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# ANTIMICROBIAL EFFECT OF SOME ORGANOTIN (IV) DERIVATIVED OF PROPAN-1, 3-DIOIC ACID

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## ABSTRACT

Three organotin (IV) derivatives of propan-1,3-dioic acid; potassium dibutyltin(IV)propan-1;3-dioate **(1),** potassium diphenltin(IV)propan-1;3-dioate **(2),** and potassium triphenltin(IV)propan-1,3-dioate **(3)** were synthesized mechanochemically. KOH was ground with propan-1,3-dioic acid to give the ligand **L:** potassium propan-1,3-dioate, followed by complexation of the ligand, **L** with $Bu_2SnO$, $Ph_2SnO$ and $Ph_3SnOH$ separately. Characterization of the ligand and complexes was done using magnetic susceptibility and Scanning Electron Microscopy (SEM). Ligand and complexes were screened for antimicrobial activity against five strains of gram-positive bacteria: *Methicillin Resist Staph aureus, Vancomycin Resist enterococci, Staphylococcus aureus, Streptococcus pyogenes* and *Bacillus cereus* and five fungi strains: *Aspergillus fumigatus, Aspergillus flavus, Aspergillus nigre, Fusarium oxysporum* and *Fusarium proliferatum.* Ciproflxacin and Ketoconazole were used as controlled drugs. Magnetic susceptibility data revealed complexes **(1), (2)** and **(3)** to be paramagnetic with values 0.144 *μeff,* 0.149 *μeff* and 0.151 *μeff,* respectively. SEM revealed that complex **(3)** pores were better filled by metals than complex **(1)** during complexation of parent organotin (IV) compound with the ligand, **L**. Antimicrobial result showed that the complexes synthesized in general exhibited significant activity (20-27 mm) against the microbes at the minimum inhibition concentrations (MIC) in the range 2.5 - 5 µg/mL (gram-positive bacteria) and 5 µg/mL (fungi) and minimum bactericidal/fungicidal concentrations (MBC/MFC) of 5 - 20 µg/mL/10 - 20 µg/mL. The complexes and ligand showed better antimicrobial effect against test microbes at than the control drugs. These complexes hold promise as antibacterial and antifungal agents that may be used as metal-base drugs/formulations.

**Keywords:** Mechanochemical synthesis, Characterization, Antibacterial and Antifungal effect, potassium Organotin (IV) Complexes.

## INTRODUCTION

The application of organotin (IV) compounds as antibacterial agents on microorganisms is traced back to the 20's decades. However, the use of this class of compounds as medicines only surfaced in the 50's decade [1]. The significant effect of organotin compounds on biological activity makes them interesting compounds [2] and their chemistry are of continuous interest due to their structural features, and potentials as biocides, homogenous catalysts, anti-fouling agents [3] anti-inflammatory and antioxidants [1]. The first organotin (IV) compound was successfully isolated in 1850s, but did not gain any form of significance in industrial applications until



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almost about one hundred years later as reported by Blunden *et al*., [4].

The vast use of organotin (IV) complexes in industries as well as its biological properties against bacterial, fungal and cancer cells lines [5, 6] made their study to receive considerable attention [6 and 7]. They find application in agriculture [8] and are known for their biomedical and commercial applications [7, 9] reported the anti-tumour activity of organotin (IV) compounds. Organotin (IV) carboxylates have also been widely studied due to their structural diversity and pharmaceutical applications [3] as antitumor and anti-tuberculosis agents [5, 10]. Other applications of organotin (IV) carboxylates include their use in the synthesis of polyesters and polyurethanes [11]. They exhibit a number of interesting structural features due to the tendency of the anionic groups to coordinate inter or intramolecularly [2, 12].

According to Saga and Yamaguchi, [13], antimicrobial chemotherapy has conferred huge benefits on human health in the 20th century, making remarkable advances resulting in the optimistic view that infectious diseases would be conquered in the near future. However, microorganisms have been reported to acquire resistance to drugs through a variety of mechanisms thereby continue to plague humanity [13]. Microorganisms' resistance is their survival strategy in response to man's activity in sacrificing them ignoring the fact that they are part of the biosphere and serve an important role in the maintenance and sustainability of ecosystems, comprising about 50% of the living biomass [7] due to their harmful effects. Increasing microorganism's resistances to drug is a global threat [14]. Jubeh *et al*., [15] reported that "the rise of multidrug-resistant bacteria has generated a great challenge in treating infections caused by bacteria with the available antibiotics/drugs". World Health Organization (WHO), categorized pathogens/multidrug-resistant bacteria as critical, high, and medium antibiotic-resistant bacteria that need urgent research in order to develop new antibacterial agents/drugs for treatments. Amongst the pathogens are the Gram-positive bacteria which cause serious infections and are of major concern and a health care problem. Multidrug-resistant bacteria like methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium* and β-lactamase-resistant *Streptococcus pneumonia* [15 and 16] are examples. There is therefore need in finding new treatments for multidrug-resistant pathogens. Thus, the need for continuous research globally.

