzaldehyde (1.52 g, 0.01mol) dissolved in 30mL ethanol was added slowly to a round bottomed flask containing 2-aminobenzoic acid (1.37 g, 0.01mol) dissolved in 20mL ethanol with continuous stirring and refluxing for one hour. After cooling the reaction mixture to room temperature, the precipitated solid product (SL_1) was filtered, washed with ethanol and diethyl ether and dried in open air. The product was recrystallized into fine yellow crystals with a yield of 78%, melting point 167-170 °C. The purity was checked by TLC. Elemental analysis: molecular formula ($C_{15}H_{13}NO_4$), calculated %C 66.41, %H 4.83, %N 5.16, %O 23.59; obtained %C 66.96, %H 4.66, %N 5.48, %O 24.00.

The reaction scheme (1) is illustrated below.

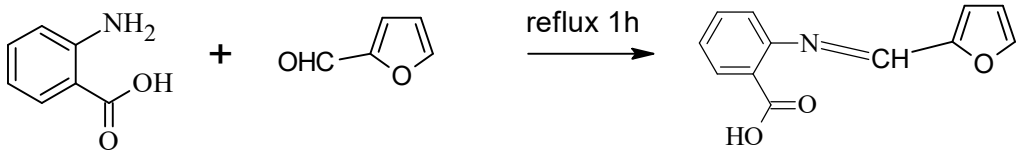


Scheme (1)

2.2.2. ***Preparation of 1-(2-carboxyphenylimino)-furan (SL_2)***

SL_2 ligand was prepared following the procedure as above by mixing (1.37g, 0.01mol) of 2-aminobenzoic acid dissolved in 20mL hot ethanol and a solution of (0.96g, 0.01mol) furan-2-carboxaldehyde in 30mL hot ethanol. The mixture was refluxed with continuous stirring for 2.5 hours. After cooling, the dark yellow precipitate produced was filtered, washed with cold ethanol and then with diethyl ether and air-dried. The product was recrystallized from ethanol to get pure yellowish-white (beige) solid product. Yield was about 75% and melting point was measured 195-196 °C. Elemental analysis: molecular formula ($C_{12}H_9NO_3$), calculated %C 66.97, %H 4.21, %N 6.50, %O 22.30; obtained %C 66.86, %H 3.96, %N 7.04, %O 22.55.

The reaction for synthesis of SL_2 Ligand is illustrated in the following scheme (2).

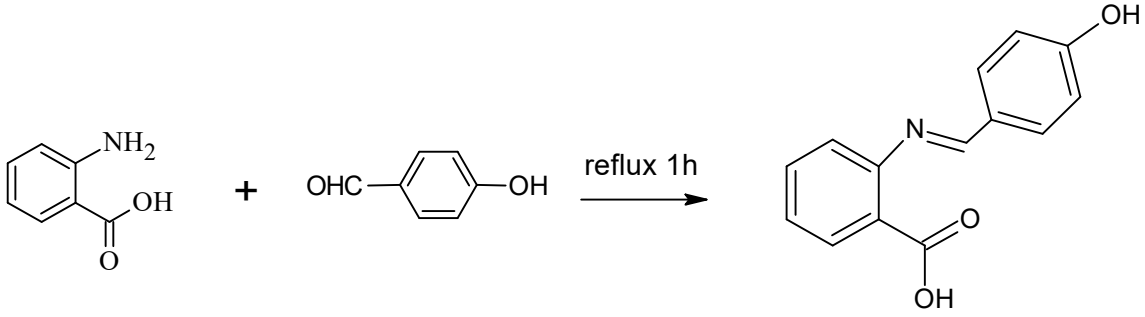


Scheme (2)

2.2.3. ***Preparation of 1-(2-carboxyphenylimino)-4-hydroxybenzene (SL_3)***

SL_3 ligand was synthesized by the condensation (1:1 molar ratio) of 2-aminobenzoic acid (1.37g, 0.01mol) dissolved in 20 mL ethanol with 4-hydroxybenzaldehyde (1.22g, 0.01mol) dissolved in 20 mL ethanol. The mixture was refluxed for nearly one hour. The yellow precipitate was collected by filtration, washed with ethanol and diethyl ether, and finally dried in open air. The product was recrystallized from hot ethanol to get a yield about 87% and melting point was 231-232 °C. Elemental analysis: molecular formula ($C_{14}H_{11}NO_3$), calculated %C 69.70, %H 4.59, %N5.80, %O 19.89; obtained %C 68.06, %H 4.22, %N5.54, %O 20.21.

SL_3 ligand structure and reaction synthesis is shown in scheme (3).

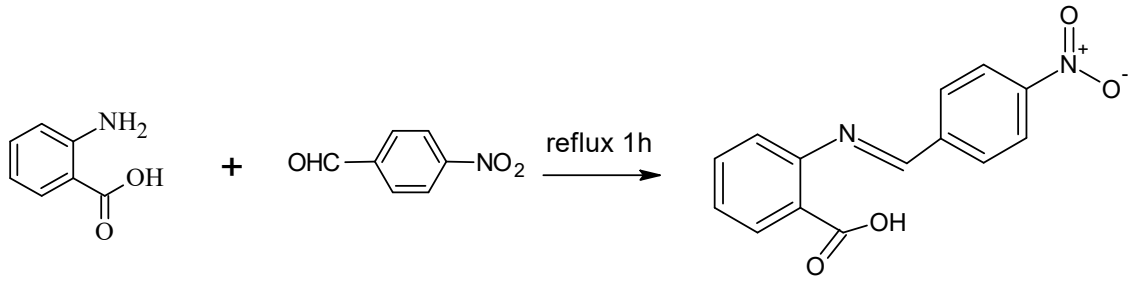


Scheme (3)

