

Synthesis, Characterization and Antifungal Activity of Some Organotin (IV) Derivatives of Hexanedioic Acid

E. N. Iornumbe¹, S. G. Yiase², R. Sha'Ato¹, and T. A. Tor-Anyiin¹

¹Inorganic Chemistry Research Group, University of Agriculture, P.M.B. 2373, Makurdi, 970001- Nigeria

²Department of Chemistry, Benue State University, Makurdi- Nigeria

Abstract: Four organotin (IV) derivatives of Hexanedioic acid: potassium dibutyltin (IV) hexanedioate (1), potassium tributyltin (IV) hexanedioate (2), potassium diphenyltin (IV) hexanedioate (3) and potassium triphenyltin (IV) hexanedioate (4) were synthesized by reacting hexanedioic acid with potassium hydroxide to give the potassium hydrogen salt followed by reaction between the salt and an organotin oxide/hydroxide to give the potassium organotin dicarboxylates. The compounds were characterized by tin content analysis, FTIR, ¹H NMR and ¹³C NMR and tested for antifungal activity against four strains of *Microsporium spp* and three strains of *Trichoephyton spp*. Result showed that the compounds synthesized in general exhibited greater fungitoxicity than the Organotin oxides, organotin hydroxide, potassium hydrogen hexanedioate and hexanedioic acid. Organotin moieties are known to play a vital role in deciding the antifungal activity of an organotin compound, this is true in this work as the order of antifungal activity was potassium triphenyltin (IV) hexanedioate > potassium diphenyl (IV) hexanedioate potassium tributyltin (IV) hexanedioate > potassium dibutyltin (IV) hexanedioate.

Keywords: Organotin derivatives, potassium hydrogen hexanedioate, Spectroscopic techniques, Antifungal Activity.

I. Introduction

The increasing interest in organotin (IV) compounds is due to their structural features and potential as biocides, pesticides, homogenous catalysts [1], wood preservatives and antifouling agent [2]. As such, they have found application in agriculture, industries and medicine [3]. The broad spectrum biological and non-biological applications depend on both nature of molecule and coordination number of tin atom [4]. The high coordination ability of tin, especially its ability to be involved in either weak or strong intra or intermolecular coordination [5] due to availability of empty 5d - orbitals of suitable energy in tetravalent tin [6] are responsible for the chemistry and structural diversity of organotin (IV) compounds. Organotin (IV) carboxylates are widely studied class of organotin (IV) compounds based on their structural diversity and potential pharmaceutical values [7] especially with reference to their antitumour [8] and antituberculosis [9] activities. These compounds are known to bind to phosphate groups of DNA in tumor cells and damage them thereby retarding the replication and synthesis of new DNA [10, 11]. Biological activity of organotin (IV) compounds has been reported severally to depend on the nature and number of organic groups (R) directly bonded to tin atom [8, 10]. The role of the ligand in transportation of organotin (IV) moiety to the target area, where organotin (IV) species perform its biocidal activity is known [10, 12]. Based on the above, scientists have been encouraged to design tin based drugs having good activity and low toxicity for cancer chemotherapy [11, 13] and other ailments. In an attempt to further explore the interesting features of these organotin compounds, we report here the synthesis, characterization and antifungal properties of four organotin (IV) dicarboxylate compounds prepared from four parent organotin compounds and hexanedioic acid as starting materials.

II. Materials and Methods

All the reagents and solvents used for the preparation of the ligands and compounds were of analytical grade, obtained from Sigma Aldrich with purity ranging from 98-99.8 %. They were used with out further purification.

2.1 Preparation of ligand, L (HCOO(CH₂)₄COOK)

The ligand (L) was prepared according to the method in our earlier report [12]. It was prepared by mixture of potassium hydroxide (0.05 mol, 2.8338 g) and hexanedioic acid (0.05 mol, 7.3808 g) completely dissolved in 50 mL distilled water and refluxed for 1 hour giving a clear solution. The solution was cooled in an ice-bath during which crystals of potassium hydrogen hexanedioate separated out and were filtered using a Buchner filtering unit and dried in a desiccator to a constant weight [14].

2.2 Synthesis of Bu₂SnO[CO(CH₂)₄COOK]₂ (1) and Ph₂SnO[CO(CH₂)₄COOK]₂ (3)

Compounds (1) and (3) were synthesized as in our earlier report [12]. Dibutyltin (IV) oxide (0.0080 mol, 1.8602 g) was refluxed in a methanol-n-propanol mixture (4:1) for 5 hours using Dean and Stark apparatus to give a clear solution of the intermediate: dibutyltin (IV) dialkoxide. Water and methanol in the mixture distilled off as an azeotrope at 67 °C and 96-98 °C, respectively and solution was cooled. To the cooled solution, 2.8883 g (0.008 mol) of potassium hydrogen hexanedioate was added and refluxed for 1 hour. The resulting mixture was kept in an oven for a period of 72 hrs at 40 °C to obtain a white crystalline product (1) [15-17]. Compound (3) was synthesized similarly using diphenyltin (IV) oxide (0.0014 mol, 0.4055g) and potassium hydrogen hexanedioate (0.0014 mol, 0.5955 g), respectively.

