

Original Research

Antimicrobial and Cytotoxicity Studies of Some Organotin(IV) *N*-ethyl-*N*-phenyl Dithiocarbamate Complexes

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Abstract

Organotin(IV) dithiocarbamate complexes owe their uniqueness and properties to the individual attributes of the organotin and the dithiocarbamate moieties. The synergy exhibited by these groups often results in enhanced biological activities in the hybrid molecule. This study reports the biological activities (antimicrobial and cytotoxicity) of some organotin(IV) *N*-ethyl-*N*-phenyldithiocarbamate complexes presented as MeSnCIL_2 , BuSnCIL_2 , PhSnCIL_2 , Me_2SnL_2 , Bu_2SnL_2 , and Ph_2SnL_2 ($\text{L} = \text{N-ethyl-N-phenyl dithiocarbamate}$). Their antimicrobial properties were studied against *K. pneumonia*, *S. aureus*, *E. coli*, *P. aeruginosa*, *B. cerues*, *A. flavus* and *C. albican*, and the results revealed varied activity of good to moderate properties. Complex PhSnCIL_2 and Ph_2SnL_2 showed the highest activities among this group of complexes due to the presence of planar phenyl group(s) within the organotin moiety, which enhances the lipophilicity of the complexes and subsequent penetration into the organisms. The complexes were further screened for cytotoxicity using the MTT assay method against the human cervical cancer cell line (HeLa cells). A remarkable anti-tumoral activity, especially for complex PhSnCIL_2 and Ph_2SnL_2 , were observed when compared to 5-Fluorouracil (5FU). The studies showed that upon further optimization, these complexes could become a leading class of compounds that possess broad-spectrum antimicrobial and anti-tumoral activities.

Keywords: organotin(IV), dithiocarbamate, cytotoxicity, antimicrobial

Introduction

Different approaches to drug discovery have arisen due to the evolution of new diseases, loss in activity of

known drugs, and the resistance of pathogens to already used drugs. Some of these methods are carried out by organic chemists and involve a synthetic approach, the development of structural analogues of existing drugs, fortuitous identification, and metal complex therapy, etc. [1]. Metal complex formation has provided a therapeutic platform [2] for making innovative and novel drugs

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to tackle new emerging diseases [3], and also combat resistance in some cases. They are formed when a metal atom is bonded to one or more Lewis bases (the ligand). The types of coordinated ligands, the oxidation state, and the coordination geometry of the complexes could be useful for identifying a variety of properties [4]. These diverse properties could influence the identity without altering the very nature of the organic fragment (ligand) in the search for the formation of new analogues [5]. A broadly studied example of these types of compound is metal dithiocarbamate complexes.

Many transition metal dithiocarbamate complexes have shown to have useful biological potential [6, 7]. However, their main group counterparts such as tin are less explored. Among the few that have been reported, organotin(IV) dithiocarbamate complexes have shown to have useful biological potential [8-11]. The dithiocarbamate group, the organotin moiety, and the coordination number of the central metal in these complexes play important roles in determining their usefulness as biological agents [12]. Furthermore, the chelation effect due to the polarity of the metal ion also plays a crucial role in their biological property. Upon complexation, the polarity of the metal center is considerably reduced as a result of the delocalization of electrons over the chelate ring and the partial sharing of the positive charge with donor groups [13]. This, consequently, increases lipophilicity and enhances the complex uptake into the cells through the lipid layer of the cell membrane. This inflow creates a disturbance in the respiratory process of the cells, and in turn affects protein synthesis, which ultimately impedes the growth of the cells [13].

