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Potential bioactive mononuclear diorganotin(IV) phenoxyacetohydroxamate complexes: synthesis, characterization and antimicrobial evaluation

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Abstract: The new diorganotin(IV) complexes of composition $[\text{Me}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2](\text{I})$ and $[\text{n-Bu}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2](\text{II})$ have been synthesized by the reactions of Me_2SnCl_2 and $\text{n-Bu}_2\text{SnCl}_2$ with potassium phenoxyacetohydroxamate ($\text{PhOAHK}=\text{C}_6\text{H}_5\text{OCH}_2\text{CONHOK}$) in 1:2 molar ratio in methanol and benzene solvent medium and characterized by elemental analyses and spectroscopic techniques (infrared, ^1H nuclear magnetic resonance and mass spectrometry). The [O,O coordination] through carbonyl and hydroxamic oxygen atoms and distorted octahedral geometry around the mononuclear tin has been inferred. The electrochemical behavior of complexes studied by the cyclic voltammetric technique has shown quasi-irreversible two-step reduction from tin (IV) to tin (II). Thermal behavior of complexes studied by the thermogravimetric technique in N_2 atmosphere has yielded SnO as the decomposition product. The *in vitro* antimicrobial activity assays against various pathogenic Gram-negative bacteria, namely, *Salmonella typhi*, *Escherichia coli*; Gram-positive *Bacillus cereus* and *Staphylococcus aureus* and fungi *Aspergillus niger* and *Alternaria alternata* by the minimum inhibitory concentration method have shown their potential as promising antimicrobial agents compared to the respective standard chloramphenicol and nystatin drugs.

Keywords: antimicrobial activity; diorganotin(IV) complexes; phenoxyacetohydroxamate; spectral studies.

Introduction

Hydroxamic acids and their derivatives with general formula RCONHOH and R-CO-NR-OH , naturally occurring

(siderophores) or synthetic derivatives, are an important class of organic bio-ligands which act as excellent chelating agents because they exhibit tautomerism and possess high physiological and biochemical activity (Codd, 2008). The medicinal and pharmacological properties of hydroxamic acid derivatives (Muri et al., 2002) as antitumor, anti-inflammatory (Pavelic et al., 2010), antibacterial, insecticidal, anti-hypertensive (Webb et al., 2008) and antimalarials (Holland et al., 1998) are well documented (Ugwu et al., 2014). Hydroxamic acids have been widely investigated as potent and selective inhibitors of a range of metalloenzymes and matrix metalloproteinases (Nishino and Powers, 1978; Dooley et al., 2003; Takayama et al., 2003; Sani et al., 2004; Senger et al., 2016; Wang et al., 2016). The literature reveals that acetohydroxamic acid and its derivatives viz. 2-(*p*-chlorobenzamido)acetohydroxamic acid (Benurestat), β butoxyphenylacetohydroxamate (bufexamac) and 2-pyridylacetohydroxamic acid are inhibitors of several metalloenzymes (Farkas et al., 1999; Benini et al., 2000; Rudzka et al., 2005; Kumar and Kayastha, 2010; Andrieux et al., 2011).

Of the organometallic compounds of the main group elements, the chemistry of organotin(IV) complexes has received immense research interest over the years (Das and De, 1995; Gielen, 2003; Shang et al., 2008) because of their interesting structural features (Yin et al., 2011) and a broad spectrum of potential applications in agriculture, medicine (Pellerito and Nagy, 2002), industry and material science. There are abundant reports on the therapeutic properties of organotin compounds as anti-cancer (Tabassum and Pettinari, 2006; Amir et al., 2014; Williams et al., 2016), non-steroidal anti-inflammatory (Demertzi, 2006), anti-hypotensive (Webb et al., 2008), antitumor (Gielen et al., 2005; Hadjikakou and Hadjiliadis, 2009; Arjmand et al., 2014), antiviral (Demertzi, 2006), antibacterial (Basu Baul, 2008) and antiparasitic agents (Niu et al., 2014). For the last two decades, there has been a tremendous research interest toward transition metal hydroxamates owing to their fascinating structural chemistry, redox ability and versatile biological significance. Despite the fact that the chemistry of organotin compounds has been one of the most active research areas because of their diversified applications, only a few scattered reports are available on organotin