2.2.4. ***Preparation of 1-(2-carboxyphenylimino)-4-nitrobenzene (SL_4)***

SL_4 ligand was synthesized as mentioned above by the condensation (1:1 molar ratio) of 2-aminobenzoic acid (1.37g, 0.01mol) dissolved in 20 mL ethanol with 4-nitrobenzaldehyde (1.51g, 0.01mol) dissolved in 20 mL ethanol. The mixture was refluxed for nearly one hour. The dark yellow precipitate was collected treated as above to get a yield of about 84% and melting point was 174-176 °C. Elemental analysis: molecular formula ($C_{14}H_{10}N_2O_4$), calculated %C 62.22, %H 3.72, %N 10.36, %O 23.68; obtained %C 62.56, %H 4.04, %N 10.20, %O 23.43.

SL_4 ligand structure and preparation is shown in scheme 4.



Scheme (4)

2.3. Template Synthesis of the Mononuclear Metal Complexes

The binary Cu, Ni and Zn mononuclear metal complexes were prepared using the reported general procedure [6, 19]. Calculated amount of the Cu, Ni and Zn salts were dissolved in hot ethanol and mixed with the solution of the previously prepared azomethine ligands (SL_1 – SL_4) in (1:2) metal to ligand stoichiometric ratio in round bottom flask. The reaction mixtures were refluxed with stirring on hot plate magnetic stirrer for three hours. The produced precipitated materials were isolated and treated to get pure compounds.

2.4. Instrumentation and physical measurements

Different spectroscopic and analytical techniques were utilized to confirm the proposed structures of the synthesized metal complexes and their parent ligands. Thermo Fisher Scientific CHN/N/O analyzer (Leco Model VTF-900 CHN-S-O 932 version 1.3x USA) instrument was used for micro-elemental analysis. Mass spectra was recorded using Thermo Scientific-LCQ fleet ion trap mass spectrometer using electrospray ionization (ESI) method.

The direct measurement of IR spectra for the solid synthesized compounds was recorded using Thermo Scientific Nicolet iS50 FT-IR spectrometer in the range 400-4000 cm^{-1} utilizing Attenuated Total Reflection (ATR) method. The instrument

model Evolution 300 UV-visible double beam Spectrophotometer was used to record the UV spectra of the prepared ligands and their metal complexes by dissolving the samples in DMSO solvent.

^{1}H NMR spectra was recorded utilizing Varian Mercury-400BB (400 MHz) spectrometer operating at 400 MHz frequency for ^{1}H nuclei in CD_3OD solutions using TMS (^{1}H) as standard.

For measuring magnetic susceptibility for metal complexes we used Gouy's method apparatus balance (Holmarc's Magnetic Susceptibility - Gouy's Method Apparatus (Model No: HO-ED-EM-08)) at room temperature with $Hg[Co(SCN)_4]$ as calibrant. The experiments for measuring molar conductivities of the metal complexes were done on Hanna instrument HI8633N Multi-range conductivity meter using freshly prepared 1.0×10^{-3} M solutions of the metal complexes in DMSO.

2.5. Antimicrobial Activity Assessment

The antimicrobial potency for the prepared Cu(II), Ni(II) and Zn(II) complexes and their parent organic ligands were tested *in vitro* using agar disc-diffusion assay method according to the Clinical and Laboratory Standards Institute (CLSI) susceptibility testing technique [21]. Two Gram-positive bacterial strains named *Streptococcus pneumonia (S. pneumonia)* ***(ATCC 49619)*** and *Staphylococcus aureus* (*S. aureus*) ***(ATCC 25923)*** and two Gram-negative bacterial strains named *Pseudomonas aeruginosa* (*P.aeruginosa*) ***(ATCC 27853)*** and *Escherichia coli* (*E. coli*) ***(ATCC25922***) were used for antibacterial experiments. The common fungal strain named *Candida Albicans* (*C. Albicans*) ***(ATCC10231)*** was used for antifungal activity tests. The growth medium for bacterial strains we used Muller Hinton Agar (MHA) and that for *C. albicans* fungus Sabouraud dextrose agar was used.

To prepare the stock solutions 0.02gm of each tested compound was dissolved in 5 mL DMSO solvent (the negative control). Whatman sterilized 6 mm filter paper discs (Whatman antibiotic assay discs-model 2017-006 from Sigma-Aldrich) containing the tested compounds were placed on the agar surface in petri dishes. The petri dishes were incubated for 24 hours at 35˚C in case of bacteria and for 48 hours at 35 ˚C fungus. To monitor the bacterial and fungal susceptibilities after the incubation period, the observed zones of complete inhibition around the holes were measured (in mm). Each test was performed in duplicate and the arithmetic mean values were recorded.

To investigate the highest activity of the prepared compounds against the bacterial and fungal strains we tested the compounds that showed good activity for minimum inhibitory concentration (MIC) values. The metal complex $[Zn(SL_4)_2]$ was evaluated

for MIC against *S. pnenmonia* as bacterial strains and *C. albicans* as fungal strains. Agar disc-dilution assay was used for MIC tests following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. The growing medium used in these experiments was Mueller-Hinton agar. For MIC screening of each chemical, we prepared concentrations in serial of 2-fold dilution 100, 50, 25, 12.5, 6.25 and 3.125 µg/disc. Each sample was repeated twice and data is recorded as arithmetic mean.

