Heliyon 7 (2021) e07693

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Synthesis, computational and biological studies of alkyltin(IV) *N*-methyl-*N*-hydroxyethyl dithiocarbamate complexes

Jerry O. Adeyemi [a,b], Gbemisola M. Saibu [c], Lukman O. Olasunkanmi [d], Adewale O. Fadaka [e], Mervin Meyer [e], Nicole R.S. Sibuyi [e], Damian C. Onwudiwe [a,b,*], Adebola O. Oyedeji [f,**]

[a] *Material Science Innovation and Modelling (MaSIM) Research Focus Area, Faculty of Natural and Agricultural Science, North-West University (Mafikeng Campus), Private Bag X2046, Mmabatho, South Africa*

[b] *Department of Chemistry, Faculty of Natural and Agricultural, Science, North-West University (Mafikeng Campus), Private Bag X2046, Mmabatho 2735, South Africa*

[c] *Risk & Vulnerability Science Centre, Walter Sisulu University, Nelson Mandela Drive, Mthatha, Private Bag X1, 5099, South Africa*

[d] *Department of Chemistry, Faculty of Science, Obafemi Awolowo University, Ile-Ife 220005, Nigeria*

[e] *Department of Science and Innovation/Mintek Nanotechnology Innovation Centre, Biolabels Node, Department of Biotechnology, Faculty of Natural Sciences, University of the Western Cape, Private Bag X17, Bellville, 7535 Cape Town, South Africa*

[f] *Department of Chemical & Physical Sciences, Faculty of Natural Sciences, Walter Sisulu University, Mthatha, South Africa*

ARTICLE INFO

Keywords:
Organotin
Dithiocarbamate
Computational study
Antioxidant
Anti-inflammatory
Cytotoxicity

ABSTRACT

Methyltin(IV) of butyltin(IV)–*N*-hydroxyethyl dithiocarbamate complexes, represented as $[(CH_3)_2Sn(L(OH))_2]$ and $[(C_4H_9)_2Sn(L(OH))_2]$ respectively were synthesized and characterized using spectroscopic techniques (^1H, ^{13}C and ^{119}Sn NMR) and elemental analysis. Both infrared and NMR data showed that, the complexes were formed via two sulphur atoms of the dithiocarbamate group. This mode of coordination was further supported by the DFT calculation, which suggested the formation of a distorted octahedral geometry around the tin atom. The complexes were screened for their antioxidant, cytotoxicity and anti-inflammatory properties. Four different assays including DPPH, nitric oxide, reducing power and hydrogen peroxides were used for the antioxidant studies, while an *in vitro* anti-inflammatory study was done using albumin denaturation assay. The complexes showed good antioxidant activity, especially in the DPPH assay. Butyltin(IV)–*N*-hydroxyethyl dithiocarbamate showed better cytotoxicity activity compared to methyltin(IV)–*N*-hydroxyethyl dithiocarbamate in the selected cell lines, which included KMST-6, Caco-2 and A549 cell lines. The anti-inflammatory activities revealed that the two complexes have useful activities better than diclofenac used as control drug.

1. Introduction

The partial reduction of oxygen in the body has continuously resulted to the production of reactive oxygen species (ROS) such as hydroxyl, superoxide, and hydrogen peroxide radicals [1]. Although, some of these products are able to protect the human body against harmful oxidative compounds [1], the excessive production of some of these radicals have been found to lead to protein, DNA and lipid damages, which consequently heighten the tendency for ageing, and various diseases such as cancer, neuro/heart diseases, etc [2]. For instance, some superoxide generated by the intrusion of microphages of infected organs have resulted in complication associated to severe influenza. Thus, the existence of free radicals, which are toxic to many cellular components causes damages and instability in the DNA makeup, which in turn favours the emergence of carcinogenesis [3]. In recent time, they have, in fact, been found to play a more complex role in the emergence of cancerous cells than initially thought. However, a steady level of antioxidant may result in low level appearance of these free radicals, which in turn creates a fine-tuning effect on the redox status of the cells [3]. The transcriptional and post-transcriptional changes of protein, which is thought to play a crucial role in the control of cell cycle, have been associated with the mechanism involved in the redox status modification of the proliferating activities of cancerous cells [3]. Since normal cell lines show a lower level of free radicals than the cancerous counterpart, it is believed that the anti-oxidative stress mechanism is highly favoured in the cancer cells. Hence, there is a need to combat or bring to the barest minimum, the

* Corresponding author.
** Corresponding author.
E-mail addresses: Damian.Onwudiwe@nwu.ac.za (D.C. Onwudiwe), aoyedeji@nwsu.ac.za (A.O. Oyedeji).

https://doi.org/10.1016/j.heliyon.2021.e07693
Received 12 June 2021; Received in revised form 24 July 2021; Accepted 29 July 2021
2405-8440/© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

level of free radicals present in the body and also proffer a suitable anticancer therapy, which has little or no side effects.