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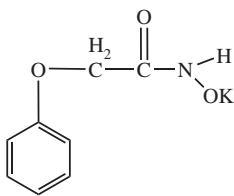


Figure 1: Structure of ($C_6H_5OCH_2CONHOK=PhOAHK$).

hydroxamates. Notably, di-organotin(IV) complexes derived from a variety of ligands exhibit a rich biochemical and physiological profile as effective drug compounds (Pellerito and Nagy, 2002). In view of the biological significance of organotin(IV) hydroxamates, the present paper aims to synthesize a new class of useful biologically important chemical compounds with low toxicity and high specificity. The di-organotin(IV) hydroxamates using Me_2SnCl_2 and $n-Bu_2SnCl_2$ as starting materials and the yet unexplored biologically important functionally substituted acetohydroxamate ligand potassium phenoxyacetohydroxamate (PhOAHK), which is known to possess fungicidal activity, have been synthesized and characterized (Figure 1). The *in vitro* antimicrobial activity of complexes has been evaluated against pathogenic bacteria and fungi.

Results and discussion

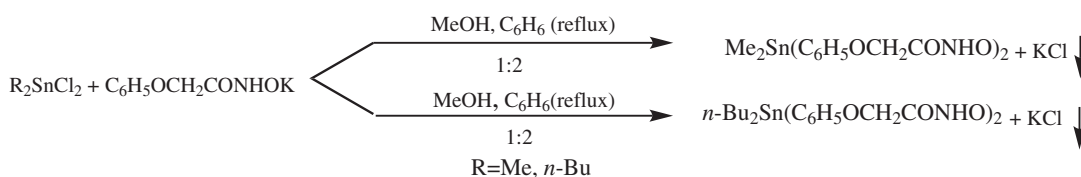
The reactions of dimethyl and di-*n*-butyltin dichloride (R_2SnCl_2) with PhOAHK in predetermined 1:2 molar ratio (metal/ligand) in anhydrous methanol and benzene under reflux afforded $R_2Sn(PhOAH)_2$ ($R=Me, n-Bu$) in quantitative yield in conformity with their elemental analyses in accordance with the following equations (Scheme 1). The complexes are melting solids and soluble in organic solvents viz. methanol, benzene and dimethylsulphoxide. The molar conductance values of $Me_2Sn(PhOAH)_2$ and $n-Bu_2Sn(PhOAH)_2$ in methanol of magnitude 8.23 and 8.61 $\Lambda m S cm^2 mol^{-1}$, respectively, are suggestive of their non-electrolytic nature. The molecular weight determination of complexes by Rast's camphor method has indicated these to exist as monomers (Khosla et al., 2008).

IR spectra

A comparison of the infrared (IR) spectra of diorganotin(IV) phenoxyacetohydroxamates with that of free ligand PhOAHK scanned in the $4500-450 cm^{-1}$ region has supported their formation. The PhOAHK exhibited characteristic bands at 3217, 1643, 1365 and $985 cm^{-1}$ attributed to $\nu(N-H)$, $\nu(C=O)$, $\nu(C-N)$ and $\nu(N-O)$ modes respectively. The complexes of composition $Me_2Sn(PhOAH)_2$ and $n-Bu_2Sn(PhOAH)_2$ displayed these bands at 3292, 3292; 1598, 1598; 1374, 1373 and 982, $989 cm^{-1}$ due to respective modes. The retention of bands due to the $\nu(N-H)$ mode in complexes has suggested the exclusion of coordination through nitrogen. The observed trend of shifts in the $\nu(C=O)$ mode to lower wavenumbers by $45 cm^{-1}$ and those of the $\nu(C-N)$ and $\nu(N-O)$ modes to higher wavenumbers have suggested bonding through carbonyl and hydroxamic oxygen atoms [O,O coordination], establishing the bidentate nature of the ligand. The appearance of new bands in the $530-499 cm^{-1}$ region (not present in the free ligand) assigned to the $\nu(Sn-O)$ mode has substantiated their formation.

