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Studies on the Synthetic and Biological Activity of Some Organotin (IV) Derivatives of Hexanedioic Acid

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Abstract: *This study assessed the antimicrobial activity of four synthesized organotin (IV) derivatives of potassium hydrogen hexanedioate,* ***L****: Bu_2SnL_2* ***(1)****, Bu_3SnL* ***(2)****, Ph_2SnL_2* ***(3)*** *and Ph_3SnL* ***(4)****. The compounds were tested for antimicrobial activity against four strains of Gram-positive bacteria*: *Staphylococcus aureus, Streptococcus pyogenes, Bacillus cereus, Corynebacterium ulcerans, four strains of Gram- negative Bacteria*: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa* and *four fungi strains of :Histoplasma capsulatum, Mucor mucedor, Penicillium helicium and Penicillium chrysogenum. Result showed that the compounds synthesized in general exhibited greater antibacterial and antifungal activity than the potassium hydrogen hexanedioate,* ***L****, and hexanedioc acid at minimum inhibition concentration(MIC) of 7.5 – 15 µg/mL , minimum bactericidal concentration (MBC) of 15 – 60 µg/mL and minimum fungicidal concentration(MFC) of 25- 50 µg/mL. Activities were very closed to that shown by standard drugs: erythromycin, fluconazole and ketoconazole. Organotin moieties are known to play a vital role in deciding the biological activity of an organotin compound, this is true in this work as the order of antibacterial activity was potassium triphenyltin (IV) hexanedioate* ***(4)*** *>potassium tributyltin (IV) hexanedioate* ***(2)****> potassium diphenyltin (IV) hexanedioate* ***(3)****> potassium dibutyltin (IV) hexanedioate****(1)****. The order of antifungal activity was potassium tributyltin (IV) hexanedioate* ***(2)****> potassium triphenyltin (IV) hexanedioate* ***(4)****> potassium diphenyltin(IV) hexanedioate* ***(3)****> potassium dibutyltin (IV) hexanedioate****(1)****.*

Keywords: *Organotin(IV) derivatives, potassium hydrogen hexanedioate, Antimicrobial Activity.*

I. Introduction

Worldwide production of organotin (IV) compounds and their derivatives in recent years have increased considerably owing to their potentials as antifertility [1-3], antiviral [4], antifouling, wood preservatives [5], anticancer, antitumour [6], antituberculosis [7] bactericidal, fungicidal[8,9] agents and as pesticides[10]. These potentials have made organotin (IV) compounds useful in agriculture, industries, medicine [11] and pharmaceuticals [12]. Wide range of biological applications of organotin (IV) complexes reported encourages scientists to design tin based drugs having good activity and low toxicity for cancer chemotherapy due to their apoptotic inducing character [13].

The development of new therapeutic agents is paramount in today's society as more cases of drug resistance are increasingly been reported [14]. The role of metal-based drugs in this regard cannot be relegated as till date, the platinum-based compounds, for instance, are among the few metal-based drugs which are available for cancer treatment. However, recent research has shown that platinum-based drugs are not effective against all forms of cancer. There is therefore an urgent need to develop new metal-based drug therapies against a wide range of diseases [15, 16] and not just for cancer alone. Organotin (IV) carboxylates are widely studied class of organotin (IV) compounds with high pharmaceutical potentials and structural diversity [12] especially with regards to their pesticidal activities [14] as well as antitumour activities against various types of cancer [6] cells.

The broad spectrum of biological and non-biological applications of organotin (IV) compounds depends on the nature and number of organic groups (R) directly bonded to tin atom [6, 9, 13] and on the anionic ligand [14]. The role of the ligand in transportation of organotin (IV) moiety to the target area, where it performs its biocidal activity is known [13, 17].

This present investigation is an extension of our previous work on the synthesis, characterization and antimicrobial activities of some organotin (IV) derivatives of hexanedioic acid [18]. Our interest in the area of therapeutic agents, especially metal-based drugs, is gingered by the search for new effective drugs for human health: in the area of antimicrobials. In an attempt to further explore the interesting features of these organotin (IV) compounds, we report here the synthesis and antimicrobial properties of four organotin (IV) derivatives of hexanedioic acid against four gram negative bacteria, four gram positive bacteria and four fungi.

II. Materials and Methods

All reagents and solvents used for the preparations/synthesis were of analytical grade, with purity ranging from 98-99.8 %. They were obtained from Sigma-Aldrich and were used without further purification.

2.1 Preparation of potassium hydrogen hexanedioate (L)

The ligand (**L**) was prepared according to the method in our earlier report [I7-20]. Potassium hydroxide (0.05 mol, 2.8338 g) and hexanedioic acid (0.05 mol, 7.3808 g) were completely dissolved in 50 mL distilled water and refluxed for 1 hour until a clear solution was obtained. 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 to a constant weight in a desiccator.