The design of new therapeutic agent is fundamental to medicinal chemistry [4]. Metal complex synthesis has emerged as one of the drug discovery strategies for the engineering of novel therapeutic agents since the discovery of cisplatin. Metal complexes have shown different useful biological properties such as antimicrobial, antioxidant, anticancer and antimalarial activities [5]. These biological activities have been generally attributed to the synergistic relationship between the ligand moiety and the metal centre. Thus, there has been an increase attention in the studies of these group of compounds [5]. One notable group that has continued to gain significant attention is the dithiocarbamate complexes.

Dithiocarbamate are soft donor ligands which have the capacity to form chelates with most metal ions in the periodic table, including actinide and lanthanide [6]. They have been reported to stabilize different metals and increase their oxidation number to form stable complexes [7]. Dithiocarbamate compound and its derivatives have emerged as a one of the useful metal chelating antioxidant [8]. This class of compound have already shown potentials to stop proliferation of cell alongside the removal of unwanted superoxide anions [9]. Likewise, the antioxidant properties of the transition metal derivatives of this compound have already been studies, however, not much is known about the antioxidant properties of the organometallic class, like the organotin derivatives [10]. However, organotin(IV) complexes have been reported to show useful cytotoxic properties against different types of cancer cell lines as reported in several literature and some of our recent studies [4, 11, 12, 13]. Their reactivity in biological systems and cells have been reported to be affected by the structural configuration. Those with more alkyl and aryl groups attached to the tin center, exert more biological effect than those with less number. Hence, significant biological activities, especially cytotoxicity, have been reported to follow the order $RSn^{3+} < R_2Sn^{2+} < R_3Sn^{+}$ [14]. For instance, the more lipophilic complexes such as those bearing the bulky phenyl group have been found to easily interact due to π-π interactions with the cellular and cytoplasmic membranes [15], which in turn enhance permeability into these cells and consequently lead cell apoptosis. Nevertheless, their selectivity against the used cell lines have been thought to also play a major role in this order.

Although, there are a few reports on the synthesis of organotin(IV) complexes (using different ligands) as potential antimicrobial and anticancer agent, not many dithiocarbamate derivatives are known for antioxidant and cytotoxicity properties. In continuation of our research interest in the development of organometallic compounds with improved biological activities, we herein report the preparation, and characterization of two new compounds of organotin and dithiocarbamate. Quantum chemical calculations (conducted in vacuo using the density functional theory method) was used to ascertain the geometry and electronic properties. The complexes were screened for their antioxidant, cytotoxicity and anti-inflammatory properties andthe effect of the alkyl derivatives on the potency of these complexes was also evaluated.

2. Materials and methods

All the reagents used in this study were procured from Merck chemical Co without further purifications. Melting points were determined using Gallenkamp melting point apparatus. The percentage elemental composition (C, H, N, and S) for these complexes were obtained using Elementar, Vario EL Cube. The infrared spectroscopy measurement was done using Alpha Bruker FTIR spectrophotometer. The Nuclear Magnetic Resonance (NMR) analysis was done using a 600 MHz Bruker Avance III NMR spectrometer for ^{1}H, ^{13}C, ^{119}Sn NMR analyses. Tetramethylsilane was used as internal standard at room temperature.

2.1. Synthesis of complexes

The synthesis of the ligand and complexes followed our earlier reported procedure [16]. Cold ammonium hydroxide (0.01 mol) and cold carbon disulphide (0.01 mol) were added dropwise, at 20 min interval, into a 250 mL round bottom flask containing an already stirring *N*–methyl–*N*–ethanolamine (0.01 mol) placed in an ice bath. Thereafter, the mixture was allowed to stir for 4 h and respective aqueous solution of alkyltin(IV) chloride (0.005 mol), dissolved in cold ethanol, was added to the stirring mixture. The stirring continued for another hour. The resulting white precipitates were filtered, rinsed with large volume of ethanol, and dried in *vacuo* (Figure 1).