2.3 Synthesis of Bu₃SnOCO(CH₂)₄COOK (2) and Ph₃SnOCO(CH₂)₄COOK (4)

Tributyltin (IV) hydroxide (0.0008 mol, 0.5000 g) and potassium hydrogen hexanedioate (0.0005 mol, 0.3146 g) were suspended in methanol and mixture was refluxed using Dean and Stark apparatus for five hours at 60 °C to 70 °C. The methanol distilled off at 64.5 °C giving white precipitate which was dried in an oven at 40 °C for 72 hours to form white crystalline solid of compound (2). Compound (4) was synthesized similarly, using triphenyltin (IV) hydroxide (0.0075 mol, 2.7432 g) and potassium hydrogen hexanedioate (0.0078 mol, 1.4441 g) respectively [14-18].

2.4 Physicochemical Measurements

Melting points were obtained with Fisher-Johns microscope hot stage melting point apparatus and were not corrected. Tin content analysis was carried out using Fansworth and Pekola method [19]. Infrared spectra from 4000 to 400 cm⁻¹ were recorded on FTIR-8400S spectrophotometer (SHIMADZU), using KBr pellets. ¹H and ¹³C NMR spectra were recorded at room temperature using NMR Nujol 400 MHz spectrophotometer.

2.5 Antifungal Activity Test

Clinical isolates of the microbes 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 and dilution method were used.

2.5.1 Agar well diffusion technique

Agar well diffusion technique was adopted for determination of antifungal activity of the organotin compounds. Sabouraud dextrose agar (SDA) was used as culture medium and was prepared according to manufacturer's instructions, sterilized at 121 °C for 15 minutes, poured into sterile petri dishes under an aseptic hood and allowed to cool and solidify. The sterile medium was seeded with 0.1 mL of standard inoculums of the test fungi and spread evenly over the surface of the medium 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 200 µg/mL of the test compounds dissolved in DMSO were introduced into their respective wells. Other wells supplemented with standard antifungal drugs; fulcin and fluconazole were used as controls. After allowing for diffusion, the media were incubated immediately at 30 °C for 7 days and checked daily for inhibition zone (area where the fungi were unable to grow), then it indicated the compounds tested showed antifungal activity. Where inhibition zones were not observed, the organotin used was inactive or concentration used may be less than required [12, 14, 18, 20].

2.5.2 Broth dilution method

The Minimum inhibition concentrations (MIC) of test compounds were obtained using the broth dilution method. Sabouraud dextrose broth was prepared in a test tube, sterilized at 121 °C for 15 minutes and allowed to cool [19]. Serial dilution of test organotin compounds in sterile broth was made to obtain the concentrations of 200 µg/mL, 100 µg/mL, 50 µg/mL, 25 µg/mL and 12.5 µg/mL. 1.5 × 10⁵ CFU/mL of test fungi in normal saline was made and introduced into each of the concentrations and incubated at 30 °C for 7 days. The 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. In order to ascertain whether the test fungi were killed completely or their growth only inhibited, minimum fungicidal concentration (MFC) was determined. Content of MIC in the serial dilution was sub cultured onto the prepared medium and incubated at 30 °C for 7 days and plates were observed for colony growth. MFC was the plate with lowest concentration of compound without colony growth [14].

III. Results and Discussion

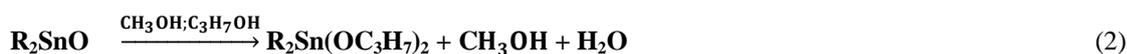
3.1 Synthesis

The synthesis of organotin (IV) derivatives of hexanedioic acid (1-4) was successfully achieved from their oxides [(C₄H₉)₂SnO, (C₆H₅)₂SnO] and hydroxides [(C₄H₉)₃SnOH, (C₆H₅)₃SnOH], respectively. The

reactions occurred in three steps as shown scheme 1. The ligand: HOCO(CH₂)₄COOK was first prepared by the reaction between KOH and hexanedioic acid: HOCO(CH₂)₄COOH according to equation 1 (scheme 1). (C₄H₉)₂SnO and (C₆H₅)₂SnO were refluxed separately in 4:1 CH₃OH and C₃H₇OH (Dean and Stark apparatus) yielding their respective propoxides as intermediates. These were further reacted with the ligand **L** HOCO(CH₂)₄COOK to produce compounds (**1**) and (**3**). (C₄H₉)₃SnOH and (C₆H₅)₃SnOH were refluxed in CH₃OH which gave their dimethoxides as intermediates (equations 3 and 5, respectively) which were further reacted with the ligand: HOCO(CH₂)₄COOK to produce compounds (**2**) and (**4**). Water produced in the process was collected in the separator of Dean and Stark apparatus, which was eventually removed by opening the tap and closing it back after its removal.



L



Where **R** = C₄H₉ and C₆H₅

Scheme 1: Preparation of Ligand and Compounds (**1-4**)

Physicochemical data of compounds synthesized are summarized in Table 1. Observed % Sn was found to agree very closely with the calculated tin content, an indication that the expected products were actually formed [14].