2.2 Synthesis of potassium dibutyltin (IV) hexanedioate Bu_2SnL_2 (1) and potassium diphenyltin (IV) hexanedioate: Ph_2SnL_2 (3)

Compounds **(1)** and **(3)** were synthesized as in our earlier report [17-20]. 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) dipropoxide. Water and methanol in the mixture distilled off as an azeotrope at 67 ^{0}C and 96-98 ^{0}C, respectively and solution was cooled. Potassium hydrogen hexanedioate (2.8883 g , 0.008 mol) was refluxed for 1 hour with the cooled solution and kept in an oven for a period of 72 hours at 40 ^{0}C to obtain a white crystalline product **(1)**. Similar procedure was also used in synthesizing compound **(3)** , using triphenyltin (IV) hydroxide (0.0075 mol, 2.7432 g) and potassium hydrogen hexanedioate (0.0078 mol, 1.4441 g) respectively.

2.3 Synthesis of potassium tributyltin (IV) hexanedioate: Bu_3SnL(2) and potassium triphenyltin (IV) hexanedioate: Ph_3SnL(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 refluxed for five hours at 60 ^{0}C to 70 ^{0}C in a Dean and Stark apparatus. The methanol distilled off at 64.5 ^{0}C giving white precipitate which was dried in an oven at 40 ^{0}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 [17-20].

2.4 Physicochemical Measurements

The physiochemical measurements which include melting points (Fisher-Johns microscope), Tin content analysis (using Fansworth and Pekola method) [19], Infrared spectra (from 4000 to 400 cm^{-1} were recorded on FTIR-8400S spectrophotometer (SHIMADZU), using KBr pellets), ^{1}H and ^{13}C NMR spectra (were recorded at room temperature using NMR Nujol 400 MHz spectrophotometer) have been reported in our earlier report [18].

2.5 Biological Investigations

The antibacterial activity of the synthesized compounds was tested on four Gram-positive bacteria: *Staphylococcus aureus, Streptococcus pyogenes, Bacillus cereus, corynebacterium ulcerans* and four Gram-negative bacteria: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa* in Mueller Hinton agar medium. The antifungal activity of the compounds was tested on four test fungi: *Histoplasma capsulatum, Mucor mucedor, Penicillium helicium and Penicillium chrysogenum* in Sabouraud dextrose agar. 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 and dilution method were used, as in our earlier report [17-21].

2.5.1 Agar well diffusion technique

The method adopted for determination of antimicrobial activity of the organotin (IV) compounds was agar well diffusion technique. Mueller Hinton agar and Sabouraud dextrose agar (SDA) were used as culture media for bacteria and fungi 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. Standard inoculums of the test microbes (0.1 mL) were used in seeding the sterile media and spread evenly over the surfaces of the media using a sterile swab. Using a standard cork borer of 6 mm diameter, a well was cut at the centre of each inoculated medium and 200 µg/mL of the test compounds dissolved in DMSO were introduced into their respective wells. Wells of the control were supplemented with standard antibacterial and antifungal drugs: erythromycin and fluconazole & Ketoconazole respectively. The media were incubated at

37 ^{0}C for 24 hours and at 30 ^{0}C for 7 days for the bacteria and fungi respectively, and checked daily for zone of inhibition: areas where the microbes were unable to grow [17- 23].Where zones of inhibition were not observed, the organotin (IV) compounds used were either inactive or concentration used were less than required to inhibit the test organisms.

2.5.2 Broth dilution method

Broth dilution method was used in determining the Minimum inhibition concentrations (MIC) of test compounds. Sabouraud dextrose broth was prepared in a test tube, sterilized at 121 ^{0}C for 15 minutes and allowed to cool. Serial dilutions of test organotin compounds (200 µg/mL, 100 µg/mL, 60 µg/mL, 50 µg/mL, 40 µg/mL, 30 µg/mL, 25 µ/mL, 20 µg/mL, 15 µg/mL, 12.5 µg/mL, 10 µg/mL and 7.5 µg/mL) in sterile broth were made. 1.5 × 10^5 CFU/mL of test fungi in normal saline was made and introduced into each of the concentrations and incubated at 30 ^{0}C for 7 days (fungi) and 37 ^{0}C for 24 hours (bacteria). 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 [17-21].