2.6. The Molluscicidal Activity Experiments

The molluscicidal activity against *Eobania vermiculata* (*E. vermiculata*) land snail were studied for the obtained metal complexes and their parent Schiff base ligands adopted reported procedure [22-23]. The snails were collected from local area and were reared for enough periods to acclimatize with laboratory conditions before assessment. In plastic tanks (size 30 × 15 × 10 cm) we maintained the snails (15 snails) between 26 - 28°C. The tanks contain some sand and fresh drinking water with neutral pH and the snails fed with commercial fish food. The water in the tank was changed every three days.

WHO guidelines were followed in the molluscicidal activity assessment of the tested complexes and their parent Schiff bases. The immersion technique and niclosamide (approved as an anthelmintic and used principally against molluscs, especially fresh water snails) as a control measure were used in experimentation [22]. We used 2mg/ml niclosamide and 10mg/ml of tested compounds dissolved in DMSO solvent to prepare the stock solution. For bioassays, the final concentrations of niclosamide ranging from 0.02mg/L to 0.2mg/L and for the examined compounds the final concentrations were 0.1mg/L to 0.5mg/L were used. The reared snails were immersed in mixed aqueous solution of the investigated compounds at the final concentrations for one day (24 hours) without food. After exposure to the tested compounds the snails were transferred to fresh water without fed for another 24 hours as a recovery period for mortality assessment. The mortality was checked after 24 hours and the 50% (LC_{50}) lethal concentration was determined. Each test was repeated twice for each compound. Leitchfield and Wilcoxon simplified method was used for dose effect evaluation [23].

3. RESULTS AND DISCUSSION

3.1 Synthesis of Schiff base Ligands and Characterization

The Schiff base ligands were successfully prepared by the condensation reaction between the primary amine anthranilic acid with vanillin, furfural, p-hydroxy benzaldehyde and p-

nitrobenzaldehyde as aldehydes. Using different physical and analytical techniques the prepared organic Schiff base ligands (SL_1, SL_2, SL_3 and SL_4) were characterized proper isolation and purification. Ligands obtained were of good yield, stable at room temperature and were colored solids. The organic ligands were soluble in hot ethanol, chloroform and DMF.

Elemental analysis was performed to confirm the proposed structure of the ligands and observations were supporting the proposed structure. In addition, the structures and molecular weights of the synthesized Schiff base ligands were confirmed by recording the mass spectrum. For the ligand SL_1 ($C_{15}H_{13}NO_4$) the observed peak at 272.0 which is equivalent to the calculated M. Wt. (271). For SL_2 ($C_{12}H_9NO_3$) the peak observed at 215.92 and the calculated M. Wt. is (215), for SL_3 ($C_{14}H_{11}NO_3$) the peak observed at 242.00 and the calculated M. Wt. is (241), and finally for SL_4 ($C_{14}H_{10}N_2O_4$) the peak was observed at 270.92 that is equivalent to the calculated M. Wt. (270). The mass spectra for all prepared Schiff bases were identical with their calculated molecular weights. This proves and confirms the proposed structures for the synthesized Schiff base ligands.

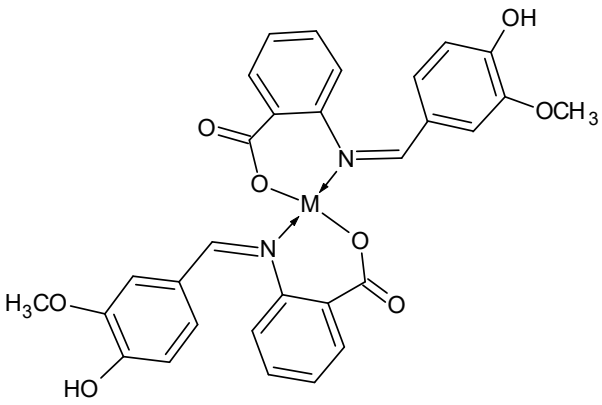
3.2. Synthesis of Metal Complexes

The targeted mononuclear Cu(II), Ni(II)and Zn(II) metal complexes were successfully synthesized using synthesized bidentate azomethine ligands following the standard reported template procedure as mentioned in the materials and methods section. The obtained metal complexes were colored solids, stable at room temperature and non-hygroscopic. They were insoluble in common organic solvents and only soluble in DMF and DMSO solvents. All synthesized complexes decomposed without melting at temperatures higher than 300 °C. The elemental analysis of the Schiff base complexes are given in table (1).

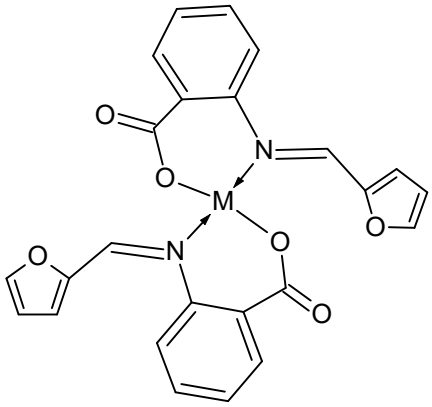
All prepared Schiff base ligands were bidentate that can coordinate to metal ions through nitrogen atom of the azomethine group and through the phenolic oxygen atom of the carboxylic group. Accordingly, the proposed structures for the synthesized Cu(II), Ni(II) and Zn(II) complexes are depicted in structures 1. The metal complexes were characterized using micro-elemental analysis, mass spectra, UV-visible, IR, NMR and Magnetic susceptibility techniques to prove the proposed structures and geometries.