2.1.1. Methyltin(IV)–N-hydroxyethyl dithiocarbamate, $[(CH_3)_2Sn(L(OH))_2]$

Yield, 2.10 g, 86 %; M. Pt, 198–200 °C; Selected IR, (cm^{-1}): 1476 ν(C=N), 1350 ν(C_2–N), 990 ν(C–S), 2950 ν(–C–H), 3320 ν(O–H), 1616 δ(O–H), 455 (Sn–S); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7. 33 (S, 2H, -OH) 4.11 (t, J = 5.4 Hz, 4H, N–CH_2), 4.02 (t, 4H, J = 5.4 Hz, CH_2–OH), 3.53 (s, 6H, CH_3–N), 2.22 (s, 6H, Sn–CH_3); ^{13}C NMR δ (ppm) = 207.3 (-NCS_2), 60.7 (-CH_2-OH), 59.0(–CH_2–N), 44.4 (CH_3–N), 31.2 (Sn–CH_3); ^{119}Sn NMR (CDCl3) δ (ppm): -331.5;

$C_{10}H_{22}N_2O_2S_4Sn$ (449.26): C, 26.73; H, 4.94; N, 6.24; O, 7.12; S, 28.55; Found: C, 26.10 H, 4.55; N, 6.05; O, 7.02; S, 29.01.

2.1.2. Butyltin(IV)–N-hydroxyethyl dithiocarbamate, $[(C_4H_9)_2Sn(L(OH))_2]$

Yield, 2.45 g, 81 %; M. Pt, 210–215 °C; Selected IR, (cm^{-1}): 1444 ν(C=N), 1335 ν(C_2–N), 988 ν(C–S), 2945 ν(–C–H), 3350 ν(O–H), 1620 δ(O–H), 444 (Sn–S); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7. 33 (S, 2H, -OH), 4.16 (t, J = 5.3 Hz, 4H, N–CH_2), 4.04 (t, J = 5.4 Hz, 4H, OH–CH_2), 3.56 (s, 6H, N–CH_3), 2.12 (t, 4H, $CH_2CH_2CH_2CH_3$), 2.01–1.93 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.53–1.46 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.00 (t, J = 7.3 Hz, 6H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) = 202.4 (-NCS_2), 60.8 (-CH_2-OH), 58.7 (–CH_2–N), 44.1 (CH_3–N), 34.4 ($CH_2CH_2CH_2CH_3$), 28.7 ($CH_2CH_2CH_2CH_3$), 26.5 ($CH_2CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_2CH_3$); ^{119}Sn NMR (CDCl3) δ (ppm): -330.8.

$C_{16}H_{34}N_2O_2S_4Sn$ (534.05): C, 36.03; H, 6.42; N, 5.25; O, 6.00; S, 24.04; Found: C, 36.01; H, 6.12; N, 4.99; O, 5.89; S, 23.98.

2.2. Computational details

Ground state equilibrium geometries of the ligands and Sn complexes were derived by geometry optimization calculations at the M06/cc-pVTZ//LANL2DZ level of theory, where cc-pVTZ and LANL2DZ basis sets were applied to the non-metallic and Sn atoms, respectively. The use of LANL2DZ and effective core potential (ECP) on the metal had been reported to improve accuracy and reduce computational cost [17, 18, 19, 20]. Modelling of structures and visualization of electron density iso-surfaces were achieved with GaussView 5.0 [21], while Density functional theory (DFT) calculations were performed with Gaussian 16

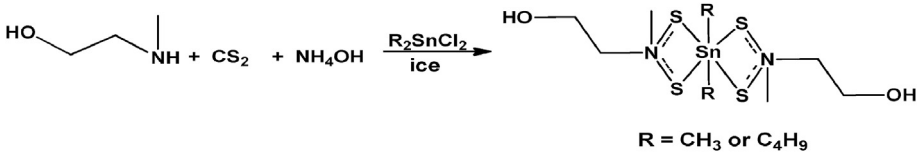

Figure 1. Synthetic scheme of the alkyltin(IV) *N*-methyl-*N*-hydroxyethyldithiocarbamate complexes.

[22], and natural bond analysis (NBO) was carried out using the NBO program [23] in Gaussian 16 (as link 607).