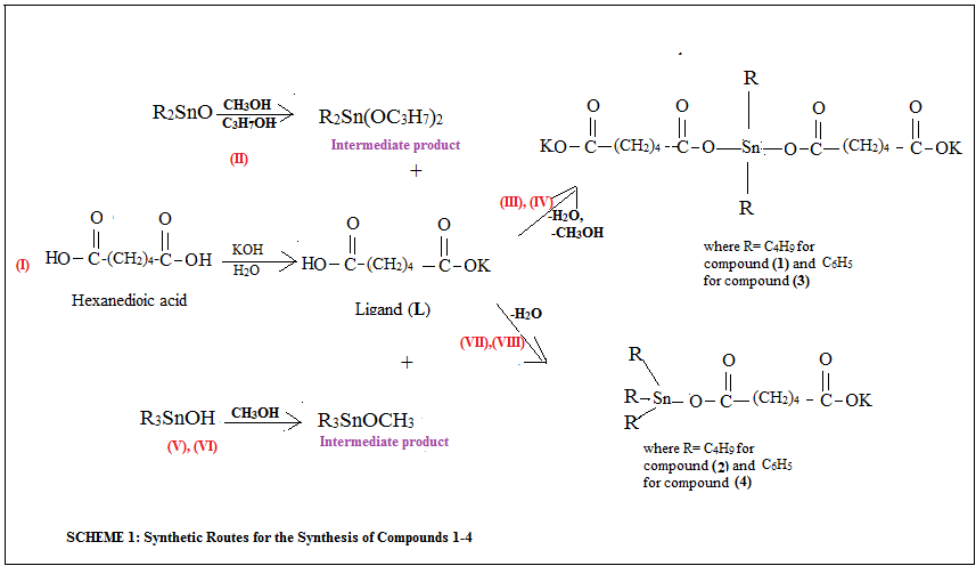
2.5.3 Minimum Bactericidal and Fungicidal Concentrations

In order to ascertain whether the test organisms were killed completely or their growth only inhibited, minimum fungicidal concentration (MFC) and minimum bacterial concentration (MBC) were determined. Content of MIC in the serial dilution were sub cultured onto prepared medium and incubated at 30 ^{0}C and 37 ^{0}C for 7 days 24 hours respectively. Plates were observed for colony growth, MFC and MBC were the plates with lowest concentration of compound without colony growth [17-21].

III. Results and Discussion

3.1 Synthesis

Synthesis of organotin (IV) derivatives of hexanedioic acid (**1-4**) was successfully achieved as earlier reported [18,19]. The reactions occurred in eight steps as shown in scheme 1. The ligand: **L**, $HOCO(CH_2)_4COOK$ was prepared by the reaction between KOH and hexanedioic acid: $HOCO(CH_2)_4COOH$ according to route 1 (scheme 1). $(C_4H_9)_2SnO$ and $(C_6H_5)_2SnO$ were refluxed separately in 4:1 CH_3OH and C_3H_7OH yielding their respective propoxides as intermediates (route II). These intermediates were further reacted with the ligand **L** $HOCO(CH_2)_4COOK$ to yield compounds **1** and **3** (routes III and IV**)**. $(C_4H_9)_3SnOH$ and $(C_6H_5)_3SnOH$ were refluxed in CH_3OH to give their dimethoxides as intermediates (routes V and VI), respectively) which were further reacted with the ligand: $HOCO(CH_2)_4COOK$ to produce compounds **2** and **4** (routes VII and VIII). Water produced in the process was collected in the separator of Dean and Stark apparatus, and eventually removed from the reaction.



SCHEME 1: Synthetic Routes for the Synthesis of Compounds 1-4

3.2 Biological activity

3.2.1 Antibacterial Activity

Antibacterial activity tests of compounds **1-4**, ligand (**L**), $HOCO(CH_2)_4COOK$ and hexanedioic acid ($HOCO(CH_2)_4COOH$) were carried out against eight bacterial strains; four Gram-Positive: *Staphylococcus aureus, Streptococcus pyogenes, Bacillus cereus and Corynebacterium ulcerans* and four Gram-negative bacteria: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa*). Reports have shown that the criteria for activity is based on zone of inhibition (mm); zone of inhibition of more than 20 mm shows significant activity, for 18-20 mm inhibition activity is good, 15-17 mm is low, and below 11- 14 mm is non-significant activity [2,24,25]. Antibacterial result in this worked revealed that the acid: hexanedioic acid and its salt, the ligand: **L**, **(**$HOCO(CH_2)_4COOK$), showed antibacterial activity ranging from 24 – 27 mm with minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC) ranging from 10 - 20 μg/mL and 20 – 40 μg/mL, respectively (table 1 and 2).

Table 1: Antibacterial Activity of Hexanedioic acid: $HOCO(CH_2)_4COOH$

Test Organism	Effect	Inhibition Zone(mm)	MIC(μg/mL)	MBC(μg/mL)
S. aureus	S	24	10	20
S. pyogenes	R	0	0	0
B. cereus	R	0	0	0
C. ulcerans	S	25	20	40
E. coli	S	26	20	40
K.. pneumoniae	S	25	10	20
P.mirabilis	R	0	0	0
P. aeruginosa	R	0	0	0

Key: S = Sensitivity, R = Resistance, *S. aureus = Staphylococcus aureus , S. pyogenes = Streptococcus pyogenes, B. cereus= Bacillus cereus C. ulcerans = Corynebacterium ulcerans, E. coli = Escherichia coli, K. pneumoniae = Klebsiella pneumoniae, P. mirabilis = Proteus mirabilis, P. aeruginosa = Pseudomonas aeruginosa*