Table 1: Elemental analysis of the Schiff base Complexes

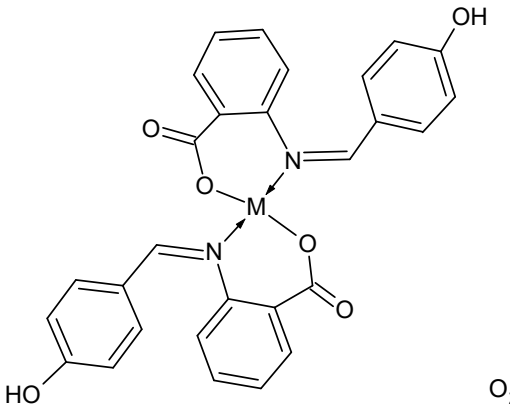
Ligand	Elemental Analysis				
	% C Calculated (found)	% H Calculated (found)	% N Calculated (found)	% O Calculated (found)	% of metal Calculated (found)
$[Cu (SL_1)_2]$	59.64 (60.00)	4.00 (3.86)	4.63 (4.60)	21.18 (21.36)	10.55 (10.20)
$[Ni (SL_1)_2]$	60.13 (59.90)	4.03 (4.52)	4.67 (4.45)	21.35 (21.69)	9.82 (10.06)
$[Zn (SL_1)_2]$	59.46 (60.02)	3.99 (4.23)	4.62 (4.58)	21.12 (21.31)	10.81 (10.80)
$[Cu (SL_2)_2]$	58.59 (59.02)	3.27 (3.24)	5.69 (5.90)	19.51 (19.05)	12.94 (13.35)
$[Ni (SL_2)_2]$	59.18 (59.55)	3.31 (3.63)	5.75 (5.52)	19.70 (19.33)	12.06 (12.00)
$[Zn (SL_2)_2]$	58.37 (58.00)	3.26 (3.73)	5.67 (5.42)	19.43 (19.66)	13.27 (13.42)
$[Cu (SL_3)_2]$	61.81 (61.44)	3.70 (3.72)	5.14 (4.86)	17.64 (17.97)	11.71 (12.04)
$[Ni (SL_3)_2]$	62.37 (62.30)	3.73 (3.89)	5.19 (5.57)	17.80 (17.31)	10.91 (11.27)
$[Zn (SL_3)_2]$	61.60 (61.20)	3.69 (3.97)	5.13 (5.62)	17.58 (17.22)	12.00 (12.44)
$[Cu (SL_4)_2]$	56.05 (55.82))	2.68 (3.02)	9.33 (9.63)	21.33 (22.00)	10.61 (11.06)
$[Ni (SL_4)_2]$	56.50 (56.01)	2.70 (3.12)	9.41 (9.87)	21.50 (20.96)	9.89 (10.17)
$[Zn (SL_4)_2]$	55.87 (55.36)	2.67 (3.02)	9.30 (9.11)	21.26 (21.58)	10.90 (11.05)



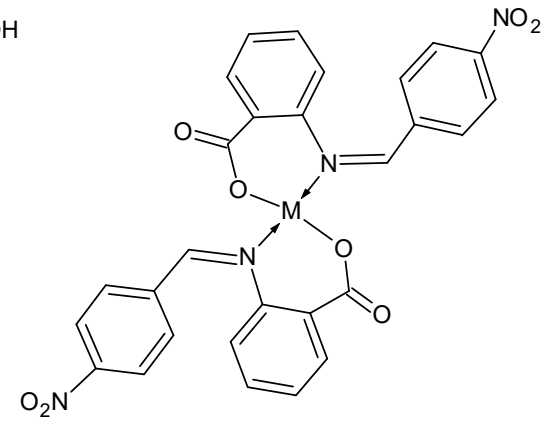
$[M(SL_1)_2]$



$[M(SL_2)_2]$



$[M(SL_3)_2]$



$[M(SL_4)_2]$

Structure 1: M = Cu, Ni, Zn

The elemental analysis (table 1) is in agreement with the proposed structures of the complexes. In addition, the mass spectra of the synthesized complexes were

carried out to determine and confirm the molecular weights. The observed mass spectra of $[Cu(SL_1)_2]$ ($CuC_{30}H_{24}N_2O_8$) is 603.79 (calculated M. Wt. = 604), the observed peak for $[Ni(SL_2)_2]$ ($NiC_{24}H_{16}N_2O_6$) was at 487.56 (calculated M. Wt. = 487). The observed mass spectra for $[Ni(SL_3)_2]$ ($NiC_{28}H_{20}N_2O_6$) and $[Cu(SL_4)_2]$ ($CuC_{28}H_{16}N_4O_8$) were 538.0 and 600.14 respectively (calculated M. Wt. = 539.17 and 600.0 respectively). These mass spectrum observations confirm and support the proposed structure for these complexes. Typical representative mass spectra of some synthesized metal complexes are shown in figures (1-2).

All ligands interact with the bivalent metals Cu, Ni and Zn atoms to form mononuclear complexes. The ligands behave as bidentate towards Cu(II), Ni(II) and Zn(II) and binding through the usual nitrogen donor atoms of the azomethine group and the oxygen atom of the carboxylic group forming square planer geometry around the metal atom (figure 3).

The elemental analysis data (table 1) indicated that the stoichiometric reaction ratio of the bidentate ligands (SL_1, SL_2, SL_3 and SL_4) with the bivalent metal atom is (2:1) L:Mmolar ratio to form tetra-coordinate monomeric Cu(II), Ni(II) and Zn (II) complexes (shown in structure 1), corresponding to the complexes general formula $[M(SL)_2]$. The coordinated atoms of the ligand are symmetrically arranged around the central metal atom in the complexes.