In an attempt to further explore the interesting features of organotin (IV) compounds, we report here the antimicrobial effects of three mechanochemically synthesized organotin (IV) derivatives of propan-1,3-dioic acid against gram-positive bacteria and fungi to evaluate their potentials as an alternative route/drugs for combating microbes that confronts man and his environment negatively causing ailments. This is



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to further expound on our earlier reported works [17].

## MATERIALS AND METHODS

### *Reagents*

All reagents used for the preparation of the ligand and complexes were of analytical grade, purchased from Sigma-Aldrich with purity ranging from 95 - 99.8 % and used without further purification.

### *Synthesis of Ligand L: $HCOOCH_2COOK$ (potassium propan-1,3-dioate)*

The ligand was prepared by neutralization reaction according to the method in our earlier report [17]. Propan-1,3-dioic acid: $HCOOCH_2COOH$ (5.255g, 0.05 mol) and Potassium Hydroxide: KOH (2.833g, 0.05 mol) were ground in an agate mortar with a pestle for 10 minutes yielding 90.24 % white solid crystals which were collected and stored in a desiccator for further analysis.

### Synthesis of potassium dibutyltin(IV) propan-1,3-dioate: $Bu_2Sn(OCOCH_2COOK)_2$ (1) and potassium diphenyltin(IV) propan-1,3-dioate: $Ph_2SnOCOCH_2COOK$, (2)

$Bu_2Sn(OCOCH_2COOK)_2$ : **(1)** was prepared as earlier reported [17]. The ligand, **L**, $HCOOCH_2COOK$ (1.510 g, 0.05 mol) and Dibutyltin (IV) oxide: $Bu_2SnO$ (1.310 g, 0.05 mol) were weighed and poured into an agate mortar and ground with a pestle [18] for 15 minutes. White solid crystals were collected as the product and kept in a desiccator for further analysis.

Similarly, $Ph_2Sn(OCOCH_2COOK)_2$, **(2)** was synthesized by grinding $HCOOCH_2COOK$, **L** (1.510g, 0.05 mol) and $Ph_2SnO$ (1.541g, 0.05 mol) in an agate mortar with a pestle for 15 minutes. A white solid crystal was obtained and kept in a desiccator until further use.

### *Synthesis of potassium triphenyltin(IV) propan-1,3-dioate: $Ph_3SnOCOCH_2COOK$ (3)*

Triphenyltin (IV) propan-1,3-dioate was synthesized by the reaction between $Ph_3SnOH$ (3.875g, 0.05 mol) and **L**, $HCOOCH_2COOK$ (1.510g, 0.05 mol) according to our earlier report [17, 18]: grinding in an agate mortar with a pestle for 15 minutes. The resulting solid was collected as the product and kept in a desiccator for further analysis.

### *Characterization*

The synthesized ligand and complexes were characterized using Scanning Electron Microscopy (SEM) and Magnetic Susceptibility Measurement. Our earlier work reported the solubility test, melting point determination and Fourier Transformed Infrared (FTIR) data of the complexes and ligand [17].

### *Antimicrobial Effect*

The antimicrobial effect of the synthesized compounds was tested on five gram-positive bacteria strains: (*Methicillin Resist Staph aureus, Vancomycin Resist enterococci, Staphylococcus aureus, Streptococcus pyogenes* and *Bacillus*



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*cereus)* and five fungi strains: (*Aspergillus fumigatus, Aspergillus flavus, Aspergillus nigre, Fusarium oxysporum* and *Fusarium proliferatum).*

Clinical isolates of the microbes used were obtained from Institute for Agricultural Research (I.A.R) as well as Veterinary Medicine and Medicinal Microbiological Department, Ahmadu Bello University Teaching Hospital, Zaria.