Table 2: Antibacterial Activity of Ligand, L: $HOCO(CH_2)_4COOK$

Test Organism	Effect	Inhibition Zone(mm)	MIC(μg/mL)	MBC(μg/mL)
S. aureus	S	27	15	30
S. pyogenes	R	0	0	0
B. cereus	R	0	0	0
C. ulcerans	S	27	15	40
E. coli	S	26	15	20
K. pneumonia	S	26	15	20
P. mirabilis	R	0	0	0
P. aeruginosa	R	0	0	0

Key: S = Sensitivity, R = Resistance, *S. aureus = Staphylococcus aureus , S. pyogenes = Streptococcus pyogenes, B. cereus= Bacillus cereus, C. ulcerans = Corynebacterium ulcerans, E. coli = Escherichia coli, K. pneumoniae = Klebsiella pneumoniae, P. mirabilis = Proteus mirabilis, P. aeruginosa = Pseudomonas aeruginosa*

Compounds **1-4** exhibited significant activity against all tested bacterial strains with the zones of inhibition observed ranging from 25-34 mm (tables 3 – 6) which are close values to that recorded for the standard drug: Erythromycin (30 -37 mm) used in this assay as control drug (table 7). They were observed at a lower MIC and MBC than that recorded for **L** and hexanedioic acid. However, there were few cases where the compounds, ligand **L, (**$HOCO(CH_2)_4COOK$) and standard drug did not show activity against some strains. Even though, erythromycin showed higher activity, it showed no activity against *Bacillus cereus, Proteus mirabilis* and *Pseudomonas aeruginosa.*

Table 3: Antibacterial Activity of Compound 1: potassium dibutyltin (IV) hexanedioate, Bu_2SnL_2

Test Organism	Effect	Inhibition Zone(mm)	MIC(μg/mL)	MBC(μg/mL)
S. aureus	S	32	7.5	30
S. pyogenes	S	26	15	30
B. cereus	S	29	7.5	15
C. ulcerans	R	0	0	0
E. coli	S	27	7.5	20
K. pneumonia	R	0	0	0
P. mirabilis	S	24	15	20
P. aeruginosa	R	0	0	0

Key: S = Sensitivity, R = Resistance

Table 4: Antibacterial Activity of Compound 2: potassium tributyltin (IV) hexanedioate, Bu_3SnL

Test Organism	Effect	Inhibition Zone(mm)	MIC(μg/mL)	MBC(μg/mL)

S.aureus	R	0	0	0
S. pyogenes	S	30	7.5	20
B. cereus	S	32	7.5	15
C.ulcerans	R	0	0	0
E. coli	S	29	7.5	15
K. pneumonia	S	30	7.5	15
P. mirabilis	R	0	0	0
P.aeruginosa	S	28	15	20

Key: S = Sensitivity, R = Resistance

Table 5: Antibacterial Activity of Compound 3: potassium diphenyltin (IV) hexanedioate, Ph_2SnL_2

Test Organism	Effect	Inhibition Zone(mm)	MIC(µg/mL)	MBC(µg/mL)
S. aureus	S	33	15	15
S.pyogenes	S	24	15	15
B. cereus	S	26	7.5	15
C. ulcerans	R	0	0	0
E. coli	R	0	0	0
K. pneumonia	S	25	7.5	15
P. mirabilis	S	27	7.5	15
P. aeruginosa	R	0	0	0

Key: S = Sensitivity, R = Resistance

Table 6: Antibacterial Activity of Compound 4: potassium triphenyltin (IV) hexanedioate, Ph_3SnL

Test Organism	Effect	Inhibition Zone(mm)	MIC(µg/mL)	MBC(µg/mL)
S. aureus	S	34	15	15
S. pyogenes	S	28	15	30
B. cereus	S	28	15	30
C. ulcerans	R	0	0	0
E. coli	S	26	15	30
K. pneumonia	R	0	0	0
P. mirabilis	S	28	15	60
P.aeruginosa	S	27	7.5	20

Key: S = Sensitivity, R = Resistance

Table 7: Antibacterial Activity of the control drug: Erythromycin

Test Organism	Effect	Inhibition Zone(mm)	MIC(µg/mL)	MBC(µg/mL)
S. aureus	S	35	10	10
S. pyogenes	S	32	10	10
B. cereus	R	0	0	0
C. ulcerans	S	37	10	10
E. coli	S	32	10	10
K. pneumonia	S	30	10	10
P. mirabilis	R	0	0	0
P. aeruginosa	R	0	0	0

Key: S = Sensitivity, R = Resistant

It was noted that compounds **1**, **3** and **4** exhibited significant activity against *Staphylococcus aureus* with zones of inhibition of 32, 33 and 34 mm (tables 3, 5 & 6) respectively, which were close to observed activity of the control drug: erythromycin (35 mm at MIC and MBC of 10 µg/mL). These synthesized compounds inhibited *Staphylococcus aureus* at low MIC (7.5-15 µg/mL) and MBC (15-30 µg/mL). The ligand **L,** $HOCO(CH_2)_4COOK$ and hexanedioic, $HOCO(CH_2)_4COOH$ acid (tables 2 and 1, respectively) showed a lower antimicrobial activity against *Staphylococcus aureus* with inhibition zones of 27 mm and 24 mm respectively. This implied that, an increase in antimicrobial activity was recorded when the salt of the acid was prepared (scheme 1, route 1) and reacted with organotin (IV) compound with R = Bu_2 or $(C_4H_9)_2$, Ph_2 or $(C_6H_5)_2$ and Ph_3 or $(C_6H_5)_3$ to synthesize compounds **1**, **3** & **4** respectively, (scheme, 1 routes III, VII & VIII). Compound **4** exhibited the highest activity while compound **2** showed no activity against the test microbe. The order for the compounds against *Staphylococcus aureus* is **4** > **3** >**1**.