Some derivatives of coordination compounds containing different organotin(IV) and dithiocarbamate moieties have been synthesized, and their anti-cancer [14-16], antimicrobial [12, 17-20], and antiradical properties [15] have been reported. Significant anti-tumoral and antimicrobial potential have been reported in the following order: $R_3Sn^+ > R_2Sn^{2+} > RSn^{3+}$ [15], which shows that the length and number of the alkyl groups attached to the tin center could influence the biological activities of these compounds. However, selectivity of the complexes toward the screened cells has been found to also affect this order [15, 21]. The interaction of the bulky phenyl group, for instance, with biomolecules within a cell, can be achieved via π - π interactions due to the high lipophilicity observed for the phenyl group. As a result of the lipophilicity, organotin(IV) compounds can easily interact with cellular membranes as well as cytoplasmic membranes [22]. The useful biological properties observed is not only limited to the presence of the organotin(IV) groups, but also to the dithiocarbamate ligands. The sulfur atoms (as donor sites) in the dithiocarbamate ligand contributes immensely to the unique stereo-electronic properties of organotin(IV) dithiocarbamate complexes that play an important role in the transportation of molecules to the targeted sites, as well as the enhancement of retention

time [23, 24]. One notable role of the dithiocarbamate group in their usage as biologically useful compounds is their ability to effectively modulate the excess toxicity associated with the organotin(IV) group, which may become harmful with increased potency [23].

Since the useful functionalities of organotin(IV) dithiocarbamate complexes in a biological system originate from the synergy created by the individual properties of the organotin(IV) and the dithiocarbamate moieties respectively [25], their unique properties continue to inspire research interest. In this report, we present a biological study involving antimicrobial and cytotoxicity activity of some organotin(IV) *N*-ethyl-*N*-phenyldithiocarbamate complexes reported in our previous work [26].

Experimental

Materials and Methods

All organotin(IV) *N*-ethyl-*N*-phenyldithiocarbamate complexes ($MeSnClL_2$, $BuSnClL_2$, $PhSnClL_2$, Me_2SnL_2 , Bu_2SnL_2 , and Ph_2SnL_2), their Synthesis procedure and characterization have been reported in our previous study [26].

Antimicrobial Analysis

Microbial strains of five bacterial (*S. aureus*, *B. cereus*, *P. aeruginosa*, *E. coli*, *K. pneumonia*) and two fungi (*A. flavus* and *C. albicans*), selected based on their clinical and pharmacological relevance, were collected from the Microbiology Department of the Federal Teaching Hospital in Abakaliki, Nigeria [27]. This study was achieved using the agar well diffusion method [28]. Sterile Muller-Hinton agar was used to prepare the petri plates by the streaking of the test cultures (10^6 CFU/mL) on the condensed agar in petri plates and allowing them to dry for 15 min. This was done in order to achieve a uniform thick layer of growth. Stock solution of the complexes at 10, 25 and 50 μ g/mL were prepared using 80% dimethylsulfoxide as a diluent [29, 30]. Wells of about 6 mm were bored into the solid agar with the help of a cork, followed by the filling of 25 μ L of the sample stock solutions with the help of a micro pipette. On each plate, 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) (20 μ L of 1.25 mg/mL) was added to give a purple colouration. These plates were then incubated at 37°C for 24 h for the bacteria strains, and at 30°C for 48 h for the fungi strains. Both Sulfamethoxazole (an antibacterial drug) and Ketoconazole (an antifungal drug) were used as positive controls for the antibacterial and antifungal studies respectively. The diluent (80% DMSO) was used as a negative control. Inhibition zones were measured in millimeters and the experiment was repeated four times. The results obtained were reported as mean \pm S.D. of the four measurements. The activity of the samples

were determined by measuring the diameter of the inhibitory zones on the surface of the agar around the bored wells.