Table 1: Physicochemical Data of Compounds Synthesized

Compound no.	%Sn observed	%Sn Calculated	Mpt.(^o C)	%yield
1	19.86	19.90	218 -220	89.46
2	25.88	25.16	365-368	99.12
3	23.05	23.34	111 – 112	96.05
4	27.91	28.33	141-142	95.59

3.2 Infrared spectroscopy

Important Infrared absorption bands of synthesized compounds are listed in Table 2. The infrared spectra of compounds taken in the region 400-4000 cm⁻¹ were compared with that of the free ligand. There are some significant changes between compounds synthesized and their free ligands as expected. An exhaustive comparison of the IR spectra of the ligands and compounds gave information about the mode of bonding of the ligands in organotin (IV) dicarboxylate compounds.

Table 2: Important IR bands of the compounds synthesized

Compound no.	1	2	3	4	L	A
V _{asym} (COO)	1564	1560	1556	1566	1568	1698
V _{sym} (COO)	1417	1410	1435	1452	1421	1427
ΔV	147	150	115	114	277	271
Sn-O	404	507	425	451	-	-
Sn-O-C	912	909	923	913	-	-
Sn-Bu	627	733	-	-	-	-
Sn-Ph	-	-	1076	1074	-	-
C-H _{arom}	-	-	3038	3047	-	-
O-H	-	-	-	-	3444	3499

L = HOCO(CH₂)₄COOK, **A** = HOCO(CH₂)₄COOH

FTIR data of free acid (**A**) showed a strong broad band around 3500 and 2400 cm⁻¹ due to V(OH) which shifted to 3444 -3246 cm⁻¹ in the free ligand (**L**) but the IR spectra of compounds (**1-4**) did not exhibit

such broad bands. The shift due to V(OH) stretching in the free ligand was an indication that one of the -COOH groups of hexanedioic acid (**A**) was deprotonated and K⁺ got coordinated to it. Presence of bands in the range 507-404 cm⁻¹ and 913-909 cm⁻¹ indicated deprotonation of -COOH group and formation of new Sn-O and Sn-O-C bonds, respectively [21], [22]. Thus, appearance of new bands in the region 507 - 404 cm⁻¹ for all compounds indicated the formation of new Sn-O bonds. The appearance of medium intensity bands in the range 1076-627 cm⁻¹ due to Sn-C-O, Sn-Bu and Sn-Ph further confirmed formation of the compounds. The interesting stretching frequencies of compounds **1-4** were those associated with COO, Sn-O, Sn-O-C, Sn-Bu and Sn-Ph groups. The bands in the range 3500 cm⁻¹ -3246 cm⁻¹ which appeared in the free ligand as the V(O-H) stretching vibrations and absent in compounds **1-4** indicated metal-ligand bond formation through these sites [5]. The absorption bands in the range 1566 -1556 cm⁻¹ and 1452 - 1410 cm⁻¹ in compounds were assigned to V_{asym}(COO) and V_{sym}(COO), respectively. V_{asym}(COO) and V_{sym}(COO) in free acid appeared at 1698 cm⁻¹ and 1427 cm⁻¹, respectively but shifted to 1568 cm⁻¹ and 1421 cm⁻¹ in the free ligand. The red shifts of the bands with respect to the free acid also served to confirm the formation of organotin (IV) dicarboxylates [23]. Mode of coordination of carboxylate group was proposed based on the magnitude of separation of the difference ΔV, between V_{asym}(COO) and V_{sym}(COO) for the carboxyl group [24]. These values are useful for determining the mode of coordinate bonding between metal and carboxyl group. The value < 200 cm⁻¹ indicates that the carboxylate moiety is bidentate, while ≥ 200 cm⁻¹ indicates monodentate [21], [5]. The magnitude of ΔV of 150 - 114 cm⁻¹ for complexes **1-4** indicated that the carboxylate ligands function as bidentate under the conditions employed while that of hexanedioic acid and ligand, (**L**) with values 271 cm⁻¹ and 277 cm⁻¹ respectively, indicated their carboxylate groups as monodentate. It is, therefore, proposed that the carboxylate group in these compounds was acting as a bidentate ligand. Therefore, we suggest a distorted octahedral geometry for diorganotin derivatives in solid state and trigonal bipyramidal structure for triorganotin compounds [14, 21].

3.3 NMR spectroscopy

¹H NMR data of synthesized compounds are summarized in Table 3. Signals of the protons in all compounds were observed within the expected range. They revealed expected aliphatic and aromatic peaks with correct integration and multiplicities. A complex pattern is observed in compounds **3** and **4** in the range 7.29-7.83 ppm due to the aromatic protons of phenyl groups of organotin moiety. Their -CH₂CH₂- protons appeared in the range 1.14 - 2.01 ppm.