Streptococcus pyogenes and *Bacillus cereus* were sensitive to all the synthesized compounds, **1-4** (tables 3– 6) with inhibition zones ranging from 26 -32 mm at MIC and MBC of 7.5-15 µg/mL and 15-30 µg/mL but showed resistance to hexanedioic acid (table 1), ligand, L (table 2) and the control drug: erythromycin (tables 7). However, erythromycin exhibited significant activity: 32 mm against *Streptococcus pyogenes* at MIC and MBC of 10 µg/mL. Since, hexanedioic acid, $HOCO(CH_2)_4COOH$ and ligand **L**, $HOCO(CH_2)_4COOK$ did not exhibit activity against these microbes until they reacted with parent organotin (IV) compounds to yield compounds **1** – **4**, the organotin (IV) moiety could have conferred the antimicrobial activity

on the compounds. Literature has shown that biological activity of organotin (IV) compounds especially depend solely on the organotin moiety; R_2Sn^{2+} and R_3Sn^{+} (where R = Bu or Ph) [26].

Corynebacterium ulcerans resisted all the synthesized compounds but was sensitive to hexanedioic acid (25 mm), L (27 mm) and erythromycin (37 mm) at MIC and MBC of 10 - 40 µg/mL. Highest antimicrobial activity in this work was exhibited by erythromycin against this test organism at lower MIC and MBC of 10 µg/mL. On the other hand, hexanedioic acid, **L** and erythromycin could not inhibit the growth of *Proteus mirabilis* and *Pseudomonas aeruginosa* at the concentrations used. Compounds **1**, **3** and **4** inhibited the growth of *Proteus mirabilis* to about 24 mm, 27 mm and 28 mm, respectively, at MIC and MCB of 7. 5 µg/mL- 60 µg/mL. Compound **2**, could not inhibit the growth of *Proteus mirabilis.* Compounds **2** and **4** (28 mm and 27 mm , respectively) showed activity against *Pseudomonas aeruginosa* while compounds **1** and **3** were resisted by the test microbe.

Hexanedioic acid, **L** and erythromycin exhibited significant antimicrobial activity 25 – 32 mm against *Escherichia coli* and *Klebsiella pneumoniae.* Compounds **1**, **2** and **4** inhibited the growth of *Escherichia coli* while compound **3** could not. On the other hand, compounds **2** and **4** showed activity with inhibition zones of 30 mm and 25 mm, respectively, against *Klebsiella pneumoniae* while Compounds **1** and **3** could not inhibit their growth.

Compounds **1** – **4**, generally exhibited significant antimicrobial activity against test microbes at relatively low MIC and MBC. MIC, being the lowest/minimum concentration of a chemical (antimicrobial drug) that prevents visible growth of microbes overnight [27] demonstrated strong antimicrobial activities of synthesized compounds **1** – **4,** against both gram-positive and gram-negative bacteria which are associated with different types of diseases such as: pneumonia, wound infections, abscesses, sinuses, inflammation of bronchiole walls, diarrhea, fever and urinary tract infection though under specific MIC's and MBC's. In medicine, MIC determination in patients done by culturing the organism using patients body fluids or tissues is very important in identifying the correct drug actually required to prescribe and administer against a diagnosed ailment [28]. It is therefore a first step in drug discovery programs [29]. The synthesized compounds indicated their potency at low MIC ranging from 7.5 - 15 µg/mL against all test microbes which were better than potency exhibited by erythromycin at some instances especially at MIC of 7.5 µg/mL and where microbes showed resistance to erythromycin but were sensitive to compounds **1** – **4**. MBC of the compounds also demonstrated that the microbes were killed at concentrations mostly ranging from15 µg/mL to 30 µg/mL. Compound **4** recorded its MBC at 60 µg/mL against *Proteus mirabilis.*

The observation that compounds **1**-**4** and **L**, exhibited higher antibacterial activity than hexanedioic acid could be as a result of the presence of metal ions in their sructures which may have increased antibacterial activity when the acid was coordinated to 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 [30]

3.2.2 Antifungal Activity

Synthesized compounds and ligand **L**, were screened for antifungal activity against four fungal strains: *Histoplasma capsulatum, Mucor mucedor, Penicillium helicium and Penicillium chrysogenum* by using dilution method [17-22]. Results for their zones of inhibition are shown in fig. 1 while MIC and MFC are shown from figures 2 - 7. The result revealed that all the compounds exhibited significant activity against test fungi with compounds **2** and **4** (trioganotin (IV) compounds) exhibiting the highest activity against *Penicillium chrysogenum* (28 mm) and *Mucor mucedor* (28 mm) respectively.