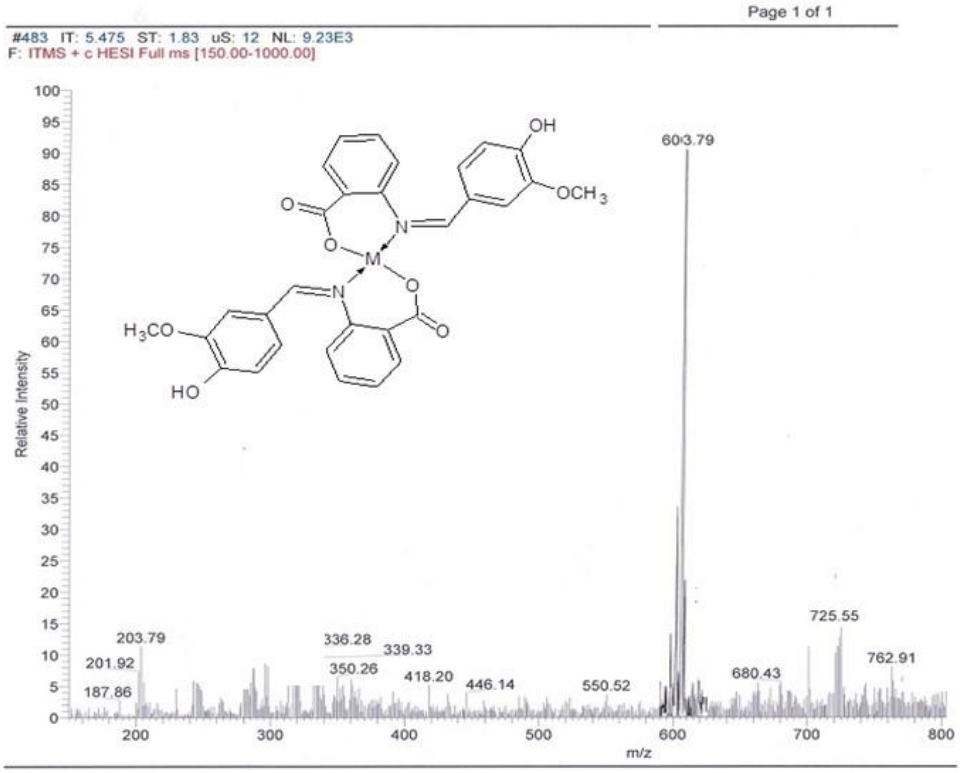


Figure 1: Mass spectra for $[Cu(SL_1)_2]$ ($CuC_{30}H_{24}N_2O_8$) complex

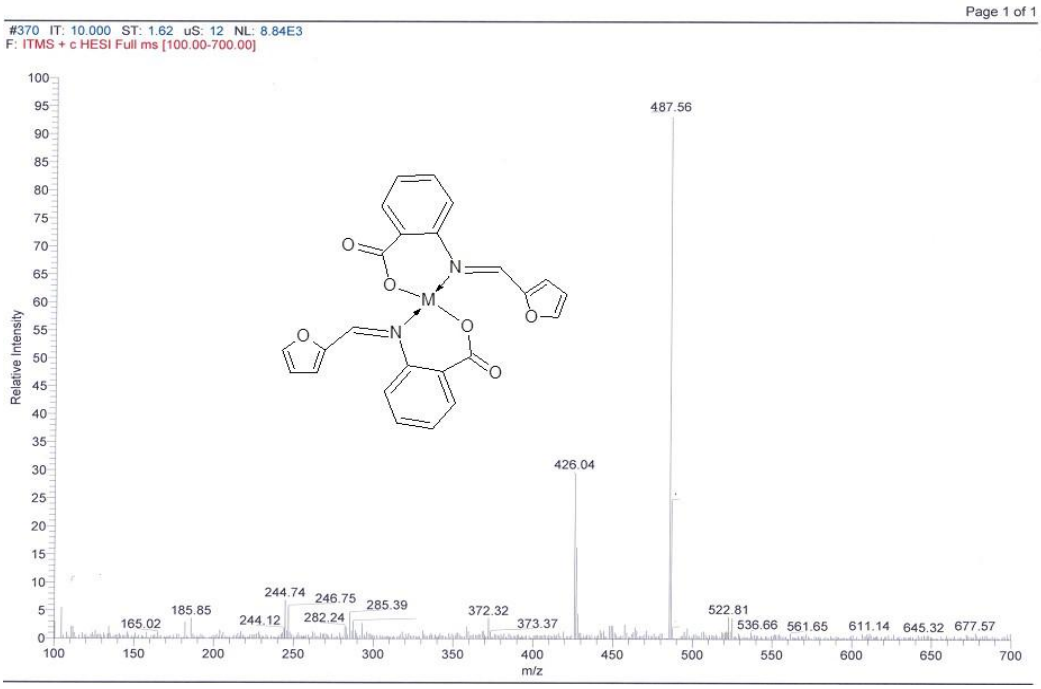


Figure 2: Mass spectra for $[Ni(SL_2)_2]$ ($NiC_{24}H_{16}N_2O_6$) complex

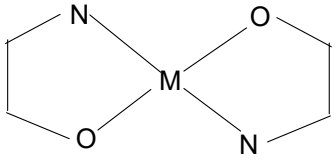


Figure 3: Square planer geometry

3.3. UV-visible Spectra and Magnetic Susceptibility measurements

The UV-visible spectral data are used to study the geometry of the prepared metal complexes. The UV-vis absorption spectra were recorded in DMSO solution (10^{-3}) for the ligands and their Cu(II), Ni(II) and Zn(II) complexes in the range of 200-800 nm at room temperature. The electronic spectra of the synthesized bidentate ligands obtained by the condensation of the different aldehydes with 2-aminobenzoic acid are nearly similar. Upon coordination with metal ions, the absorption bands of the corresponding metal complexes were observed somewhat shifted to longer wavelength with low frequency (red shift) (i.e. positive solvatochromism).