1H NMR spectra

A comparison of the 1H nuclear magnetic resonance (NMR) spectra of di-organotin(IV) hydroxamates with that of free ligand has further supported their formation. The free PhOAHK exhibited proton resonances due to NH, aromatic and aliphatic $-CH_2-$ groups at δ 8.08; δ 6.79–7.31 and δ 4.24–4.90 ppm, respectively. Complexes of composition $[Me_2Sn(PhOAH)_2]$ and $[n-Bu_2Sn(PhOAH)_2]$ have displayed these diagnostic resonances at δ 9.12–10.92, δ 9.16–10.88 ppm; δ 6.85–7.30, δ 6.84–7.29 ppm and δ 3.61–4.72, δ 3.45–4.71 ppm respectively. The signals due to methyl and *n*-butyl groups attached to tin appeared at δ 0.76 ppm and at δ 0.84–0.88 (t; CH_3), 1.26–1.35 (m; γCH_2), 1.39–1.48 (m; βCH_2) and 1.55–1.63 (m; αCH_2) ppm range, respectively.



Scheme 1: Synthesis of complexes.

Table 1: Mass spectra of $[\text{Me}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$ and $[\text{n-Bu}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$.

$[\text{Me}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$	m/z (%)	$\text{n-Bu}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$	m/z (%)
$[\text{Me}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$	480 (2.8)	$[\text{n-Bu}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$, Di-tin fragments	565
Di-tin fragments	Molecular peak		
$[\text{Me}_4\text{Sn}^{119}_2(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]^+$	630 (3.5)	$[\text{n-Bu}_4\text{Sn}^{119,120}_2(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]^+$	799 (6.4)
$[\text{Me}_2\text{Sn}^{119}_2(\text{C}_6\text{H}_5\text{OCH}_2\text{CONO})(\text{CH}_2\text{CONO})]^+$	505 (4.2)	$[\text{n-Bu}_3\text{Sn}^{119,119}_2(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})(\text{CH}_2\text{CONHO})]^+$	648
Mono-tin fragments		Mono-tin fragments	
$[\text{Me}_2\text{Sn}^{122}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})(\text{CH}_2\text{CONO})]^+$	390 (5)	$[\text{n-Bu}_2\text{Sn}^{119}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})(\text{CH}_2\text{CONHO})]^+$	474 (7.8)
$[\text{Sn}^{116}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONO})(\text{CH}_2\text{CONO})]^+$	353 (25)	$[\text{n-Bu}_2\text{Sn}^{120}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})]^+$	400 (100)
$[\text{Me}_2\text{Sn}^{119}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})]^+$	315 (100)	$[\text{n-Bu}_2\text{Sn}^{119}(\text{CH}_2\text{CONHO})]^+$	306 (15)
$[\text{Me}_2\text{Sn}^{119}(\text{CH}_2\text{CONHO})]^+$	222 (96)	$[\text{Sn}^{120}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})]^+$	286
$[\text{Me}_2\text{Sn}^{120}\text{O} + \text{H}^+]^+$	167	$[\text{n-Bu}_2\text{Sn}^{120}]$	234 (4.5)
$[\text{Me}_2\text{Sn}^{120}]$	150 (3)	$[\text{n-BuSn}^{120}\text{O} + \text{H}^+]^+$	194 (6)
$[\text{C}_6\text{H}_5\text{OCH}_2]^+$	107 (20)	$[\text{Sn}^{120}\text{O}]$	136
		$[\text{C}_6\text{H}_5\text{OCH}_2]^+$	107 (8)

Mass spectra

The electrospray ionization mass spectra (ESI-MS) of $[\text{Me}_2\text{Sn}(\text{PhOAH})_2]$ (I) and $[\text{n-Bu}_2\text{Sn}(\text{PhOAH})_2]$ (II) have been recorded. Complex (I) has displayed a low intense molecular ion peak at m/z (%) 480 (2.8). Complexes (I) and (II) have exhibited the most abundant peak at m/z (%) 315 (100) and 400 (100) corresponding to $[\text{Me}_2\text{Sn}^{119}(\text{PhOAH})]^+$ and $[\text{n-Bu}_2\text{Sn}^{120}(\text{PhOAH})]^+$, respectively. The fragment ions observed at higher than molecular mass at m/z (%) 630 (3.5) and 799 (6.4) in (I) and (II) have occurred due to the association of Me_2Sn - and $\text{n-Bu}_2\text{Sn}$ - moiety with the respective complexes (Table 1). Most of the significant peaks have been rationalized in terms of fragment ions of specific composition and fit in well with a successive fragmentation pattern of mononuclear complexes. Based on physicochemical and spectral studies, six-coordinate distorted octahedral geometry around tin in complexes may tentatively be proposed as shown in Figures 2 and 3.