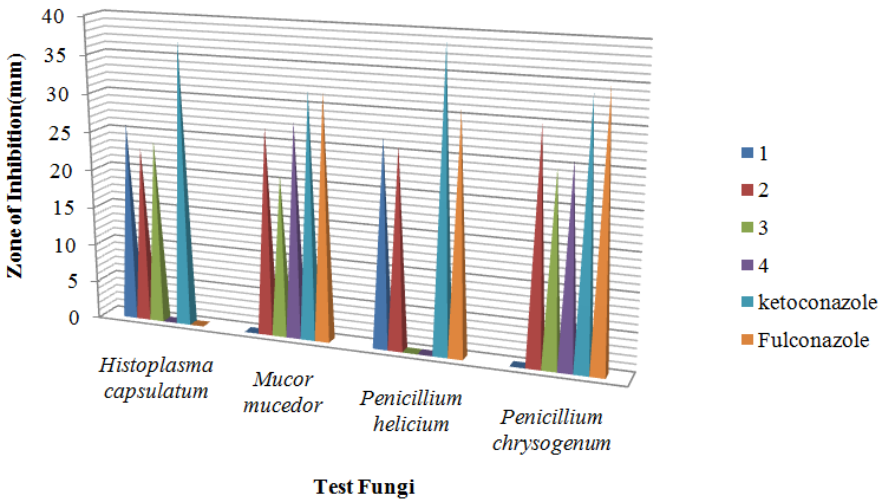


Figure 1: Zone of Inhibition of compounds against test fungi

This activity occurred at the MIC and MFC of 25 µg/mL and 100 µg/mL respectively, for both compounds (fig. 2 and 5). The standard drug: ketoconazole showed a higher antifungal activity with the zone of inhibition of 35 mm and 32 mm against *Penicillium chrysogenum* and *Mucor mucedor* respectively, observed at the same MIC and MFC (50 µg/mL). Since the MIC of compounds **2** and **4** observed are lower than the MIC observed for ketoconazole(50 µg/mL) against these same microbes, they seem to be more effective antifungal agents than this standard drug. Fluconazole exhibited activity against *Penicillium chrysogenum* (35 mm) and *Mucor mucedor* (32 mm) at the MIC of 50 µg/mL & 25 µg/mL, respectively and MFC of 50 µg/mL (fig. 6 and 7). These microbes were resistant to compound **1**but sensitive to compound **3** with the respective zone of inhibition of 20 mm and 24 mm (fig. 1) observed at MIC of 25 µg/mL. Of all the compounds synthesized, only compound **2**, the tributyltin(IV) compound, that showed activity for all the test fungi with MIC between 25- 50 µg/mL (fig.3) as also demonstrated by ketoconazole with MIC/MBC at 50 µg/mL (fig.7).

Compounds **1**, **2** and **3** exhibited significant antifungal activity against *Histoplasma capsulatum* with observed zones of inhibition of 26 mm, 23 mm and 23 mm respectively, which were observed at MIC & MFC of 50 µg/mL & 100 µg/mL, 50 µg/mL & 200 µg/mL and 50 µg/mL & 100 µg/mL, respectively. This fungi resisted compound **4** and fluconazole but sensitive to ketoconazole which exhibited the highest activity of 37 mm at MIC and MFC of 50 µg/mL. Ketoconazole have similar MIC (50 µg/mL) with compounds **1**, **2** and **3**, however, the compounds recorded higher MFC which signified that only higher concentrations of the compounds could effectively kill *Histoplasma capsulatum*.

Compounds **1** and **2** inhibited the growth of *Penicillium helicium* (27 mm and 28 mm, respectively) at the same MIC of 25 µg/mL and MFC of 100 µg/mL. Fuconazole and ketoconazole exhibited antifungal activity of 31 mm and 39 mm respectively at the same MIC and MFC of 50 µg/mL. Compounds **3** and **4** could not inhibit the growth of *Penicillium helicium* at the concentrations used.