Table 3: ¹H NMR data of compounds (**1-4**) synthesized

Proton no.	1	2	3	4
ii, v	2.45	2.39	2.01	1.96
iii - iv	1.46	1.42	1.23	1.14
a	1.11	1.66	-	-
b	1.36m	1.64	-	-
c	0.82t(7.6)	1.64t	-	-
α	1.29m	1.68m(7.1)	7.83	7.78
β	-	-	7.36	7.34
γ	-	-	7.50	7.43
δ	-	-	7.29	7.44

a. Chemical shift(δ) in ppm, J(¹H-¹H)

b. Multiplicity is given as s = singlet, t = triplet, m = multiplet

c. Figure 1 shows the numbers assigned to protons and carbons in the proposed structure of synthesized compounds for ease of reference.

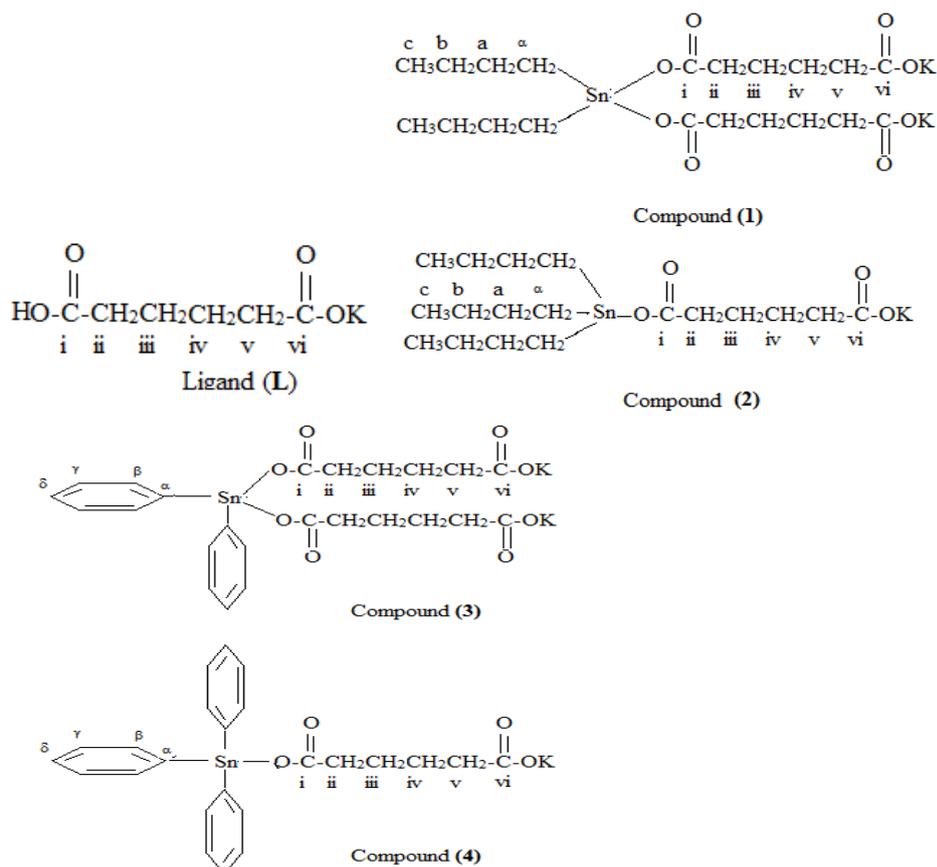


Figure 1: Numbering of Protons and Carbons in the Structures of Synthesized Compounds (1 – 4)

Butyl protons found in compounds (1) and (2) (assigned a and b in fig. 1) showed complex peaks due to $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ in the range 1.11-1.66 ppm and a clear triplet due to the terminal methyl group (c) around 0.82-1.64 ppm with ($^1\text{H}-^1\text{H}$) coupling of 7.2 Hz. In all the compounds, methylene protons (ii and v) bonded to carboxyl group (i and vi) showed peaks in the range 1.42 - 2.45 ppm. ^{13}C NMR spectral data of compounds (1-4) are given in Table 4. All carbon atoms present in the ligand and its derivatives were assigned numbers and alphabets as shown in figure 1. The carboxyl carbons (i and vi) of all compounds were assigned signals in the range 167.21-181.77 ppm which are in agreement with literature [17].

Table 4: ^{13}C NMR data of compounds (1 - 4) synthesized

Carbon	1	2	3	4
ii, v	34.20	35.97	38.77	40.46
iii – iv	24.83	25.19	27.32	27.57
i, vi	167.25	181.77	175.19	176.21
a	24.83	25.19	-	-
b	17.00	24.97	-	-
c	14.17	25.03	-	-
α	17.07	25.17	138.72	136.79
β	-	-	138.39	136.58
γ	-	-	126.46	128.88
δ	-	-	133.20	129.56

The carbons of $-\text{CH}_2$ group (ii, vii) coordinated to carboxyl groups (i, viii) were assigned signals in the range 34.20-40.46 ppm for both butyl and phenyl organotin compounds. Signals for butyl carbons (a and b)

appeared at 17.00-25.19 ppm while $-CH_3$ appeared at 14.17 ppm and 25.03 ppm, respectively for compounds **1** and **2**. Phenyl carbons were assigned signals in the range 126.46 -138.72 ppm with $\alpha(Sn-C)$ at 138.72 ppm and 136.79 ppm for compounds **3** and **4**, respectively. The α signals due to (Sn-C) bond in butyl for compounds **1** and **2** appeared at 17.07 ppm and 25.17 ppm, respectively. These signals are in agreement with earlier report [14, 21].