2.3. Antioxidant study

2.3.1. 2,2- diphenyl-1picrythydrazyl hydrate (DPPH) free radical scavenging assay

The 2,2- diphenyl-1picrythydrazyl hydrate (DPPH) free radical scavenging capacity of the compounds were estimated according to previously reported procedure [24] using DPPH assay. The stock solution of the DPPH was prepared in 100 mL of methanol and kept in the dark for 30 min. This was followed by the preparation of 50 μM stock solution of the complexes in ethanol. The prepared stock solution of the complexes was then serially diluted to 25, 12.5, 6.25, 3.12 and 1.56 μM, followed by the addition of 1 mL of 0.1 mM DPPH to each diluted concentration. Thereafter, this mixture was properly mixed and incubated for 30 min in the dark at room temperature followed by the pipetting of 250 μL of each mixture in triplicates into a 96-welled microplate. The absorbance of these mixtures was then measured at a wavelength of 515 nm using a microplate reader (model 680-BIO-RAD, USA). Ascorbic acid was used as a positive control over similar concentration range. All experiments were done in triplicates. The percentage scavenging properties estimated from the DPPH assay methods was obtained using the following equation in (1)

$$(\%)\ \text{inhibition} = [\ (A_c - A_t)\ /A_c] \times 100 \quad (1)$$

where A_c = absorbance of the control (containing all reagents except the test compound), and A_t = absorbance of the test compound.

2.3.2. Nitric oxide scavenging assay

The procedure used in the nitric oxide scavenging study followed an already reported method [25]. Sodium nitroprusside (2 mL, 10 mM) made in phosphate-buffer saline (0.5 mM) of pH 7.4 was mixed with the respective complexes (0.5 mL). The prepared mixture was then incubated for 3 h at 25 °C. After which, 0.5 mL of this mixture was mixed with Griess reagent (0.33 % sulphanilamide dissolved in 20 % glacial acetic acid and mixed with 1 mL of naphthylethylenediamine chloride (0.1% w/v)). The mixture of the complex and Griess reagent was then incubated for 30 min at room temperature, and thereafter, 250 μL of this mixture was measured at an absorbance of 540 nm in a 96-welled microplate, whilst using sodium nitroprusside in methanol as the negative control. This experiment was carried out in triplicates for each of the complex. The percentage scavenging properties estimated from the nitric oxide assay methods was obtained using the following equation in (2)

$$(\%)\ \text{scavenged [NO]} = [\ (A_c - A_t)\ /A_c] \times 100 \quad (2)$$

where A_c = absorbance of the control (containing all reagents except the test compound), and A_t = absorbance of the test compound.

2.3.3. Hydrogen peroxide scavenging assay

The scavenging activity of hydrogen peroxide on the compounds at different concentration was determined using an established literature method [26]. About 4 mL solution of the complexes were prepared in 1 % DMSO at graded concentration (50, 25, 12.5, 6.25, 3.12 and 1.56 μM) and mixed with 0.6 mL of hydrogen peroxide solution (4 mM) prepared in a phosphate buffer (0.1 M: pH 7.4) and incubated at room temperature for 10 min. Thereafter, 250 μL of the mixture was pipetted into a 96-well microplate and the absorbance was measured at 405 nm using a microplate reader (model 680-Bio-Rad). The percentage of hydrogen peroxide scavenged by the complexes was calculated as follows (see eq. (3)):

$$(\%)\ \text{scavenged [H}_2\text{O}_2\text{]} = [\ (A_c - A_t)\ /A_c] \times 100 \quad (3)$$

where A_c = absorbance of the control (containing all reagents except the test compound), and A_t = absorbance of the test compound.

2.3.4. Ferric reducing power antioxidant assay

The procedure used in the ferric reducing assay followed an already reported method [27]. This method is based on the ability for Fe^{3+} to become reduced by a reducing agent to Fe^{2+}. Thus, Various concentration of the complexes (0.2 mL) was mixed with equal volume of phosphate buffer and potassium ferricyanide. The resulting mixture was sonicated and incubated for 20 min at 50 °C. When these mixtures where adjudge cooled, trichloroacetic acid (10 %, 0.2 mL) was added to the mixture and centrifuged for 10 min at 4500 rpm. Thereafter, 100 μL of the prepared solution was mixed with 20 μL of the ferric chloride solution and, 100 μL of distilled water and then measure at an absorbance of 700 nm. Similarly, the control was prepared using the same procedure but without the test complexes. Furthermore, ascorbic acid at various concentrations was used as standard.

2.4. Cytotoxicity study

The toxicity effect of the complexes was investigated on human non-tumorigenic immortalized fibroblast (KMST-6), and immortalized colorectal adenocarcinoma (Caco-2) and alveolar basal epithelial adenocarcinoma (A549) cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as previously described [28]. The cells were bought from American Type Cell Culture (Manassas, VA, USA). They were seeded in 96 well plate at a density of 1×10^5 cells/mL in Dulbecco's Modified Eagle Medium (DMEM) for KMST-6 and Caco-2 cells, and DMEM-F12 for the A549 cells. All media were supplemented with 10 % fetal bovine serum (FBS) and 1 % Penicillin-Streptomycin. The cells were treated with 0–100 μM of the complexes for 24–48 h. The MTT dye (10 μL of 5 mg/mL per 100 μL of media) was added to each well and incubated for 3 h. This was followed by the addition of 100 μL of DMSO to dissolve the insoluble formazan. The 1 % DMSO and doxorubicin were used as vehicle and positive controls, respectively. Assays were carried out in triplicates. The absorbance of each well was read at a wavelength of 570 and 700 nm using the POLARstar Omega microplate reader (BMG Labtech, German). Changes in morphology of the cells caused by the treatments were monitored and photographed on EVOS XL digital inverted microscope. The percentage cell viability was estimated using the formula (see eq. (4)):