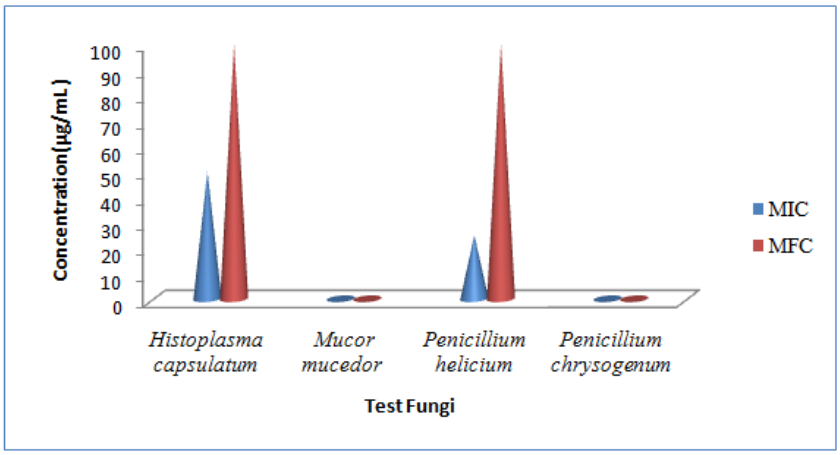


Figure 2: Minimum Inhibition Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of compound **1**

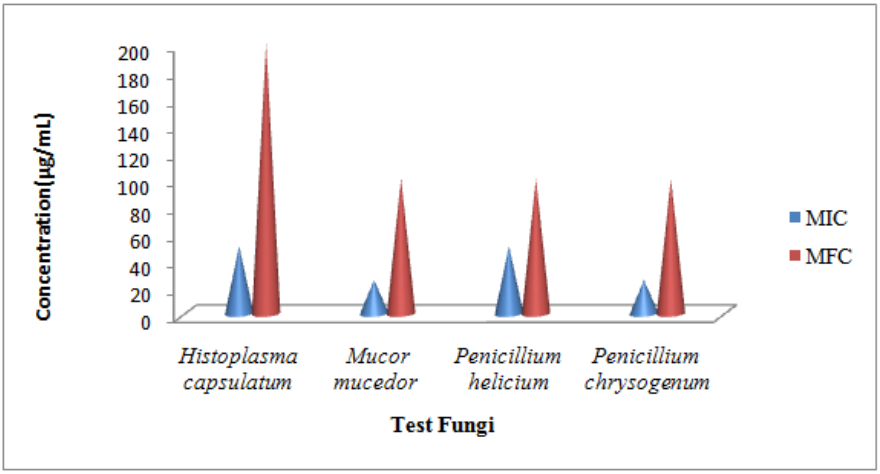


Figure 3: Minimum Inhibition Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of compound **2**

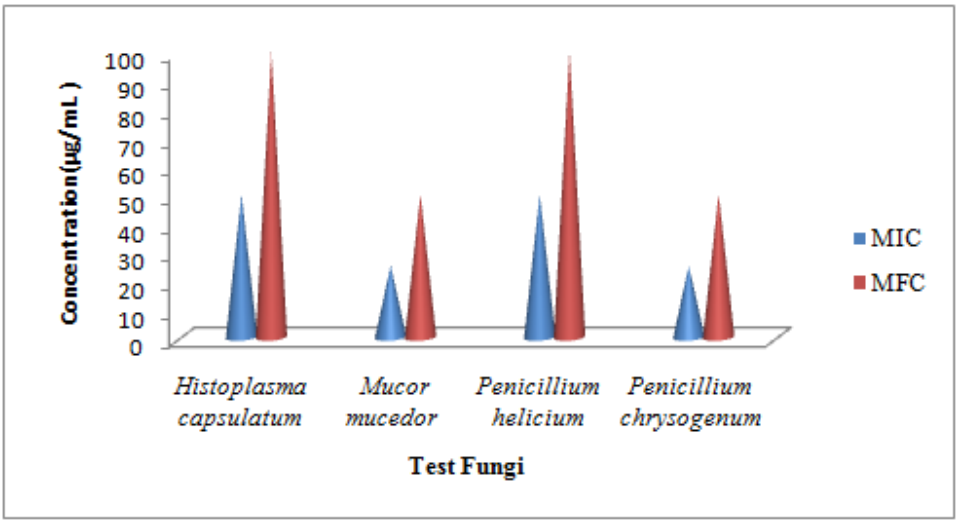


Figure 4: Minimum Inhibition Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of compound **3**

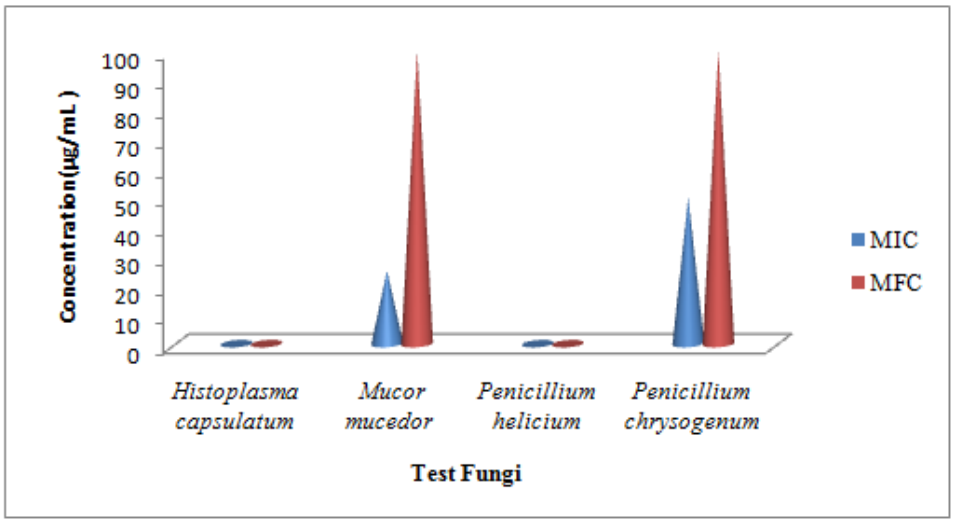


Figure 5: Minimum Inhibition Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of compound **4**