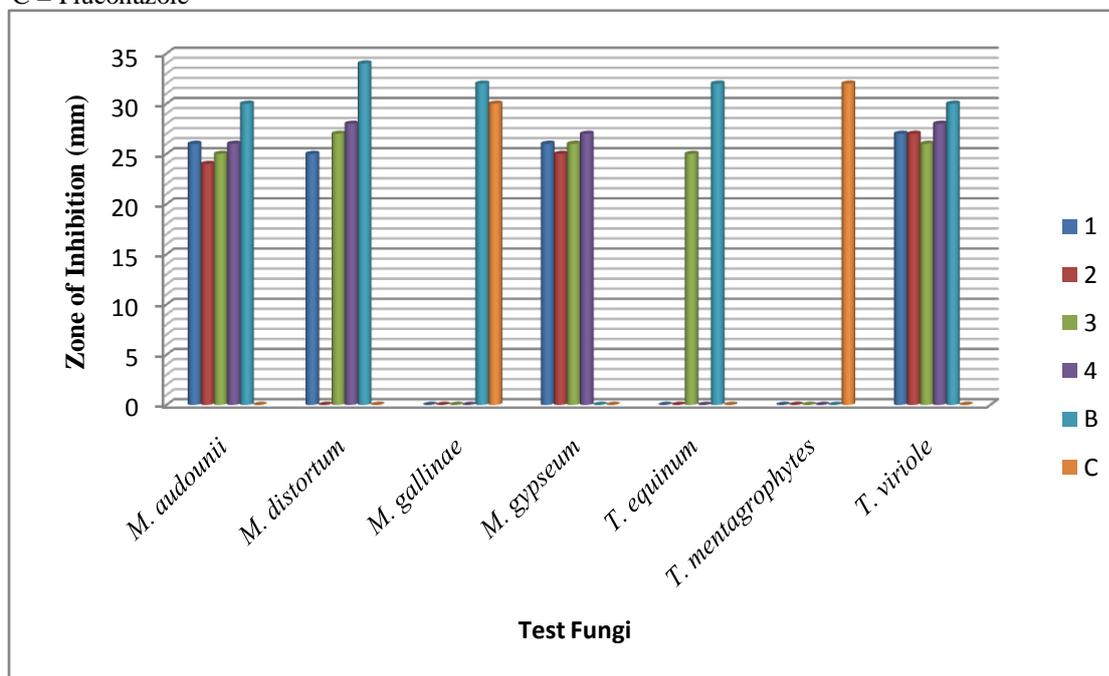
3.4 Antifungal activity

The ligand **L** and its organotin (IV) compounds (**1- 4**) were screened for antifungal activity against seven fungal strains (Microsporium audounii, Microsporium distortum, Microsporium gallinae, Microsporium gypseum, Tricheophyton equinum, Tricheophyton mentagrophytes and Tricheophyton viriole) by agar well diffusion/ diffusion method and zones of inhibition were obtained. Fulcin (B) and fluconazole (C) were used as standard drug in this assay. The results are shown in Table 5 and Fig. 2. This revealed that all compounds showed high antifungal activity comparable to the standard drugs. However, there were few cases where the compounds did not show antifungal activity.

Table 5: Zone of Inhibition (mm) of compounds (**1-4**)

Fungus	1	2	3	4	B	C
M. audounii	26	24	25	26	30	-
M. distortum	25	-	27	28	34	-
M. gallinae	-	-	-	-	32	30
M. gypseum	26	25	26	27	-	-
T. equinum	-	-	25	-	32	-
T. mentagrophytes	-	-	-	-	-	32
T. viriole	27	27	26	28	30	-

Key: M= Microsporium, T = Tricheophyton, B = Fulcin, C = Fluconazole



Key: M= Microsporium, T = Tricheophyton, B = Fulcin, C = Fluconazole

Figure 2: Zone of Inhibition of Compounds against Test Fungi

It was observed that all synthesized compounds (**1- 4**) showed high antifungal activity against Microsporium gypseum with compound (**4**) exhibiting the highest activity which was not exhibited by the standard drugs: fulcin and fluconazole at the concentrations used. All compounds (**1-4**) also inhibited the growth of Microsporium audounii and Tricheophyton viriole with compound (**4**) showing the highest antifungal activity which was close to the activity exhibited by standard drug, fulcin (B). Fluconazole (C), did not inhibit the growth of both fungi at the concentration used in this study. Only compound **3** showed activity against Tricheophyton equinum which was slightly lower than the activity of fulcin but higher than fluconazole which