***Agar Well Diffusion Technique***

Agar well diffusion method as reported in our previous [17] was adopted for determination of antimicrobial activity of the synthesized ligand and organotin (IV) compounds. Sabouraud dextrose agar (SDA) and Mueller Hinton agar were used as culture media for fungi and bacteria respectively. They were prepared according to manufacturer's instructions, sterilized at 121 $^0$C for 15 minutes, poured into sterile petri dishes under an aseptic hood and allowed to cool and solidify. The sterile media were seeded with 0.1 mL of standard inoculums of the test microbes and spread evenly over the surfaces of the media using a sterile swab. A well was cut at the Centre of each inoculated medium using a standard cork borer of 6 mm diameter and 20 µg/mL of the test compounds dissolved in DMSO were introduced into their respective wells. Other wells supplemented with erythromycin and fluconazole as control drugs for bacteria and fungi, respectively. The media were incubated at 30 $^0$C for 7 days and at 37 $^0$C for 24 hours for the fungi and bacteria respectively. The media were checked daily for inhibition zones [19 - 21].

***Broth Dilution Method***

Broth dilution method was adopted for Minimum Inhibition Concentration (MIC) and Minimum Batericidal/Fugicidal Concentration (MBC/MFC). Sabouraud dextrose agar (SDA) was prepared according to standard, poured in test tubes sterilized at 121 0C for 15 minutes and allowed to cool.Serial dilution of the ligand and organotin compounds in sterile broth was made to obtain the concentrations of 20 µg/mL, 10 µg/mL, 5 µg/mL, 2.5 µ/mL and 1.25 µg/mL. 1.5 × 105 CFU/mL of test bacteria and fungi in normal saline was made, introduced into each of the concentrations and incubated at 30 $^0$C for 7 days. Test tubes were observed for turbidity (growth) and the lowest concentration of a compound in the broth which showed no turbidity was recorded as minimum inhibition concentration. To further ascertain whether the test bacteria and fungi were killed completely or their growth only inhibited, MBC and MFC were determined. Contents of MIC in the serial dilution were sub cultured onto prepared medium and incubated at 30 $^0$C for 48 hours (bacteria) and 7 days (fungi). Plates were observed for colony growth. MFC was the plate with lowest concentration of compound without colony growth [22].



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## RESULTS AND DISCUSSION

Ligand was prepare by neutralization reaction according to Equation 1, with the percentage yield of 90.24 % (Table 1)

$KOH + HCOOCH_2COOH \xrightarrow{\text{Grinding}} HCOOCH_2COOK + H_2O$ (1)

Compounds **(1), (2)** and **(3)** synthesis occurred by the complexation of the ligand with the parent organotin compounds as shown in Equations (2), (3) and (4) respectively with the percentage yields of 98.55 %, 97.69 % and 98.00 %, respectively (Table 2).

$Bu_2SnO + 2HCOOCH_2COOK \xrightarrow{\text{Grinding}} Bu_2Sn(COOCH_2COOK)_2 + H_2O$ (2)

$Ph_2SnO + HCOOCH_2COOK \xrightarrow{\text{Grinding}} Ph_2Sn(COOCH_2COOK)_2 + H_2O$ (3)

$Ph_3SnOH + HCOOCH_2COOK \xrightarrow{\text{Grinding}} Ph_2SnCOOCH_2COOK + H_2O$ (4)

Where Bu is $C_4H_9$ and Ph is $C_6H_5$

**Table 1: Yield and Description of Ligand, L: $HCOOCH_2COOK$**

| S/N | Time (m) | Reacting mass of propanedioic acid (g) | Reacting mass of KOH (g) | Theoretical mass of Ligand (g) | Actual mass of Ligand (g) | Percentage yield (%) |
|---|---|---|---|---|---|---|
| **1** | 10 | 5.2550 | 2.8330 | 7.1700 | 6.4700 | 90.24 |

**Table 2: Yields and Description of the Synthesized Compounds: (1), (2) and (3)**

| **Compounds** | **Mass of Ligand:L (g)** | **Mass of Organotin(g)** | **Theoretical Yield (g)** | **Actual Yield (g)** | **Percentage Yield (%)** | **Colour of compound** |
|---|---|---|---|---|---|---|
| $Bu_2SnL_2$ **(1)** | 1.5100 | 1.3100**(A)** | 2.7192 | 2.6800 **(1)** | 98.55 **(1)** | White Crystals |
| $Ph_2SnL_2$ **(2)** | 1.5100 | 1.5410 **(B)** | 2.9646 | 2.8964 **(2)** | 97.69 **(2)** | White Crystals |
| $Ph_3SnL$ **(3)** | 1.5100 | 3.8750 **(C)** | 5.184 | 5.0840 **(3)** | 98.00 **(3)** | White Crystals |

Key: **L** =$HOCOCH_2COOK$ **(1)** = $Bu_2Sn(OCOCH_2COOK)_2$, **(2)** = $Ph_2Sn(OCOCH_2COOK)_2$, **(3)** = $Ph_3SnOCOCH_2COOK$, (**A)** = $Bu_2SnO$, **(B)** = $Ph_2SnO$ **(C)** = $Ph_3SnOH$,

The high percentage yields recorded using mechanochemical method for synthesis of both ligand and complexes collaborates the report by Dafa *et al*., [23] who enumerated high percentage



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yields of products as one of the several advantages of this method over the solvent method.