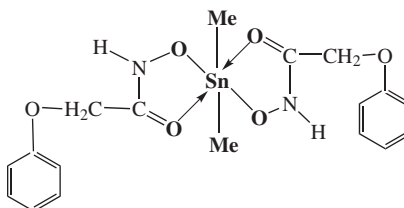
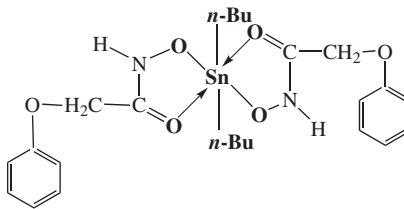
Cyclic voltammetry

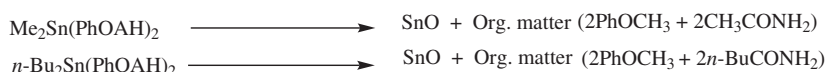
Complex of composition $[\text{Me}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$ exhibited two reduction waves at 0.573 and +0.727 V and one feeble oxidative peak at -0.559 V as a counterpart of a former reductive peak. $[\text{n-Bu}_2\text{Sn}(\text{C}_6\text{H}_5\text{OCH}_2\text{CONHO})_2]$ displayed two reduction waves at +0.725 and -0.554 V and one oxidation wave at -0.520V. No anodic counterpart of reductive wave at +0.725 V appeared in regions different from those observed for free ligand (one oxidative and one reductive peak), suggesting these to be metal centered rather than ligand centered. The I_{pa}/I_{pc} ratio (<1) has suggested

quasi-irreversible reduction. The electrochemical data reveal that the tin (IV) state is easily reduced to tin (II) by a two-step reduction process.

Thermogravimetric study

The thermal behavior of (I) and (II) studied by the thermogravimetric analysis (TGA) technique in the N_2 atmosphere has shown these to be thermally stable up to 88.30°C and 109.17°C, respectively. Mass loss of 71.87 and 76.06% in a single step in the 88.30°C–360.25°C and 109.17°C–435.25°C range accounted for the formation of SnO as the gray-black residue and methyl phenyl ether

**Figure 2:** Proposed structure of $[\text{Me}_2\text{Sn}(\text{PhOAH})_2]$.**Figure 3:** Proposed structure of $[\text{n-Bu}_2\text{Sn}(\text{PhOAH})_2]$.



Scheme 2: Thermal decomposition of complexes.

and acetamide/pentanamide as the tentative volatile organic decomposition products in accordance with the equations in Scheme 2.

Antimicrobial activity

The *in vitro* antimicrobial activity of the ligand (PhOAHK) and di-organotin(IV) hydroxamates has been evaluated against selected Gram-positive bacteria *Bacillus cereus* and *Staphylococcus aureus* and Gram-negative bacteria *Salmonella typhimurium* and *Escherichia coli* and pathogenic fungi *Aspergillus niger* and *Alternaria alternata* at different concentrations in dimethyl sulfoxide (DMSO) using the standard minimum inhibitory concentration (MIC) method recommended by the National Committee for Clinical Laboratory Standards. The commercial antibiotics chloramphenicol and nystatin have been used as standards for the comparison of results.

Antibacterial activity

PhOAHK showed inhibitory effect against test bacteria in the MIC 12.5–25 $\mu\text{g/mL}$ range. Both complexes I and II have shown remarkably enhanced inhibitory activity at the MIC 1.56–3.125 $\mu\text{g/mL}$ range (Figure 4) relative to that of chloramphenicol at the MIC 3.91–7.80 $\mu\text{g/mL}$ range against test bacteria.

Antifungal activity

The ligand PhOAHK has been observed to exhibit high inhibitory effect against *A. niger* and *A. alternata* at MIC 1.56 and 3.125 $\mu\text{g/mL}$, respectively. Complexes of composition $[\text{Me}_2\text{Sn}(\text{PhOAH})_2]$ and $[\text{n-Bu}_2\text{Sn}(\text{PhOAH})_2]$ have shown inhibitory activity similar to that of the ligand against *A. alternata* at MIC 3.125 $\mu\text{g/mL}$ and a lower activity than the ligand against *A. niger*. The antifungal activity of complexes has been found to be quite promising against *A. alternata* compared to standard nystatin, which shows MIC 3.90 $\mu\text{g/mL}$ against test fungi (Figure 5).