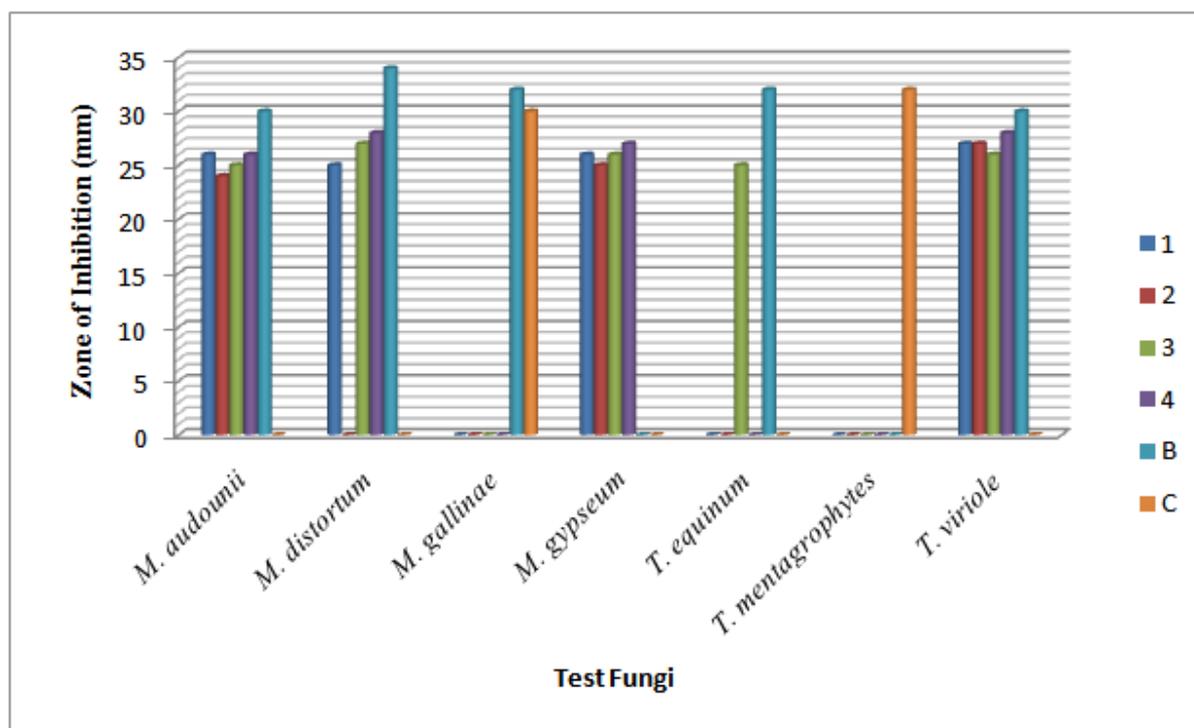
exhibited no activity at all against the test fungus. Implying that compound (3) can be used in drugs design against such fungus than fulcin. None of the synthesized compounds exhibited antifungal activity against *Microsporium gallinae* and *Tricheophyton mentagrophytes*. It was observed that compound (4) exhibited the highest ability to inhibit the growth of fungi, thus, the compound with the highest antifungal activity in this study. This was reflected in its magnitude of zones of inhibition shown in Table 5 and Fig. 2.

MIC of the compounds was obtained at the concentrations of 25 µg/mL while their MFC revealed that all the fungi growths were not just inhibited but were completely killed. Overall, compounds 1 – 4 showed good antifungal activity at the concentrations used. Antifungal activity of free acid A, free ligand L and parent organotin (IV) oxide/hydroxide against test fungi were also determined. Results (zone of inhibition) are shown in Table 6 and Fig. 3.

Table 6: Zone of Inhibition (mm) of acid, Ligand and Parent organotin (IV) compounds used.

Fungus	W	X	Y	Z	A	L
<i>M. audounii</i>	-	-	-	-	22	24
<i>M. distortum</i>	-	-	24	-	-	-
<i>M. gallinae</i>	-	-	-	27	21	23
<i>M. gypseum</i>	-	-	26	24	23	24
<i>T. equinum</i>	24	26	-	26	-	-
<i>T. mentagrophytes</i>	-	-	25	-	-	-
<i>T. viriole</i>	25	24	23	-	23	25

Key: W= Bu_2SnO , X= Bu_3SnOH , Y= Ph_2SnO , Z= Ph_3SnOH ,
A = $\text{HOCO}(\text{CH}_2)_4\text{COOH}$, L = $\text{HOCO}(\text{CH}_2)_4\text{COOK}$



Key: W = Bu_2SnO , X= Bu_3SnOH , Y= Ph_2SnO , Z = Ph_3SnOH , A = $\text{HOCO}(\text{CH}_2)_4\text{COOH}$, L = $\text{HOCO}(\text{CH}_2)_4\text{COOK}$

Figure 3: Zone of inhibition of parent organotins, acid and free ligand.