Cytotoxicity Analysis (MTT Assay)

The cells used for this study were the Human cervical carcinomas cells (HeLa). They were acquired from ATCC, USA. These cells were cultured in EMEM (Belgium) in a culture flask (25 cm³) that contained 100 U mL⁻¹ penicillin, 10% fetal bovine serum and 100 µg mL⁻¹ streptomycin. The viability of the cells were ascertained using MTT assay in a 96-well plate containing 2.5×10^2 cells/well in 100 µL EMEM. They were then incubated at 37°C for 15 h, and the medium was replaced along with the addition of complexes at different concentrations of 25, 50, 100, and 150 µg/mL. They were further incubated at 37°C for another 48 h, followed by the MTT assay. Untreated cells were used as positive control and 5-Fluorouracil was also used as a standard. In the assay, the medium was changed to one containing 10% MTT reagent (5 mg/mL in PBS), and incubated at 37°C for 4 h. Subsequently, this assay was removed and the formazan crystals were dissolved in DMSO (100 µL), followed by the absorbance reading in a Mindray MR-96A microplate reader at 570 nm using DMSO as a blank. These assays were carried out in quadruplet.

Results and Discussion

Antimicrobial Studies

All the compounds synthesized were screened against bacterial strains (Gram positive (+): *B. cerues*, *S. aureus*; and Gram negative (-): *E. coli*, *P. aeruginosa*, *K. pneumonia*) and fungi strains (*A. flavus* and *C. albican*). This screening was conducted in three different concentrations of 10, 25,

50 µg/mL. The obtained results were taken as a measure of antimicrobial potential. Furthermore, no significant activity was observed at 10 and 25 µg/mL. However, the complexes showed appreciable activities at 50 µg/mL and these results have been presented in Table 1 and summarized in Fig. 1. The halos formed around the bored wells were the measure of the sample inhibition on the screened microorganism and these were classified accordingly as: 1-9 mm, weakly active; 10-13 mm, moderately active; 13-17 mm, active; and above 17 mm, very active [31, 32].

Generally, all the complexes showed better activity than the parent ligand, which exhibited no activity at 50 µg/mL. The dissimilarity in the antimicrobial activities for these groups of complexes with the same ligand showed that some of them are specific to a particular group of bacteria [33]. Hence, from the observed activities, both the bacteria and fungi used were very susceptible to the compounds, and their activities ranged from moderate to good. These activities have been collectively attributed to complexation based on Overton's concept and Tweedy's chelation theory [34]. Overton's concept suggests that lipid-soluble compounds are generally favored by lipid membranes [34], while Tweedy's chelation theory [34], suggests that the polarities of metal ions are reduced in complexes. Tweedy's theory thus implies that the tendency for lipophilicity is enhanced in the chelate ring with the metal center and favors permeation into the cell membranes [35].

The activities may also be attributed to the intrinsic biological effects of organotin(IV) moiety [36, 37]. The partial sharing of positive charge of the metal ion with the sulfur donor atoms and the overlapping of the ligand's orbitals with consequent electron delocalization over the whole chelate are the two main factors that contribute to the reduction in polarity of the metal center [34]. All the phenyltin(IV) derivatives in the *N*-ethyl-*N*-phenyl dithiocarbamate compounds (PhSnCIL₂ and Ph₂SnL₂), showed useful

Table 1. Summary of antimicrobial screening of complexes

Compounds	<i>P. aeruginosa</i>	<i>E. Coli</i>	<i>K. pneumonia</i>	<i>S. aureus</i>	<i>B. cerues</i>	<i>A. flavus</i>	<i>C. albican</i>
L	na	na	na	na	na	na	na
SFMT	28±0.0	30±0.4	26±0.0	23±0.7	26±0.4	na	na
(KTCZ)	na	na	na	na	na	22±0.7	27±0.7
MeSnCIL ₂	na	17±2.1	14±0.0	08±1.4	na	10±0.4	10±2.1
BuSnCIL ₂	18±0.7	21±0.0	19±0.0	14±0.7	na	11±1.4	15±0.7
PhSnCIL ₂	20±0.0	18±0.7	19±0.7	15±0.7	10±0.7	17±0.4	14±0.4
Me ₂ SnL ₂	na	11±0.4	na	11±0.7	na	na	na
Bu ₂ SnL ₂	20±0.4	19±0.4	19±2.1	13±1.4	10±1.4	14±0.4	11±0.4
Ph ₂ SnL ₂	18±0.0	23±0.4	23±0.4	16±0.0	13±0.4	16±0.7	15±0.4