The bands at around 340 - 365 nm were observed in the UV-vis spectra of the Ligands SL_1, SL_2, SL_3, and SL_4 can be assigned to $n\rightarrow\pi^*$ transitions of the azomethine group [24]. Some bands in the spectra of the free ligands were shown at lower energy in the range of 260-280 nm may be attributed to $n\rightarrow\pi^*$ transitions due to conjugation of π bond in the benzene ring [25]. While the bands appeared at higher energies are attributed to $\pi\rightarrow\pi^*$ of the benzene ring and CH=N group. These bands were shifted (red shift) in the spectra of the corresponding metal complexes with

some changes in frequencies and intensities indicating the coordination of the ligands to the metal atoms and the participation of nitrogen atom of the CH=N group and the oxygen atom of the phenolic group in bonding with metal atom centre [2].

The spectra of some Cu(II), Ni(II) and Zn(II) complexes compared to those of the free ligands show that the bands appear at lower intensities and shifted to longer wavelength (batho-chromic effect) due to coordination with metal ions [26-27]. The weak band shoulder observed in the range of 440-465 nm in the spectra of complexes may be assigned to metal-ligand charge transfer (MLCT) transitions that expected for complexes of metals with low oxidation state [24]. In the transition metal complexes due to coordination with ligands, there is a change in electron distribution between the metal and the ligand resulting in charge transfer bands.

In addition, two bands appearing at 380–395 and 420–460 nm may be assigned to d–d transition of the single d electron of the metal ion suggesting the four-coordinated geometry for the metal complexes [26].

When the UV spectra of the complexes compared with that of free ligands we noticed the $n\rightarrow\pi^*$ absorption bands of the organic ligands (due to azomethine) shifted to longer wave length with lower intensity on coordination with metal atoms confirming the coordination of the nitrogen atom of the azomethine group [24].

The monomeric nature of the Cu(II), Ni(II) and Zn(II) complexes with Schiff base ligands and their geometry were supported by the magnetic susceptibility values obtained. At room temperature the μ_{eff} values for some Ni(II) complexes showed diamagnetic nature that implies the presence of square planar geometry around the Nickel metal ion in case of coordination with the bidentate Schiff base ligands [28]. Similarly the μ_{eff} values for Cu(II) complexes at room temperature found in the range of 1.82-1.85 BM which is less than 1.90 and is close to 1.73 BM the spin-only value [29]. This implies the presence of square planar geometry around the copper metal ion in case of bidentate ligands [30-31]. In case of Zn complexes, the tetrahedral geometry is preferred; this was supported by the diamagnetic nature and the non-electrolytic behavior observations for zinc complexes.

In conclusion the metal ions Cu, Ni and Zn form four-coordinate complexes of the type $[M(SL_n)_2]$ with the bidentate ligands and the spectral and magnetic data indicating square-planar geometry for copper and nickel complexes and tetrahedral geometry for zinc complexes.

3.4. FT-IR Spectra

In order to locate the coordination sites that may connect the ligands with the metal

ions in chelation process we recorded FT-IR spectra for both free ligands and their prepared metal complexes. The IR spectra for the free ligands and their complexes were nearly similar. It is well known that the bands position and peak intensities are expected to be amended on coordination. On comparing the observed IR bands of the free ligands with the corresponding metal complexes we noticed some shift in the band position and change in intensity. In the FT-IR spectrum of free ligands a strong band appeared in the range of 1580-1615 cm^{-1}which is specific to the stretching vibrations of the azomethine (-CH=N-) linkage band [32]. It was observed that this band was shifted to lower frequency by 5 to 16 cm^{-1} in the IR spectra of the corresponding metal complexes. This can be explained on the basis of coordination due to the donation of the electrons from nitrogen atom of the -CH=N- group to the metal atom [6, 19]. This supports the suggestion of coordination of the N atom of the azomethine group with the metal ion [6, 32-33]. The bands of the asymmetric and symmetric νCOOH stretching vibrations were observed in the range of (1550-1560) and (1390 – 1430) cm^{-1} of the free ligands [34-35]. A lower shift in these frequencies by nearly 10 to 20 cm^{-1} range. This can be explained due to the participation of the oxygen atom of the carboxylic group in bonding formation with metal atom in complexes. The monodentate binding nature of the carboxylic group was indicated by the large difference in the asymmetric νCOOH and symmetric νCOOH bands observed in the IR spectra of the metal complexes [35]. The formation of M-O bond was confirmed by observing the absence (in IR spectra of the complexes) of the stretching vibrations of the OH of the carboxylic group bands appeared in the range 2900 - 2965 cm^{-1}in the IR spectra of the free ligands and losing the proton of the COOH group [32]. Moreover, new bands in the IR spectra of the metal complexes appeared in the range of 515 – 550 (or 470-520) cm^{-1} may assigned to (νM-O) band vibrations and 410-460 cm^{-1} may be assigned to (νM-N) band vibrations [6, 35-36]. These bands support the formation of M-O and M-N bonds respectively on complexation with metal atoms [6]. These bands were not observed in the spectra of the ligands, which proves the coordination of the metal ions with oxygen atom of the carboxylic group and azomethine nitrogen of -CH=N- group.

Therefore, the IR spectra reveal that the ligands act as bidentate molecules and coordinate to the metal ions via oxygen atom of the carboxylic group and nitrogen atom of the azomethine group. These IR spectral data are in accord to the proposed

structures of the ligands and their corresponding complexes.