The acid (A): $\text{HOCO}(\text{CH}_2)_4\text{COOH}$ exhibited lower antifungal activity against test fungi than the ligand (L), $\text{HOCO}(\text{CH}_2)_4\text{COOK}$ and synthesized compounds (1-4). This is in agreement with our report [12] on octanedioic acid and in literature [17] that carboxylic acids have weaker antifungal activity. Ability of ligand and its derivatives to inhibit growth of test fungi more than hexanedioic acid could be as a result of the presence of metal ions in their structures which may have increased antifungal activity when the acid was coordinated K^+ and Sn^{4+} . This is in agreement with the known fact that many biologically active compounds become more active upon complexation than in their uncomplexed forms [17]. The findings that potassium organotin (IV)

dicarboxylates (**1-4**) are more active than their parent organotin (IV) compounds: Bu_2SnO , Bu_3SnOH , Ph_2SnO , Ph_3SnOH , ligand and dicarboxylic acid was also observed for other studies where organotin (IV) chlorides and methylacrylic acid were used as parent organotin and ligand, respectively [12, 22]. Literature has shown that biological activity of organotin compounds especially diorganotin (IV) compounds depend solely on the organotin moiety; R_2Sn^{2+} and R_3Sn^+ (where R = Bu or Ph) [25]. The carboxylate groups influence the delivery of organotin (IV) moiety to the point of action [10]. The high activities of compounds (**1-4**), appear to be a combined effect of the metal ions and carboxylate groups. Since diorganotin (IV) compounds are not known for their high biological activities, the activity of compounds (**1**) and (**3**) in this study could probably be due to the potassium and Sn ions present in their structures. However, potassium triphenyltin (IV) hexanedioate (**4**) exhibited antifungal activity more than its diphenyl counterpart (**3**) while potassium dibutyltin (IV) octanedioate (**1**) exhibited higher activity than its tributyl counterpart (**2**). The observation that the triorganotin (IV) compounds (**2** and **4**) are more active agrees with the notion that the number of carbon atoms in an organotin moiety affects its activity [14, 26].

IV. Conclusion

Four organotin (IV) derivatives (**1-4**) of hexanedioic acid were synthesized and characterized by FTIR, NMR (^1H and ^{13}C). FTIR data revealed that the mode of coordination in all the compounds was monodentate while the NMR confirmed the formation of the compound. Antifungal activity result showed that generally, all compounds synthesized in this study exhibited high antifungal property. Compound (**3**), a diphenyl tin (IV) dicarboxylate showed higher antifungal than compound (**1**) its dibutyl counter part while compound (**4**), a triphenyl tin (IV) dicarboxylate showed higher antifungal activity than compound (**2**) its tributyl counter part. As such, we suggest the use of these compounds in the design of tin based drugs having good activity and low toxicity for ailment(s) chemotherapy since the fungi used in this study are responsible for some health challenges. Organotin (IV) compounds have been applied in design of drugs for cancer chemotherapy [11]. The order of activity was compound (**4**) > (**3**) > (**1**) > (**2**).