$$(\%)\ \text{cell viability} = \frac{\text{mean value of test compounds}}{\text{mean value of untreated}} \times 100 \quad (4)$$

2.4. In vitro anti-inflammatory assay

The method adopted followed an already reported procedure in literature [29]. 2 mL of the complex or standard drug was mixed with a mixture of 2.8 mL of phosphate buffered saline (pH 6.4) and 0.2 mL of an egg albumin obtained from fresh egg. This mixture was the incubated for 15 min at 37 °C and thereafter boiled in a water bath for 5 min at 70 °C. The resulting mixture was then cooled and then the measure at an absorbance of 655 nm using a microplate reader (model 680-Bio-Rad, made in USA) after dispensing 250 μL of the mixture into a 96-welled microplate. Diclofenac was used as the standard drug. The concentration of the samples and the standard drug used are 50, 25, 12.5, 6.25, 3.12 and 1.56 μM. This study was carried out in triplicates for each of the complex. The percentage inhibition of protein denaturation was calculated suing Eq. (5)

$$\%\ \text{Inhibition} = \left[\frac{Vt}{Vc} - 1\right] \times 100 \quad (5)$$

where, Vt = the absorbance of the test sample, Vc = absorbance of the control. The compounds' concentration for 50 % inhibition (IC_{50}) was determined by the dose-response curve.