3.5. ^{1}H NMR Spectroscopy

The ^{1}H NMR spectra of the prepared ligands carried out for some compounds and chemical shifts for signals were observed. The sharp singlet around 7.21-7.65 ppm appeared in the spectrum of the ligands may be due to the azomethine protons (CH=N) and confirms its formation [19, 26-27]. The free ligands exhibit a characteristic singlet signal at range of δ 8.47 -8.90 ppm that is assignable to carboxylic (COOH) group [16, 38]. This singlet disappeared in the spectrum of the corresponding metal complexes supporting the involvement of carboxylic group of the anthranilic acid in coordination through the displacement of COOH proton [16]. The phenyl multiple of the ligands was shown at a range of 6.49-6.92 ppm [19]. A signal at δ 3.846 ppm was observed in the spectrum of the ligand SL_1 which may attributed to methoxy (-OCH_3) group [37].

3.6. *Molar conductivity of metal complexes*

The conductivity nature for the prepared Cu(II), Ni(II) and Zn(II) complexes were examined in DMSO (10^{-3} M) solution at room temperature 23.8 °C. The molar conductivity measurements showed very low values in the range 2.06 - 3.49 $S.cm^2.mol^{-1}$suggesting non-electrolytic nature of the metal complexes and hence they are non-ionic and no charged ions present outside the coordination sphere of the metal complexes [6, 32].

3.7 Biological Assessment/ Investigation

3.7.1 Antibacterial and antifungal activities

The synthesized ligands and their complexes were assessed for antimicrobial behavior utilizing two Gram-positive and two Gram-negative bacterial strains and one fungal strain using agar disc-diffusion assay and the estimation of activity was done by measuring the zones of complete inhibition (in mm) around the holes after the incubation period. Each experiment was repeated twice, and the arithmetic mean values of the duplicate measurements were recorded (table 2).

Table 2: microbial activity of the free ligands and their metal complexes

Compound	Zone of inhibition (mm)				
	Gram-positive bacteria		Gram-negative bacteria		Fungus
	Streptococcus pneumoniae	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia Coli*	*C. albicans*
SL_1	9.6	9.4	R	R	10.0
SL_2	15.6	12.2	R	R	11.6
SL_3	8.2	7.8	R	R	10.2
SL_4	14.8	12.8	R	R	16.4
$[Cu (SL_1)_2]$	9.2	8.6	R	R	10.8
$[Ni (SL_1)_2]$	10.4	10.2	R	R	13.5
$[Zn (SL_1)_2]$	12.3	11.2	R	R	15.6
$[Cu (SL_2)_2]$	12.1	11.0	R	R	14.2
$[Ni (SL_2)_2]$	13.2	11.6	R	R	14.3

$[Zn(SL_2)_2]$	**20.4**	**16.6**	**6.8**	**5.2**	**22.7**
$[Zn(SL_3)_2]$	**16.2**	**12.5**	**R**	**R**	**18.2**
$[Cu(SL_4)_2]$	**14.6**	**12.2**	**R**	**R**	**16.3**
$[Ni(SL_4)_2]$	**15.0**	**13.5**	**R**	**R**	**14.8**
$[Zn(SL_4)_2]$	**30.2**	**22.6**	**4.6**	**6.8**	**22.8**

***** Key to interpretation*: *R = Resistant, less than 10 mm = inactive, 10–15 mm = weakly active, 15–20 mm = moderately active; more than 20 mm = highly active.***

The tested organic ligands (SL_1, and SL_3) showed inactivity against the Gram-positive bacteria with zones of inhibitions < 10 mm), While the ligands (SL_2 and SL_4) showed weak activity with zones of inhibition between (11.6-14.8 mm) against both Gram-positive bacterial strains *S. pneumonia* and *S. aureus*. The weakly active ligands have hetrocyclic moiety (i.e furan ring) and nitro group substituent in addition to the azomethine (-CH=N -) and COOH groups that may enhanced the activity of these ligands a little more than other ligands. The examined ligand compounds did not show any effect against the Gram-negative bacteria, which showed resistance to these compounds. The antifungal test for the prepared ligand compounds exhibit week influence on the growth of the fungal strain *C. albicans* with a diameter of inhibition zones range between 10.0 -16.4 mm.

On chelation and formation of metal complexes there were remarkable enhancement in the activity against the Gram-positive bacterial species *S. pneumoniae* and *S. aureus* under the same conditions. The inhibition zones for metal complexes were in the range of (9.2– 30.2 mm) against *S. pneumonia* and (8.6-22.6 mm) against *S. aureus* bacterial strains. Similarly on chelation, the antifungal activity was increased and the inhibition zones were in the range of (10.8-22.8 mm) against *C albicans* fungal strains. This activity enhancement might be because of the influence of the bivalent metal ion of the complexes. Moreover, this enhancement in the activity can be explained based on Tweedy's chelation theory and the effect of the metal ion on the normal cell processes [20, 24]. On chelation the polarity of the metal ions is reduced due to the partial sharing of the positive charge with the donor atoms of the ligands. This will result in delocalization of π-electrons within the entire chelate ring system formed during coordination, which increase the lipophilic character of the central metal atom and hence increase the liposolubility of the metal chelates and enhances the penetration through the lipid layers of the microbial cell membranes [6, 39]. Moreover, may be the hydrogen bond that may formed through the N atom of the -CH=N- group with the cell constituents brings about obtrusion with the normal cell process [36, 40].

The bacterial strains S. *pneumoniae* was more susceptible to metal complexes

compared to *S. aureus* the Gram-positive bacteria. This may be due to the difference in cell wall structure of these microorganisms [36]. Moreover, the metal complexes in general have better antifungal activity compared to the antibacterial activity. This difference in the activity may be due to the impearmeability of the cells of the microbes or may be due to the difference in riboisomes of the microbial cells [36, 40].