References

- [1]. M. H. Bhatti, S. Ali, F. Huma, S. Shahzadi, Organotin (IV) Derivatives of N- Maleoylamino Acids: Their Synthesis and Structural Elucidation, *Turkish Journal of Chemistry*, 29, 2005, 463-476.
- [2]. N. Awang, J. Baba, N. S. A. Mohdyusuf, N. F. Kamalodin, Synthesis and Characterisation of Organotin (IV) N-benzyl-N-isopropylthiocarbamate Compounds: Cytotoxic Assay on Human Hepatocarcinoma cells (HepG2), *American Journal of Applied Sciences*. 7(8), 2010, 1047-1052.
- [3]. B. Traore, L. Diop, M. Sidibe, New Halo- and Organotin (IV) Phenylarsenato Adducts and Derivatives, *Scientific Study and Research*. 13(4), 2012, 387-391.
- [4]. T. Muhammad, A. Saqib, A. S. Naseer, M. Niaz, N. T. Muhammad, K. Nasir, R. K. Muhammad, Catalytic, biological and DNA binding studies of Organotin (IV) carboxylates of 3-(2-fluorophenyl)-2-methylacrylic acid: Synthesis, spectroscopic characterization and X-ray structure analysis, *Polyhedron*, 57, 2013, 127-137.
- [5]. X. Xiao, D. Dafeng, H. Xiao, L. Jingwen, T. Min, Z. Dongsheng X. Lin, Self-assembly of triorganotin(IV) moieties with 1,2,4,5-benzenetetracarboxylic acid: Synthesis, characterizations and influence of solvent on the molecular structure, *Journal of Organometallic Chemistry*, 713, 2012, 143-150.
- [6]. M. Gielen, An Overview of Forty Years Organotin Chemistry Developed at the Free Universities of Brussels ULB and VUB, *Journal of the Brazilian Chemical Society*, 14 (6), 2003, 870-877.
- [7]. Q-F Wang, C-L. Ma, G-F He, Z. Li Synthesis and characterization of new tin derivatives derived from 3,5,6-trichlorosalicylic acid: Cage, chain and ladder X-ray crystal structures. *Polyhedron* 49, 2013, 177-182.
- [8]. H. Pruchnik, F. P. Pruchnik, Butyltin (IV) Citrates and Tartrates: Structural Characterization and their Interaction with Nucleotides, *Journal of Organometallic Chemistry*, 729, 2013, 60-67.
- [9]. M. M. Amini, A. Amirreza, A. Vajihah, R. K. Hamid, S. W. Ng, Synthesis, Characterization and Molecular Structures of di- and triorganotin (IV) complexes with Anthracenecarboxylic acid: The Structural diversity in organotin 9-anthracenecarboxylates, *Journal of Organometallic Chemistry*, 6, 2007, 3922 -3930.
- [10]. A. S. Farooq, S. Muhammad, A. Saqib, M. A. Syed, N. T. Muhammad, R. Corrado, Synthesis, spectroscopic characterization, X-ray structure and biological screenings of organotin (IV) 3-[(3,5-dichlorophenylamido)]propanoates, *Inorganica Chimica Acta*, 400, 2013, 159 - 168.
- [11]. H. Yin, H. Liu, M. Hong, Synthesis, structural characterization and DNA-binding properties of organotin (IV) complexes based on Schiff base ligands derived from 2 hydroxy-1-naphthaldy and 3- or 4-aminobenzoic acid, *Journal of Organometallic Chemistry*, 713, 2012, 11-19.
- [12]. E. N. Iornumbe, S. G. Yiase, R. Sha'Ato, T. A. Tor-Anyiin, Synthesis, Characterization and Antifungal Activity of Some Organotin (IV) Derivatives of Octanedioic Acid, *International Journal of Science and Research*, 4(5), 2015, 2095-2101.
- [13]. E. C. Carraher Jr. and M. R. Roner, Organotin polymers as anticancer and antiviral agents. *Journal of Organometallic Chemistry*, 751, 2014, 67-82.
- [14]. E. N. Iornumbe, Synthesis, Aqueous Solubility and Antifungal Studies of Some Organotin(IV) Dicarboxylates, Ph.D Thesis, University of Agriculture Makurdi-Nigeria, 2015.
- [15]. J. Szorcsik, A. Nagy, L. Pellerito, T. Yamaguchi, K. Yoshida, Preparation and Structural Studies on Organotin (IV) Complexes formed with Organic Carboxylic Acids, *Journal of Radianalytical Chemistry*, 256 (1), 2003, 3-10.
- [16]. Q. M. Amua, Synthesis, Characterization and Aqueous solubility studies of some Organotin (IV) Carboxylates, M.Sc Thesis. Benue State University, Makurdi-Nigeria, 2006.
- [17]. S. Hadi, R. Mita, Nurhasanah, Comparative Study on the Antifungal Activity of some Di- and Tributyltin (IV) Carboxylate Compounds. *Modern Applied Science Journal*, 3(1), 2009, 12-17.

- [18]. S. Hadi, B. Irawan, Efri, Antifungal Activity Test of some Organotin (IV) Carboxylates, *Journal of Applied Science Research*, 4(11), 2008, 1521-1525.
- [19]. M. Farnsworth, J. Pekola, Determination of Tin in Inorganic and Organic Compounds and Mixtures, *Journal of Analytical Chemistry*, (31), 1959, 410 – 413.
- [20]. M. Cheesbrugh, *District Laboratory Practices in Tropical Countries Part 1*. Cambridge University Press, Cambridge, 2000.
- [21]. S. Ahmed, M. H. Bhatti, S. Ali, F. Ahmed, Organotin (IV) Derivatives of 1-Ethyl 1,4-Dihydro-7-Methyl-4-Oxo-1,8-Naphthyridine-3-Carboxylic Acid (Nalidixic Acid): Synthesis, Structural Elucidation and Biological Activities. *Turkish Journal of Chemistry*, (30), 2006, 193 – 202.
- [22]. M. Tariq, S. Ali, A. N. Shah, N. Muhammad, N. M. Tahir, N. Khalid, R. M. Khan, Catalytic, Biological and DNA Binding Studies of Organotin(IV) Carboxylates of 3-(2-fluorophenyl)-2-methylacrylic acid: Synthesis, spectroscopic characterization and X-ray structure analysis, *Polyhedron*, (57), 2013, 127–137.
- [23]. M. M. Amini, A. Amirreza, A. Vajihel, R. K. Hamid, H. Taraneh, N. K. Ali, Di and triorganotin (IV) Carboxylates derived from triorganotin (IV) iodide with mixed organic groups on tin: Cyclic, hexameric triorganotin (IV) carboxylates, *Inorganica Chimica Acta*, 362, 2009, 355 – 360.
- [24]. M. A. Choudhary, M. Mazhar, U. Salma, S. Ali, X. Q. Lan, K. C. Molloy, Synthesis and Characterization of Organotin Compounds containing Silicon and Germanium and Crystal structure of Precursor Carboxyl-ethyltrichlorogermanium, *Synthetic Reactions of Inorganic Metal-organotin Chemistry*, (31) 2001, 277-295.
- [25]. H. K. Okoro, O. S. Fatoki, F. A. Adekola, J. B. Ximba, R. G. Synman, B. Opeolu, "Human exposure, Biomarkers and Fate of Organotin in the Environment, *Reviews of Environmental Contamination and Toxicology*, 213, 2011, 27-54.