***Characterization***

Melting points, solubility and FTIR data of ligand and compounds have been reported in our previous work [17] which showed the stability and purity of the ligand and compounds. FTIR data indicated bidentate mode of coordination in the compounds and monodentate in the ligand. Complexation was confirmed to occur at the carbonyl carbon of the compounds and ligand.

***Magnetic Susceptibility Result***

The behavior of the compounds in magnetic field was determined using magnetic susceptibility at room temperature (Table 3). The data revealed compounds **(1), (2)** and **(3)** to be paramagnetic with values 0.144 *μeff,* 0.149 *μeff* and 0.151 *μeff,* respectively. Being paramagnetic implied that the compounds are weakly magnetic. This is in agreement with the report by Marcon and Ostanina [24] who spelt out magnetic susceptibility measurements of - $-1 < \chi m < 0$ to be diamagnetictic, $0 < \chi m \geq 1$: paramagnetic and $\chi m > 1$ as ferromagnetic. According to Gupta *et al*., [25] tin exhibits Pauli paramagnetism due to the absence of unpaired localized spin states.

**Table 3: Room Temperature Magnetic Susceptibility of Compounds**

| **Compounds** | | $\mu_{eff}$ **(B.M)** |
|---|---|---|
| $HOCOCH_2COOK$ | **L** | **-** |
| $Bu_2Sn(OCOCH_2COOK)_2$ | **(1)** | 0.154 |
| $Ph_2Sn(OCOCH_2COOK)_2$ | **(2)** | 0.149 |
| $Ph_3SnOCOCH_2COOK$ | **(3)** | 0.151 |

***Morphology of Compounds (SEM)***

The Scanning Electron Micrographs of $Bu_2Sn(OCOCH_2COOK)_2$ and $Ph_3SnOCOCH_2COOK$ are presented in Figure 1 and Figure 2, respectively. The surface morphology of complexes **(1)** and **(3)** were investigated using Scanning Electron Microscope (SEM). The images were recorded at 20 kV with magnification x 750 and x 3000 respectively. The micrograph of **(1)** and **(3)** revealed filled pores by the metal during complexation [26]. The pores sizes in both complexes are different, indicating that the complexes are different and may possess different properties. The result shows differences in particle shape and pore sizes as well.



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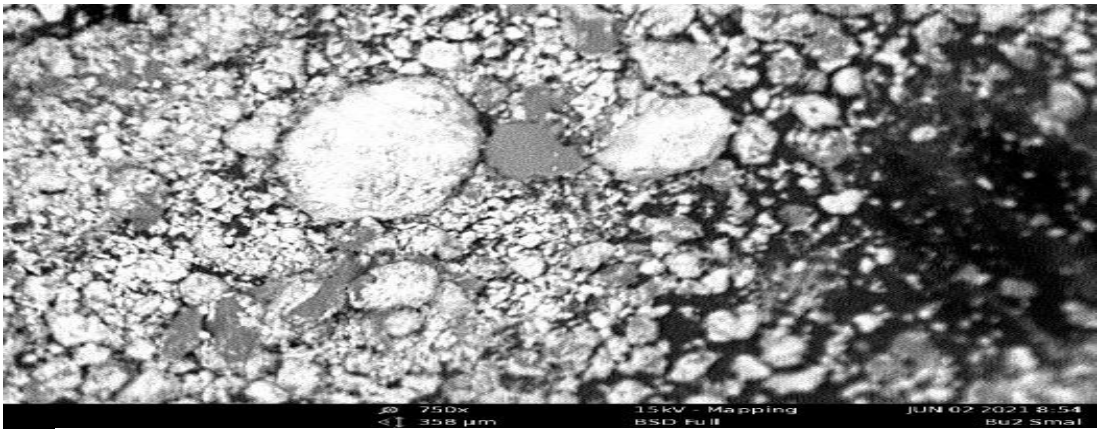