50 µg/mL (quadruplet results); na = not active

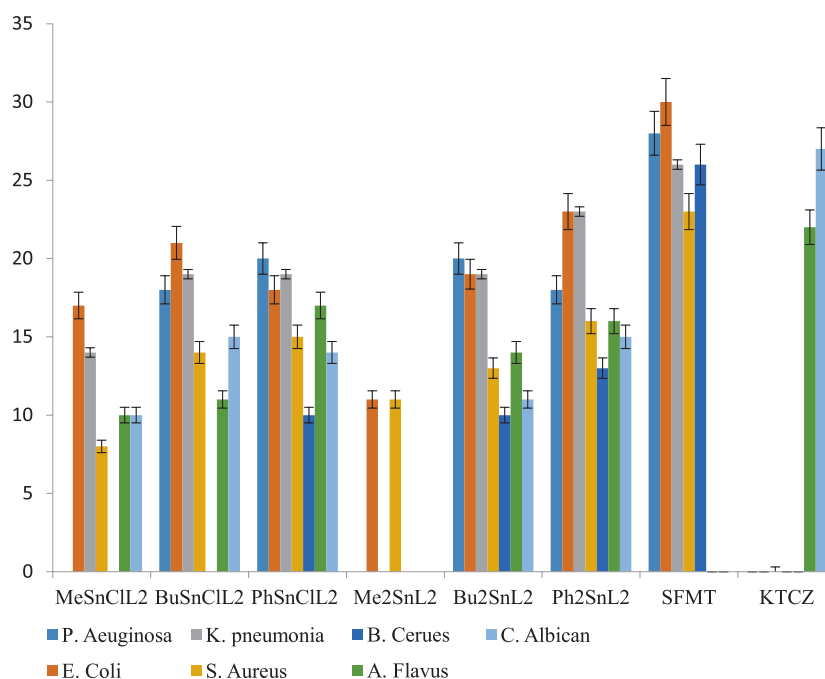
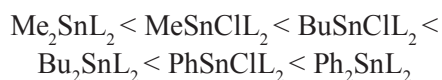


Fig. 1. Histogram showing the antimicrobial activities of the organotin(IV) *N*-ethyl-*N*-phenyl dithiocarbamate complexes.

activity, which ranged from moderate to very active antimicrobial activity when compared to both standard drugs used for the screened bacteria and fungi organisms. These may be due to the increased lipophilicity originating from the presence of the phenyl group in the organotin moiety, thereby causing a favorable inflow of the complexes through the lipid bilayer of the bacteria organisms [38]. However, the di-substituted organotin complexes showed better activity than their mono-substituted counterpart, which is in agreement with what has been reported in the literature [39]. Thus, the antimicrobial activity is structure-dependent and follows the pattern:



This observed pattern also suggested higher susceptibility for the Gram negative (-) than the Gram positive (+) bacteria, due to the structural differences in the cell walls and membranes of both groups of bacteria. In Gram positive (+) bacteria, the presence of a cell wall does not allow for easy penetration because of an outer lipid membrane (originating from lipopolysaccharide) which contributes to the antigenic specificity of these organisms [40-43]. The Gram negative (-) bacteria only has a simpler cell membrane (that lacks the rigidity of the cell wall), which made them more susceptible to the complexes than the Gram positive (+) bacteria. Me₂SnL₂ and MeSnCIL₂ showed the weakest activities due to the small size of the methyl group. However, due to selectivity, Me₂SnL₂ exhibited weaker activity compared to MeSnCIL₂, which contradicted the expected structural relationship.