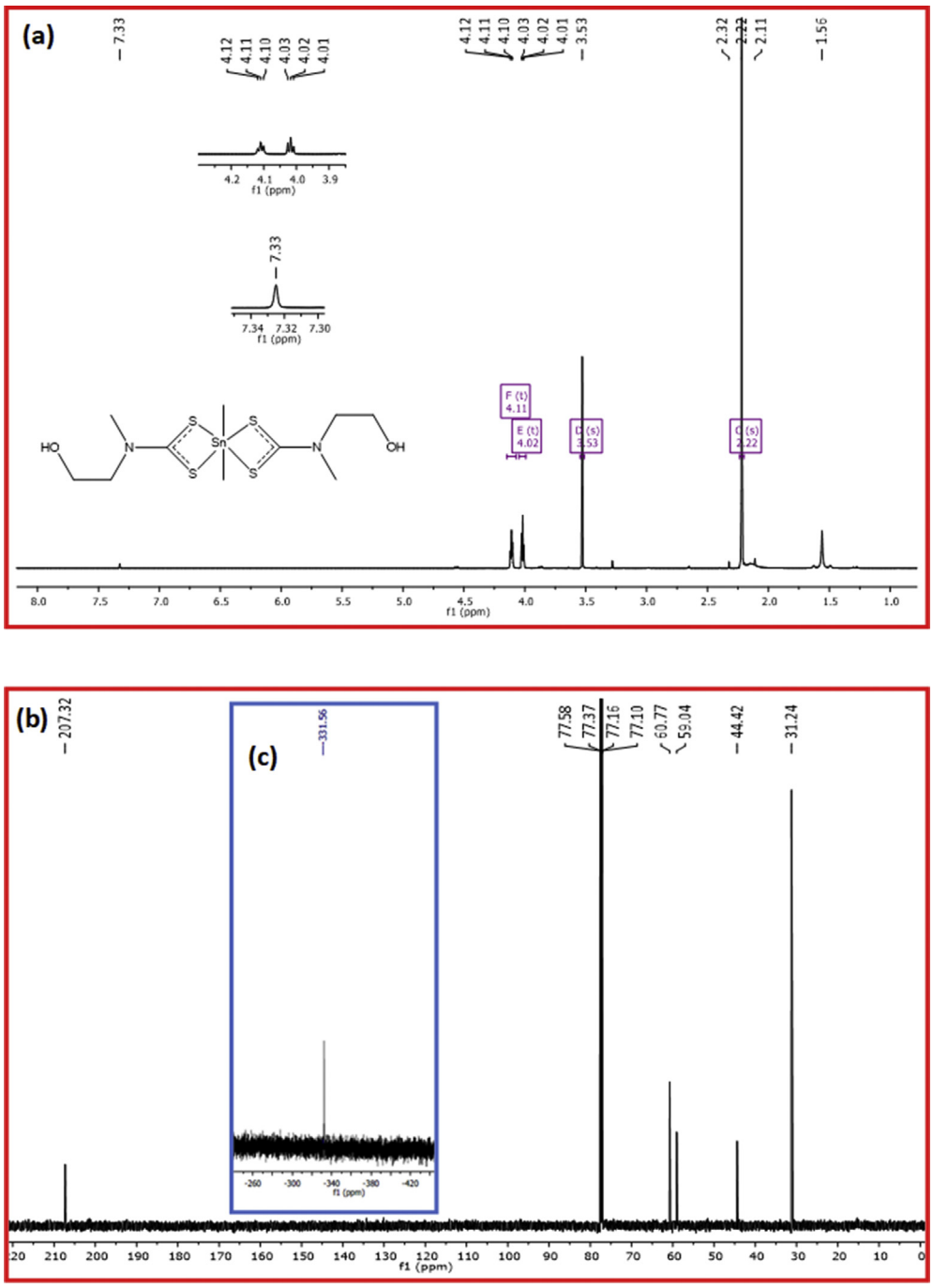

Figure 2. (a) ^{1}H and (b) ^{13}C NMR spectra with inset of ^{119}Sn NMR spectrum (c) for **$[(CH_3)_2Sn(L(OH))_2]$ (1).**

3. Results and discussion

3.1. Spectroscopic studies

The FTIR spectra of the complexes were compared with similar reported complexes in related compounds. The relevant bands, which are significant in understanding the structural features of dithiocarbamate complexes are the stretching vibration of ν(C–S), ν(C=N) and ν(M−S) found at 1060–940 cm^{-1}, 1580–1450 cm^{-1} and 455–250 cm^{-1}, respectively [30]. In these complexes, the stretching vibration of ν(C=N), which is often associated with the delocalization of electron towards the metal centre, was found between 1476 – 1444 cm^{-1} [31]. The second stretching band emanating due to ν(C–S) of the thioureide band was found as a single band in all the complexes between 990 – 988 cm^{-1}. This indicated that the dithiocarbamate ligand was bonded to the tin atom in a bidentate fashion via the two available sulphur atoms [32]. Other notable bands found in the region between 455 – 444 cm^{-1} and 3350–3320 cm^{-1} were associated with dthe ν(M−S) and the ν(−OH) stretching vibrations, respectively.

In the proton NMR spectra, the signals of the –OH group was found at 7.33 ppm [16]. Methylene proton (HO–CH_2–CH_2–N-) signals which are attached to electronegative –N and –OH, on the opposite sides (HO–CH_2–CH_2–N-), were found as triplets and somewhat downfield in the range 4.16–4.02 ppm due to the deshielding effect of these electronegative atoms [33, 34]. In the organotin(IV) moiety bearing different alkyl groups, hydrogen signals from methyl group of **$[(CH_3)_2Sn(L(OH))_2]$** was found as a strong singlet at 2.22 ppm, whilst the proton signals associated with the methylene and methyl