The enhanced antimicrobial activity of complexes relative to free ligand may be explained on the basis of chelation theory, whereby the polarity of central metal

ion is reduced because of partial sharing of its positive charge with the ligand on complexation, which favors permeation of the complex through the lipid cell membrane (Chaudhary et al., 2002). The observed promising antimicrobial activity of complexes can also be attributed to the biological significance associated with organotin moiety and phenoxyacetohydroxamate ligand.

Conclusions

The monomeric dimethyl and *n*-butyltin(IV) complexes of the biologically important phenoxyacetohydroxamate ligand have been synthesized and characterized by physicochemical and various spectral techniques. The [O,O coordination] through hydroxamic and carbonyl oxygens has been inferred. The six-coordinate distorted octahedral geometry around tin in mononuclear complexes has been indicated. The complexes are electrochemically active, depicting two electron quasi-irreversible reduction. The thermal behavior of the complexes has shown them to undergo decomposition in a single step to yield SnO as residue. The antimicrobial activity of complexes studied

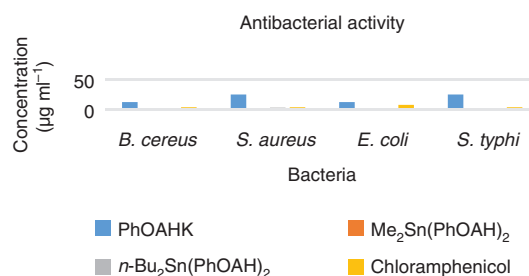


Figure 4: *In vitro* antibacterial spectrum.

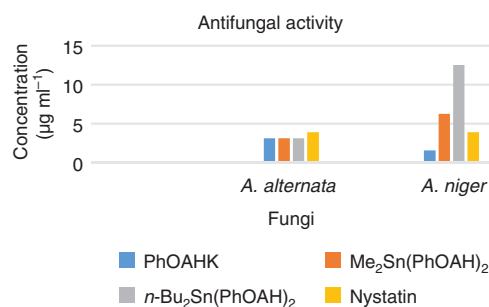


Figure 5: *In vitro* antifungal spectrum.

against pathogenic bacteria and fungi by the MIC method has shown complex $[\text{Me}_2\text{Sn}(\text{PhOAH})_2]$ to be most effective against *B. cereus*. The diorganotin(IV) complexes have shown promising antibacterial and antifungal activity against all the test bacteria and fungi – even better than the standard antibacterial and antifungal drugs chloramphenicol and nystatin, respectively.

Experimental

Materials and instrumentation

The purity of dimethyltin dichloride (Merck, Hohenbrunn, Germany) and di-butyltin dichloride (Merck, Hohenbrunn, Germany) was checked by their melting point (105°C and 42°C), respectively. Phenoxyacetic acid (Merck, Hohenbrunn, Germany) and hydroxylamine hydrochloride (Sisco, Bombay, India) were used as such without further purification. The purity was checked by their melting point at 98°C–102°C and 151°C, respectively. The reagent-grade solvents were dried and distilled prior to use. Potassium phenoxyacetohydroxamate was synthesized by a reported method (Hauser and Renfrow, 1967). The carbon, hydrogen and nitrogen analyses were obtained on a Carlo-Erba 1106 Elemental Analyzer. Tin was estimated as tin dioxide by treating the complex with conc. H_2SO_4 (2 volume) and conc. HNO_3 (3 volume) and heating to 800°C. The molar conductance (10^{-3} M solution in methanol) of complexes was measured at $18 \pm 1^\circ\text{C}$ using CON 510; Bench conductivity/TDS meter (cell constant $K=1.0$). The molecular weights of the complexes were determined by the Rast's camphor method. The IR spectra were recorded in KBr pellets on a Nicolet-5700 FTIR Spectrophotometer (Thermo Electron Corporation, Netherlands). ^1H NMR spectra were recorded on a BRUKER AVANCE II 400 Spectrometer (Billerica, MA, USA) using TMS as an internal standard and DMSO- d_6 as the solvent. The ESI-MS were recorded on a Waters QTOF-MICROMASS mass spectrometer (Water Corporation, Milford, USA). Cyclic voltammetric measurements were carried out on an Autolab Potentiostat 128N electrochemical analyzer (Metrohm Autolab B.V., Kanaalweg, Netherlands) in methanol in single compartmental cell of volume 10–15 mL containing a three-electrode system comprising a Pt-disk working electrode, Pt-wire as auxiliary electrode and Ag/AgCl electrode as reference electrode. The supporting electrolyte was 10^{-2} M KCl in 10^{-4} M methanol. Thermograms (TGA curves) were recorded on a NETZSCH STA 449F1 thermal analyzer (NETZSCH Technologies India Pvt. Ltd., Chennai, India) in N_2 atmosphere. A heating rate of $10^\circ\text{C}/\text{min}$ was employed. The thermocouple used was Pt/Pt-Rh 10% with a temperature range of 10°C – 800°C .