Zn(II) metal complexes with Zn metal ion showed higher antibacterial and antifungal activity compared with other analogous Cu(II) and Ni(II) complexes. This may be attributed to higher stability constant of Zn(II) complexes compared to other Cu(II) and Ni(II) complexes [40]. Therefore, the more effective factors that affect the antimicrobial activity are nature of the central metal atom and the substituents and moieties that present in the ligands. So the better antimicrobial activities of zinc complexes may be attributed to the zinc metal ion and presence of some active moieties like heterocyclic ring and nitro group along with the azomethine group in the ligands.

The observed antifungal test of showed that $[Zn(SL_2)_2]$ and $[Zn(SL_4)_2]$ were having highest zones of inhibition of 22.7 and 22.8 mm respectively, and the antibacterial test showed that the complex $[Zn(SL_4)_2]$ was having the highest zone of inhibition (30.2 mm) against the bacterial strains, S. *pneumoniae*. These observations encourage us to investigate the minimum inhibitory concentration (MIC) to quantify the lowest concentration of the tested chemicals.

The MIC investigation was carried out by screening the complexes showed highest potency against S. *pneumonia* bacterial strains and *C. albicans* as fungal strains using Agar disc-dilution assay according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. Mueller-Hinton agar was used as growing medium. Solutions of 100, 50, 25, 12.5, 6.25 and 3.125 µg/disc were used for the MIC investigations. The highest potency exhibited by the complex $[Zn(SL_4)_2]$ was observed against S. *pneumonia* bacterial strains with MIC value of 25µg/disc.

3.7.2 Molluscicidal Activity

Selected ligands (SL_2 and SL_4) and their corresponding metal complexes ($[Zn(SL_2)_2]$ and $[Zn(SL_4)_2]$) were tested for their molluscicidal activity against one land snail *Eobania vermiculata* (*E. vermiculata*). The Toxicity and lethal dose (LD_{50}) was determined for the tested compounds according to WHO guidelines using immersion technique and using niclosamide as positive control [27]. The mortality of the tested snails were determined after 24 hours of exposure in working solution with

different concentrations of 0.1, 0.2, 0.3, 0.4, 0.5 mg/L of the tested compounds. Each molluscicidal experiment was repeated in duplicate (due to limited sources of experiments) for each compound and dose effect evaluation was done using Leitchfield and Wilcoxon method [41].

The observations indicate that the ligands and their complexes did not show any activity at concentrations below 0.3 mg/L. The complexes showed good activity at concentration of 0.45 mg/L and the complex **[**$Zn(SL_2)_2$] showed highest activity that can be interpreted might be due to the presence of heterocyclic moiety in these compounds. It is also noted that the complexes are more active than their parent ligands, which may be explained because of the presence of metal ion that may enhance the molluscidal activity. The LC_{50} of the complexes was at concentration of 0.45 mg/L, while the LC_{50} of the ligands was at higher concentrations of 0.6 mg/L.

CONCLUSION

In the present work we synthesized some bidentateSchiff base ligands from 2-amino benzoic acid as primary amine which was condensed with different substituted aromatic aldehydes. These ligands were used to synthesize Cu(II), Ni(II) and Zn(II) complexes. The ligands and their complexes were characterized using different spectroscopic, physical and physicochemical techniques.

The results showed that the first type of bidentate ligands reacted with the bivalent metal ions forming symmetrical square planar complexes with 2:1 (L : M) reaction stoichiometric ratio. These ligands were coordinated through oxygen of the OH carboxylic group and the nitrogen atom of the azomethine group. The proposed structures of the prepared copper and nickel and zinc complexes were consistent with the chemical, physical, spectroscopic data and thermal analysis.

The synthesized ligands and their corresponding complexes were examined for their antibacterial and antifungal susceptibility. Ligands SL_1, and SL_3 showed inactivity against the Gram-positive bacteria with zones of inhibitions (< 10 mm), While the ligands SL_2 and SL_4 showed weak activity with zones of inhibition between (11.6-14.8 mm) against both gram positive bacterial strains *S. pneumonia* and *S. aureus*. The examined ligand compounds did not show any effect against the Gram-negative bacteria, which showed resistance to these compounds. The antifungal test for the prepared ligand compounds exhibit week influence on the growth of the fungal strain *C. albicans* with zone of inhibition range between 10.0 -16.4 mm.

The metal complexes showed remarkable enhancement in the activity under the same conditions. The Zn(II)

metal complexes show higher antibacterial and antifungal activity compared with other analogous Cu(II) and Ni(II) complexes. Complexes $[Zn(SL_2)_2]$ and $[Zn(SL_4)_2]$ showed 22.7 and 22.8 mm zones of inhibitions respectively against *C. albicans* fungus. Moreover, the antibacterial test showed the complex $[Zn(SL_4)_2]$ exhibit highest zone of inhibition of 30.2 mm against the bacterial strains, S. *pneumoniae*.

The MIC investigation was carried out by screening selected complexes that have highest activity against S. *pneumonia* bacterial strains and *C. albicans* as fungal strains. The highest potency exhibited by the complex $[Zn(SL_4)_2]$ was shown against S. *pneumonia* bacterial strains with MIC values of 25µg/disc.

The molluscicidal activity tests against the land snail *E. vermiculata* indicated that the ligands and their complexes did not show any activity at concentrations below 0.3 mg/L. The complexes showed good activity at concentration of 0.45 mg/L and the complex $[Zn(SL_2)_2]$ showed highest activity. It is also noted that the complexes were more active than their parent ligands, which may be explained because of the presence of metal ion that may enhance the molluscidal activity.

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