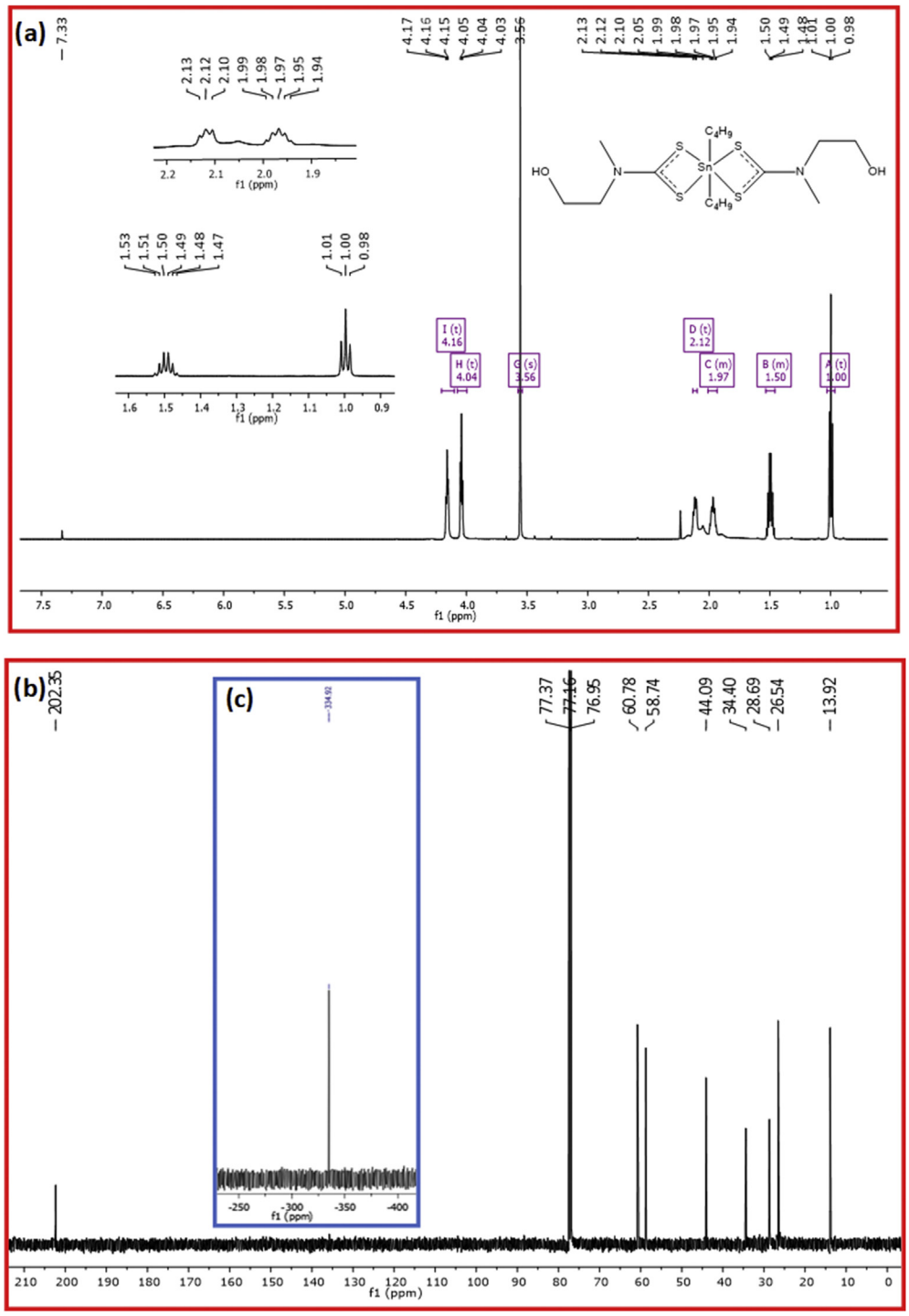

Figure 3. (a) ^{1}H and (b) ^{13}C NMR spectra with inset of ^{119}Sn NMR spectrum (c) for **[$(C_4H_9)_2$Sn(L(OH))$_2$] (2)**.

groups in **[$(C_4H_9)_2$Sn(L(OH))$_2$]** were found around 2.12–1.0 ppm [35].

The ^{13}C NMR spectra of **[$(CH_3)_2$Sn(L(OH))$_2$]** is presented in Figure 2. In all the complexes, the NCS_2 carbon resonance appeared around 207–202 ppm. The somewhat upfield shift is attributed to the deshielding of the C atom of the thioureide group upon bonding with the electropositive metal centre. Other notable carbon resonances in the complexes were found approximately at 60, 59 and 45 ppm for $–CH_2$-OH, $–CH_2$-N, $CH_3–$N respectively. The reason for the downfield values of these methylene and methyl carbons can be attributed to their attachment to the electronegative –OH and –N groups, which causes these carbons to be deshielded compared to free methylene and methyl carbons [34]. The methylene and methyl carbon resonances for the organotin(IV) moieties were found in the range between 34 – 13 ppm for the **[$(C_4H_9)_2$Sn(L(OH))$_2$]** complex and at approximately 31 ppm for the **[$(CH_3)_2$Sn(L(OH))$_2$]** [35].

The range of chemical shift of ^{119}Sn NMR are already established for different geometries, which gives an idea on the nature of coordination about the Sn atom [36]. In this study, the ^{119}Sn NMR spectra, presented as insets in Figures 2c and 3c, showed a singlet at approximately -331 ppm, which suggest a hexa-coordinated geometry about the metal centre in all the complexes [36].