Antimicrobial activity

The *in vitro* antibacterial and antifungal activity of di-organotin(IV) hydroxamate complexes was studied against test bacteria and fungi by the MIC method in a 96-well microtiter plate (tissue culture grade) by the twofold serial dilution method using oxidation-reduction colorimetric indicator Resazurin dye blue in its oxidized state, which turned pink when reduced by viable cells according to Clinical and Laboratory Standards Institute (CLSI M07-A9). A stock solution of test

ligand and complexes was prepared in DMSO (100 $\mu\text{g}/\text{mL}$) for the twofold serial dilution. The test material (complex) (100 μL) was then added in the first row of wells in the microtiter plate. After proper mixing (broth and test complex), 100 μL was withdrawn from the first well (containing test complex) with a sterile tip and same was added to 100 μL of the broth in the second well. Then, 100 μL was withdrawn from the second well and added to the third well. This way a range of twofold serial dilutions were prepared from the initial 100 $\mu\text{g}/\text{mL}$ to 50, 25, 12.5, 6.25, 3.125 and 1.56 $\mu\text{g}/\text{mL}$. The resazurin indicator (0.18%) prepared in distilled water, sterilized by filtration and stored at 4°C for a week was added to each well. The wells were inoculated with 10 μL of the bacterial culture/fungi culture, and the contents were mixed properly on a flat surface. The plates thereafter were wrapped with aluminium foil and incubated at 37°C for 24 h in the case of bacteria and at 28°C for 72 h for fungi. A change in color from purple to pink indicates the growth of bacteria and fungi. The lowest concentration of test complex that prevented this color change was considered as MIC. The results were compared with a standard antibacterial drug for *S. typhi*, *E. coli*, *B. cereus* and *S. aureus* (chloramphenicol) and an antifungal drug for *A. niger* and *A. alternata* (nystatin). All the experiments were carried out in triplicate (Greenwood et al., 1997).

Syntheses of $[\text{Me}_2\text{Sn}(\text{PhOAH})_2]$ and $[\text{n-Bu}_2\text{Sn}(\text{PhOAH})_2]$

To a solution of Me_2SnCl_2 (0.80 g, 0.0036 mol) and $\text{n-Bu}_2\text{SnCl}_2$ (1.11 g, 0.0036 mol) in distilled benzene (10 mL), an equimolar amount of potassium phenoxyacetohydroxamate (1.5 g, 0.0073 mol) in methanol (10 mL) was added in separate experiments and refluxed for 24 h. The white solid formed during the course of the reaction was filtered and identified as KCl. The addition of petroleum ether to the filtrate gave light brown solids (yield = 1.52 g = 87% and 1.73 g = 84%, respectively). For $\text{C}_{18}\text{H}_{22}\text{O}_6\text{N}_2\text{Sn}/480$ (%) Calc. C 45.00; H 4.58; N 5.83; Sn 25.00. Found: C 44.87; H 4.33; N 5.42; Sn 24.87. λ_{m} : 8.23 $\text{S cm}^2 \text{mol}^{-1}$. M.pt: 85°C – 87°C . For $\text{C}_{24}\text{H}_{34}\text{O}_6\text{N}_2\text{Sn}/564$ (%) Calc. C 51.06; H 6.02; N 4.95; Sn 21.27. Found: C 51.43; H 6.41; N 4.69; Sn 22.48. λ_{m} : 8.61 $\text{S cm}^2 \text{mol}^{-1}$. M.pt: 101°C – 103°C .

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