Figure 1, SEM micrographs of $Bu_2Sn(OCOCH_2COOK)_2$ at x750

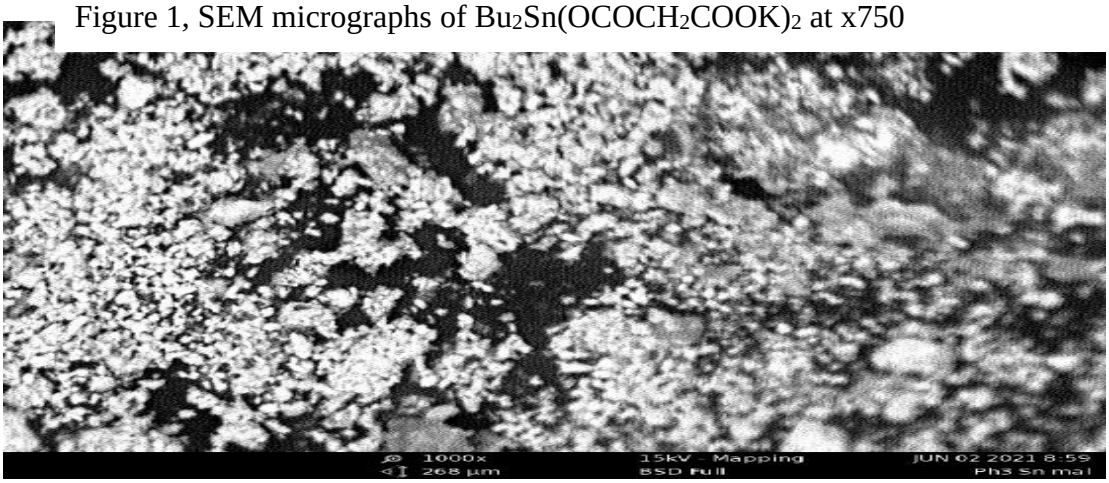


Figure 2: SEM micrographs of $Ph_3SnOCOCH_2COOK$ at 3000 Magnification

***Antibacterial Effect***

The antimicrobial effects of the L and complexes **(1), (2)** and (**3**) are shown in Tables 4-7, while that of the control drugs: ciprofloxacin (bacteria) and Ketoconazole (fungi) are shown in Table 8

**Table 4: Antimicrobial Activity of L: $HOCOCH_2COOK$**

| | **Effects** | **Zone of Inhibition (mm)** | MIC **(µg/mL)** | MBC/MFC **(µg/mL)** |
|---|---|---|---|---|
| *Methicillin Resist Staph aureus* | S | 24 | 10 | 10 |
| *Vancomycin Resist enterococci* | S | 22 | 20 | 20 |
| *Staphylococcus aureus* | S | 26 | 10 | 10 |
| *Streptococcus pyogenes* | R | 0 | - | - |
| *Bacillus cereus* | R | 0 | - | - |
| *Aspergillus fumigatus* | S | 21 | 10 | 20 |
| *Aspergillus flavus* | S | 24 | 5 | 10 |
| *Aspergillus nigre* | R | 0 | - | - |
| *Fusarium oxysporum* | S | 21 | 5 | 20 |
| *Fusarium proliferatum* | S | 23 | 5 | 20 |

**Key**: S = Sensitive, R = Resistant



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**Table 5: Antimicrobial Activity of (1): $Bu_2Sn(OCOCH_2COOK)_2$**

| **Test Organisms** | **Effects** | **Zone of Inhibition (mm)** | MIC (**µg/mL**) | MBC/MFC **(µg/mL)** |
|---|---|---|---|---|
| *Methicillin Resist Staph aureus* | S | 23 | 5 | 10 |
| *Vancomycin Resist enterococci* | S | 24 | 5 | 10 |
| *Staphylococcus aureus* | R | 0 | - | - |
| *Streptococcus pyogenes* | R | 0 | - | - |
| *Bacillus cereus* | S | 26 | 2.5 | 5 |
| *Aspergillus fumigatus* | S | 23 | 5 | 20 |
| *Aspergillus flavus* | S | 24 | 5 | 10 |
| *Aspergillus nigre* | R | 0 | - | - |
| *Fusarium oxysporum* | S | 25 | 5 | 10 |
| *Fusarium proliferatum* | R | 0 | - | - |