The mode of action as suggested for compounds containing the azomethine group (>C=N) may involve hydrogen bond formation with the active center of the cell constituents through the azomethine group, which consequently interferes with the cell process and ultimately results in death [44]. In addition, the number of the chloride ions in the organotin(IV) moiety play a key role in the antimicrobial activity of the complexes [39]. From this study, the organotin complexes with a single chloride ion showed lower activity compared to their counterpart without the chloride ion. This correlates well with other reports on the bactericidal activities of this class of compounds with a similar number and type of organic groups bonded to the Sn(IV)-center ($\text{R}_3\text{Sn}^+ > \text{R}_2\text{Sn}_2^+ > \text{RSn}_3^+ > \text{Sn}_4^+$, bactericidal activity and toxicity scale) [39]. It is also possible for the biological activity of organotin complexes to decrease if the alkyl moiety attached to the tin metal is too large (e.g, octyl group) or too small (e.g, methyl group). Therefore, in the search for an organotin complex with useful antimicrobial properties, the ratio between the lipophilicity and solubility properties of these complexes in an organism are an important factor to be considered [45]. One major improvement often associated with the replacement of the chloride ion with an organic ligand is the reduction in the side effect, such as toxicity, which could also reduce antimicrobial activity. Hence, a right balance for the substitution and the availability of the chloride ion is needed.

Cytotoxicity Studies

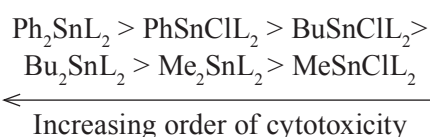
HeLa cell is an immortal cell line obtained from a common human cervical cancer cell [21]. In this

Table 2. Viabilities (%) of the HeLa cell lines at different concentrations for the complexes.

No	25 $\mu\text{g mL}^{-1}$	50 $\mu\text{g mL}^{-1}$	100 $\mu\text{g mL}^{-1}$	150 $\mu\text{g mL}^{-1}$	IC ₅₀
MeSnCIL ₂	83.14 \pm 3.22	82.21 \pm 3.08	81.38 \pm 6.54	80.54 \pm 1.27	>4000
BuSnCIL ₂	36.28 \pm 3.15	33.23 \pm 10.00	21.22 \pm 13.33	21.33 \pm 14.54	8.12
PhSnCIL ₂	32.23 \pm 8.32	25.18 \pm 21.23	27.98 \pm 14.20	25.18 \pm 18.55	4.37
Me ₂ SnL ₂	31.13 \pm 10.67	30.44 \pm 2.24	31.28 \pm 5.49	30.21 \pm 13.06	12.30
Bu ₂ SnL ₂	41.68 \pm 5.61	39.78 \pm 14.60	30.62 \pm 13.75	26.56 \pm 14.37	11.75
Ph ₂ SnL ₂	32.33 \pm 6.10	30.65 \pm 9.01	29.30 \pm 7.17	28.16 \pm 8.25	0.01
Control 1	100.00 \pm 0.68	100.00 \pm 0.51	100.00 \pm 0.79	100.00 \pm 0.79	--
Control 2	103.09 \pm 1.43	105.01 \pm 2.43	104.09 \pm 2.43	104.09 \pm 2.43	--
5FU	35.97 \pm 3.25	28.47 \pm 6.14	23.54 \pm 2.90	17.72 \pm 4.34	40

study, the IC₅₀ values for the compounds obtained are summarized in Table 2. These results suggested a concentration-dependent profile with some outstanding activity toward the used cell line. Furthermore, cytoselectivity toward the used cell line was also observed for the complexes, and some of the activity (in IC₅₀) obtained were better compared to the standard drug (5-Fluorouracil (5FU)), with an IC₅₀ value of 40 μM . However, some of these complexes displayed high IC₅₀ values due to selectivity or low cytotoxic activity as the case may be.