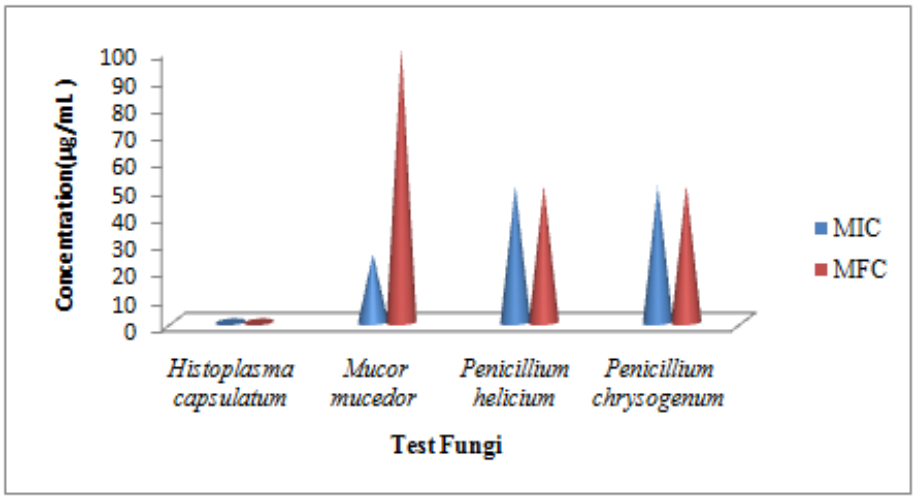


Figure 6: Minimum Inhibition Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of Fulconazole

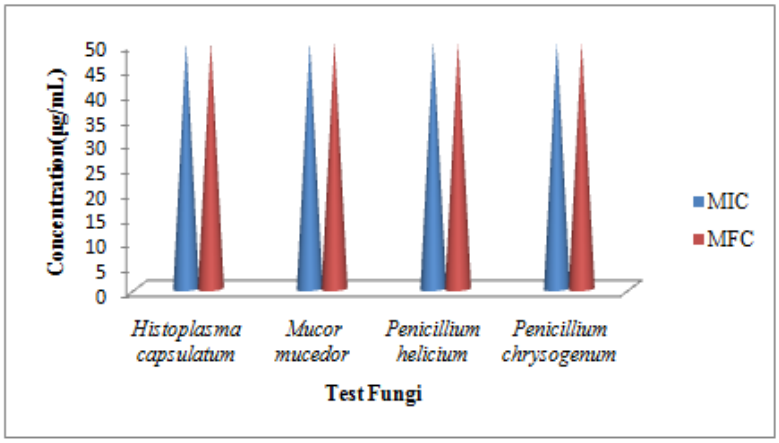


Figure 7: Minimum Inhibition Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of Ketoconazole

Generally, this study demonstrated that compounds **2** and **4**, the triorganotin (IV) compounds showed slightly greater antifungal activity than compounds **1** and **3**, the diorganotin (IV) counter parts. This implied that antifungal activity of these compounds are dependent on the nature of organic groups attached to the metal centre in the order Ph > Bu, that is Ph_3 > Ph_2 > Bu_3 > Bu_2. This is consistent with literature and may be due to the bulky organo group which increases lipophilicity of these compounds [31] as well as their permeability through the cell membrane [2, 3, 23, 25]. Literature has reported that, carboxylate groups influence the delivery of organotin (IV) moiety to the point of action [13]

IV. Conclusion

Biological activity result in this study generally showed that, all compounds synthesized exhibited high antibacterial and antifungal property at low MIC and MBC/MFC. Compound **4**, a triphenyltin (IV) dicarboxylate showed higher antifungal activity than compound **2** its tributyl counterpart while compound **3**, a diphenyltin (IV) dicarboxylate showed higher antifungal activity than compound **1**, its dibutyl counterpart. The order of antifungal activity for compounds **1**-**4** is **4** > **2** > **3** >**1**. Even though, compound **4** showed highest activity (34 mm) against *Staphylococcus aureus,* compound **2** exhibited slightly higher activity against other strains of bacteria. The order of antibacterial activity in this study therefore, is **2** > **4** > **1**> **3**. Since diorganotin (IV) compounds are not known for their high biological activities, the activity of compounds (**1)** being slightly above compound **3**, in this study could probably be due to the potassium and Sn ions present in their structures. 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 microorganisms used in this study are responsible for some health conditions.

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