Key: S = sensitive, R = Resistant

The Ligand exhibited antibacterial effect against the gram-positive bacteria: *Methicillin Resist Staph aureus, Vancomycin Resist enterococci and Staphylococcus aureus* with the zones of inhibitions 24 mm, 22 mm and 26 mm respectively at the minimum inhibition concentrations of 10 µg/mL, 20 µg/mL and 10 µg/mL, respectively. These effects were observed at the MBC of 10 – 20 µg/mL. (Table 4). **L** could not inhibit the growth of *Streptococcus pyogenes* and *Bacillus cereus.* Complex (**1)** was active against *Methicillin Resist Staph aureus (*23 mm*), Vancomycin Resist enterococci* (24 mm) and *Bacillus cereus* (28 mm) at the MIC of 2.5 – 5 µg/mL .and MBC of 5 – 10 µg/mL. No activity was shown against *Staphylococcus* aureus and *Streptococcus pyogenes by* **(1)** at the concentrations investigated (Table 5). Complex **(2)** had effect on *Methicillin Resist Staph aureus* (22 mm), *Vancomycin Resist enterococci* (26 mm) and *Streptococcus pyogenes* at the MIC of 5 µg/mL, 2.5 µg/mL and 2.5 µg/mL, respectively. The MBC was observed in the range 10-20 µg/mL.. Complex **(2)** could not inhibit the growth of *Staphylococcus aureus* and *Bacillus cereus* (Table 6). **L** and Complex **(2)** showed effects on the same bacteria, however, complex **(2)** exhibited its effect at a lower MIC and the same MBC, implying that complex **(2)** has a higher activity (Table 6) against the bacteria than **L** (Table 4). Complex **(3)** on the other hand showed effect against *Vancomycin Resist enterococci* (27 mm) at MIC of 2.5 µg/mL, MBC of 5 µg/mL and *Streptococcus pyogenes* (26 mm) at MIC of 5 µg/mL, MBC of 10 µg/mL (Table 7). Complex **(3)** did not show any effect on *Methicillin Resist Staph aureus, Streptococcus pyogenes* and *Bacillus cereus* at the concentrations investigated. Complex (3) exhibited a higher and better activity against *Vancomycin Resist enterococci (*27 mm*)* at lower concentrations than Complex **(2), (1)** and **L**. Ciprofloxacin, the control drug also inhibited the growth of *Vancomycin Resist enterococci* (30 mm) at a MIC and MBC of 10 µg/mL (Table 8). Despite ciprofloxacin inhibiting the growth with



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inhibition zone of 30 mm, complexes **(3), (2)** and **(1)** are better antibacterial agents against *Vancomycin Resist enterococci.*

**Table 6: Antimicrobial Activity of (2): $Ph_2Sn(OCOCH_2COOK)_2$**

| **Test Organisms** | **Effects** | **Zone of Inhibition (mm)** | MIC (**µg/mL**) | MBC/MFC **(µg/mL)** |
|---|---|---|---|---|
| *Methicillin Resist Staph aureus* | S | 22 | 5 | 20 |
| *Vancomycin Resist enterococci* | S | 26 | 2.5 | 10 |
| *Staphylococcus aureus* | R | 0 | - | - |
| *Streptococcus pyogenes* | S | 24 | 2.5 | 10 |
| *Bacillus cereus* | R | 0 | - | - |
| *Aspergillus fumigatus* | R | 0 | - | - |
| *Aspergillus flavus* | S | 23 | 5 | 20 |
| *Aspergillus nigre* | R | 0 | - | - |
| *Fusarium oxysporum* | R | 0 | - | - |
| *Fusarium proliferatum* | S | 24 | 5 | 10 |

Key: S = sensitive, R = Resistant

**Table 7: Antimicrobial Activity of (3): $Ph_3SnOCOCH_2COOK$**

| **Test Organisms** | **Effects** | **Zone of Inhibition (mm)** | MIC (**µg/mL**) | MBC/MFC **(µg/mL)** |
|---|---|---|---|---|
| *Methicillin Resist Staph aureus* | R | 0 | - | - |
| *Vancomycin Resist enterococci* | S | 27 | 2.5 | 5 |
| *Staphylococcus aureus* | R | 0 | - | - |
| *Streptococcus pyogenes* | S | 26 | 5 | 10 |
| *Bacillus cereus* | R | 0 | - | |
| *Aspergillus fumigatus* | R | 0 | - | - |
| *Aspergillus flavus* | S | 25 | 5 | 10 |
| *Aspergillus nigre* | R | 0 | - | - |
| *Fusarium oxysporum* | R | 0 | - | - |
| *Fusarium proliferatum* | S | 26 | 5 | 10 |

Key: S = sensitive, R = Resistant

Ciprofloxacin is higher in activity than the ligand. The complexes are seen to exhibit better effects on the test bacteria than the ligand and control drugs due to the presence of metal in their structures which is absent in ciprofloxacin. This agrees with the report of Das.Santos and



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Das.Maia [1] who reported antibacterial effects of metal derivatives on gram-negative and gram-positive bacteria. The synergic effect between the ligand and metal ions, and the cells of gram-positive bacteria enhanced the bioactivity of the complexes [27].