In general, the organotin complexes with the di-substituted alkyl/aryltin(IV) groups induced better cytotoxic activity than their mono-substituted derivatives [46, 47]. The phenyltin(IV) derivatives (PhSnCIL₂ and Ph₂SnL₂) showed outstanding activities when compared with the standard drug 5FU. In some cases, mono-substituted alkyl/aryltin complexes showed good activities, especially in those of butyl and phenyl derivatives. Possible structural-activity relationships showed that all the complexes have outstanding cytotoxic activities, except complex MeSnCIL₂, which gave an IC₅₀ value greater than 4000 μM . Complex Ph₂SnL₂ showed the best activity among this group of organotin(IV) dithiocarbamate compounds, with an IC₅₀ value of 0.01 μM , which was better compared to the standard drug (5FU). This has been attributed to the improved lipophilicity due to the presence of one or more phenyl groups in the complexes. The order of activity for this group thus follows:



Several mechanisms have been presented for the possible mode of action of anticancer drugs [48]. However, the lipophilicity of this drug plays a crucial role in their interaction with the cells. An increase in the length of the carbon chain in organotin(IV) compounds

often increase its cytotoxicity toward cancerous cells [23, 49]. The nature of the alkyl/aryl group on the tin metal center often influences lipophilicity. The phenyl group in an organotin molecule can induce π - π interaction with biomolecular cells, which also contributes to the enhanced lipophilicity [23]. Also, the nature of the ligand moiety is important in their functionality as useful biological molecules [50]. Other possible routes of interaction/mechanism with cancerous cells have been proposed. These include interaction with nitrogenous bases, which consequently interferes with the DNA replication and transcription or by affecting the multi-enzymes complexes, which also helps in DNA transcription and replication, thereby inhibiting cell proliferation [11]. Therefore, DNA may likely be the targets of these complexes as reported in literature [51].

The cytotoxic activity observed for these complexes against the HeLa cell line generally indicated remarkable anti-tumoral activity. They have possible potential, upon further optimizations/modifications and testing in other cells lines, as lead compounds in the fight against cancerous diseases.

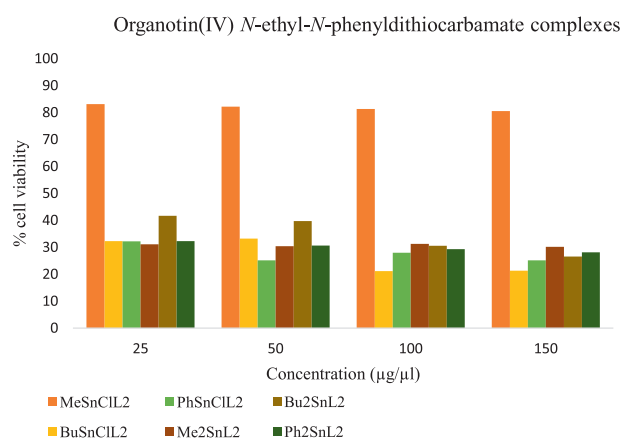


Fig. 2. Histogram representation of the percentage (%) cell viability to concentration for the complexes.

Conclusions

The evaluation of the antimicrobial and cytotoxic activities of the complexes has been achieved. These complexes showed good activity against a wide range of bacterial [both Gram positive (+) and negative (-)] and two fungi organisms, with complexes bearing the phenyl group (PhSnClL_2 and Ph_2SnL_2) showing the best activities due to the lipophilic nature of their molecules in a biological system. These complexes, through a weak intermolecular contact with cell membranes, may alter the cell membrane of the organisms, thus causing death by interrupting the transportation of useful nutrients into their cell by deprivation. Similarly, the cytotoxicity study of these complexes favours the molecules with longer chains and those of aryl derivatives due to the increased lipophilicity upon complexation. The complexes PhSnClL_2 and Ph_2SnL_2 exceptionally showed good selectivity toward the HeLa cell line, with outstanding activities better than the standard 5-Fluorouracil drug used. From the relationship deduced from the structural-activity of the complexes, it is apparent that the biological activity of organotin(IV) dithiocarbamate complexes is highly influenced by the number and the nature of alkyl/aryl group attached to the tin in addition to the lipophilicity and selectivity. The results obtained in this study showed that these complexes, upon further screening *in vivo*, may lead to the development of a new class of drugs which are potent against cancer cells and also act as a broad spectrum antimicrobial agent.

Conflict of Interest

The authors declare no conflict of interest.

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