**Table 8: Antimicrobial Activity of Control drugs: Zone of Inhibition (mm)**

| Test Organisms | Ciprofloxacin | Ketokonazole |
|---|---|---|
| *Methicillin Resist Staph aureus* | 0 | - |
| *Vancomycin Resist enterococci* | 30 | - |
| *Staphylococcus aureus* | 26 | - |
| *Streptococcus pyogenes* | 27 | - |
| *Bacillus cereus* | 0 | - |
| *Aspergillus fumigatus* | - | 0 |
| *Aspergillus flavus* | - | 25 |
| *Aspergillus nigre* | - | 0 |
| *Fusarium oxysporum* | - | 0 |
| *Fusarium proliferatum* | - | 0 |

Key: S = sensitive, R = Resistant

All complexes and ligand with the exception of complex **(3)**, exhibited antibacterial effects against *Methicillin Resist Staph aureus.* **L**, showed the highest inhibition zone of 24 mm at MIC and MBC of 10 µg/mL (Table 4), followed by complex **(1)** with inhibition zone of 23 mm, at MIC and MBC of 5 µg/mL and 10 µg/mL, respectively. Despite, the higher inhibition zone shown by **L**, complex **(1)** exhibited a better effect on the test microbe since its effect was observed at a lower MIC of 5 µg/mL (Tables 4 and 5). Thus, the order of effect against *Methicillin Resist Staph aureus* is **(1) > L > (2) > (3).**

All the synthesized complexes and ligand inhibited the growth of *Vancomycin Resist enterococci.* However, complex **(3)** showed the highest antibacterial effect with the inhibition zone of 27 mm at a much lower MIC (2.5 µg/mL) and MBC of 10 µg/mL (Table 7). Ciprofloxacin exhibited a higher inhibition zone of 30 mm but at a higher MIC of 10 µg/mL (Table 8). This places complex **(3)** higher in antibacterial effect than ciprofloxacin. The order of activity is: **(3) > (2) > (1) > L**. These complexes and ligand are potential agents for fighting *Vancomycin Resist enterococci* in the environment.

None of the synthesized complexes showed effect against *Staphylococcus aureus.* The ligand, **L**, inhibited its growth (26 mm) equal to that shown by the control: ciprofloxacin (26 mm) at the same MIC and MFC (Table 8). **L** can therefore be used to as potential antibacterial agent against Staphylococcus *aureus.*

Complexes **(2)** and **(3)** showed activity against *Streptococcus pyogenes* with the inhibition zones of 24 mm and 26 mm at MIC/MBC of 2.5 µg/mL/10 µg/mL (Table 6) and 5 µg/mL/10



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µg/mL (Tables 6 and 7), respectively. The control showed effect with inhibition zone of 27 mm at MIC and MBC of 10 µg/mL (Table 8). Complexes **(2)** and **(3)** showed higher effects than the control since their activities were observed at lower MIC. However, complex **(2)** exhibited higher effect than **(3)**. Thus, the order is **(2) > (3)** against *Streptococcus pyogenes.* This bacteria resisted complex **(1), L** and the control drug: ciprofloxacin.

Only complex **(1)** showed effect against *Bacillus cereus.* It inhibited the growth of this bacteria at the MIC of 2.5 µg/mL and MBC of 5 µg/mL (Table 5). Ciprofloxacin just like complexes **(2), (3)** and **L** could not inhibit the growth of *Bacillus cereus.* The bacteria resisted them at the concentrations investigated. They were very sensitive to **(1)** as demonstrated by its significant inhibition zone: 26 mm. Complex **(1)** is a potential antibacterial agent against this microorganism.

Metal complexes have been reported to have chelating property [28]. The synergistic effect between the metal and the ligand are known to affect the lipophilicity of these coordination compounds allowing them to get across the lipid membrane of the microorganisms more easily [1] thus exerting their effects.

***Antifungal Effect***

The antifungal effects of **L** and complexes **(1), (2)** and (**3**) are shown in Tables 4-7, while that of the control drugs: Ketoconazole (fungi) is shown in Table 8. Generally, complexes **(1), (2)** and **(3)** as well as the **L** showed significant antifungal effect against *Aspergillus fumigatus, Aspergillus flavus, Aspergillus nigre, Fusarium oxysporum, Fusarium proliferatum.* Complex (**1**) and **L,** showed antifungal activity/effect against *Aspergillus fumigatus* with the inhibition zone 21 mm (Table 4) and 23 mm, (Table 5) respectively, at the MIC/MFC of 10 µg/mL/20 µg/mL and 5 µg/mL/20 µg/mL, respectively. Both compounds exhibited their effects at the same MFC (20 µg/mL) but different MIC. Complex **(1)** showed higher activity than the **L**. Complexes **(2)** and **(3),** and ketoconazole the control drug: could not inhibit the growth *Aspergillus fumigatus.*

Complexes **(1), (2)**, **(3)** as well as **L** and ketoconazole showed antifungal effect against *Aspergillus flavus* with the inhibition zones of 24 mm, 24 mm, 23 mm, 25 mm and 25 mm respectively at the MIC/MFC of 5 µg/mL/10 µg/mL, 5 µg/mL/10 µg/mL, 5 µg/mL/20 µg/mL, 10 µg/mL/10 µg/mL, respectively (Tables 4-8). Complex **(3**) showed the highest activity 25 mm, similar to that exhibited by ketoconazole. Despite their similar inhibition zones, **(3)** exhibited its activity at a lower MIC (5 µg/mL)(Table 7) compared to that of the control (10 µg/mL)(Table 8). This effect is followed by that exhibited by Complex (**1)** and **L** with the same inhibition zones 24 mm and MIC/MFC: 5 µg/mL/10 µg/mL. This effect is very close to that of **(3)** and control. Complex **(2)** showed the least effect: 23 mm at MIC and MFC: 5 µg/mL and 20 µg/mL, respectively. Compound (3) showed a better



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antifungal effect on *Aspergillus flavus* similar to ketoconazole, the control. All the Complexes and ligand synthesized in this investigations are potential antifungal agents against *Aspergillus flavus* and can compete well with ketoconazole. The order of effect on *Aspergillus flavus* is **(3) > (1) = L > (2).**

None of the complexes and ligand showed any effect on *Aspergillus nigre*, including the control drug. The resistance could be due to the inability of the complexes, **L** and control to penetrate the cells of the organism to exert their effect at MIC of 5 µg/mL and MFC of 20 µg/mL (Table 4). Complex **(1)** exhibited the highest effect against *Aspergillus nigre* with inhibition zone of 24 mm at MIC of 5 µg/mL and MFC of 10 µg/mL (Table 5). Complex **(2)** and **(3)** as well as the control, could not inhibit the growth of *Aspergillus nigre*. Complex **(1)** and **L**, are potential antifungal agents against A*spergillus nigre.* The order is (1) > L.

Complexes **(2)** and **(3)** as well as **L**, exhibited effect against *Fusarium proliferatum* while complex (1) did not inhibit the growth of the organism. L inhibited the growth with the inhibition zone of 23 mm at the MIC of 5 µg/mL and MFC of 20 µg/mL Complex **(2)** exerted its effect with the inhibition zone of 24 mm, MIC of 5 µg/mL and MFC of 10 µg/mL. Complex **(3)** exerted the highest effect against the test fungi with the inhibition zone of 26 mm, MIC of 5 µg/mL and MFC of 10 µg/mL (Table7). The ligand inhibited the growth at a higher concentration implying its lower activity compared to. (**3**) and **(2).** The order of activity is thus, **(3)> (2) > L**

The Significant antibacterial and antifungal activity exhibited by L and complexes **(1), (2)** and **(3)** may be due to the presence hydrolysable groups that generate intermediates moieties such as $R_nSn(4-n)+(n=2$ 0r 3) which possess the ability to bind with DNA or proteins of test microbes using their heteroatom oxygen for [29].

## CONCLUSION

Ligand: **L** and its metal complexes **(1), (2), (3)** were synthesized mechanochemically by grinding as a green method of synthesis, characterized and tested for antimicrobial effect. The magnetic susceptibility data revealed that the ligand and complexes are paramagnetic. The antimicrobial studies revealed that **L** and its complexes **(1), (2)** and **(3)** showed significant activity against gram-positive bacteria and fungi at lower MIC and MBC/MFC compared to the control drugs: ciprofloxacin and ketoconazole. The presence of additional metal (Sn) in the complexes increased perhaps enhanced the complexes antimicrobial effects on the test microbes. According to Das.Santos and Das Maia (2019), metal derivatives exhibit better antibacterial effects on gram-positive bacteria. The antimicrobial activity of the complexes were observed to be better than that exhibited by the Ligand, **L**. Equations 1-4, showed that the



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complexes have additional tin (Sn) apart from potassium metal in their structures compared to the free ligand: **L** that has only the metal potassium. The increased antimicrobial effect is reflected in the activities of the complexes inhibiting the growth of microorganisms at lower MIC (2.5 - 5 µg/mL) and MBC/MFC (5 - 10 µg/mL) irrespective of their inhibition zones (23 – 27 mm). These complexes and ligand with enhanced antimicrobial effects on test microbes are potential antimicrobial agents that would be useful in the design and formulation of metal-based drugs for treatment of ailments caused by the test microbes or for control management of the test microbes in the environment in comparism with standard drugs/formulations.

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