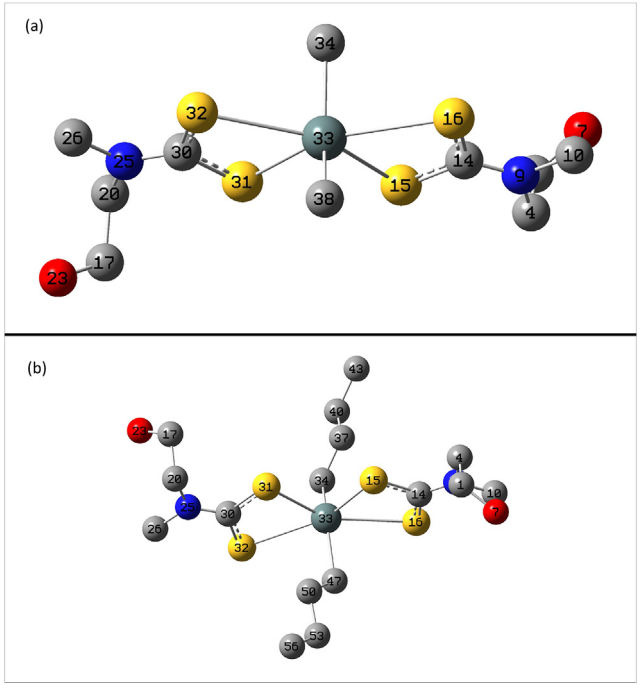

Figure 4. Optimized ground state equilibrium structures of **[$(CH_3)_2$Sn(L(OH))$_2$] (1)** (a) and **[$(C_4H_9)_2$Sn(L(OH))$_2$] (2)** (b) at M06/cc-TVPZ//LANL2DZ level.

3.2. Molecular and electronic structures

Optimized structures of the Sn complexes are shown in Figure 4, showing the numbering of atoms for ease of discussion. The structures in Figure 4 are displayed without H atoms for simplicity. Hessian calculations of the structures yielded all-positive vibrational frequencies, indicating that the structures represent the ground state equilibrium geometries of the studied Sn complexes. Selected geometry parameters of the ground state structures are listed in Table 1 and quite comparable to literature data for similar complexes [13, 37, 38]. The Sn–S bonds appear to exhibit both covalent and coordinate covalent bond characteristics such that the lengths of the covalent Sn–S bonds range from 2.54646 Å to 2.55600 Å, while the dative Sn–S bonds are in the range of 2.94214 Å to 2.95479 Å. The observed two ranges of bond lengths indicate that the dithiocarbamate ligand behaved as a bidentate unsymmetric or anisobidentate ligand [13, 39]. Such asymmetric Sn–S bonds are commonly observed for Sn-dithiocarbamate complexes with monodentate co-ligands, which could assume cis or trans orientation with respect to the Sn–S bonds of the bidentate dithiocarbamate [13]. The results suggest that the geometry parameters of the complexes are not largely affected by the alkyl chain length of the co-ligands (i.e. $–CH_3$ and $–C_4H_9$ in **[$(CH_3)_2$Sn(L(OH))$_2$]** and **[$(C_4H_9)_2$Sn(L(OH))$_2$]** respectively) as the Sn–S bond lengths of **[$(CH_3)_2$Sn(L(OH))$_2$]** are only ca. 0.01 Å shorter than those of **[$(C_4H_9)_2$Sn(L(OH))$_2$]**. Other bond lengths and angles are also not significantly different. Previous studies on organotin(IV) dithiocarbamate complexes with alkyl co-ligands had reported similar observations [40]. The C–Sn–C bond angles for the Sn-alkyl centered bonds are between 140 - 143°, suggesting that the alkyl groups coordinate to the central Sn atom in a trans configuration [13]. The complexes assumed distorted octahedral structures with dithiocarbamate ligand bite angles (S–Sn–S) between 65.4 °C and 65.7 °C, and the Sn–S–C–S torsion angles suggest near co-planarity.

Table 1. Geometry parameters of the optimized ground state equilibrium structures of the Sn complexes at M06/cc-pVTPZ//LANL2DZ level.

Geometry Parameters	[$(CH_3)_2$Sn(L(OH))$_2$] 1	[$(C_4H_9)_2$Sn(L(OH))$_2$] 2
Sn33–S15	2.54646	2.55600
Sn33–S16	2.94214	2.95479
Sn33–S31	2.54679	2.55600
Sn33–S32	2.94366	2.95478
S15–C14	1.75395	1.75284
S16–C14	1.69398	1.69515
S31–C30	1.75398	1.75284
S32–C30	1.69393	1.69515
C14–N9	1.33944	1.33962
C30–N25	1.33948	1.33962
S15–Sn33–S16	65.71190	65.41597
S31–Sn33–S32	65.41607	65.41607
S15–C14–S16	120.67356	120.69904
S31–C30–S32	120.68404	120.69893
C–Sn–C	140.81251	143.19581
Sn33–S15–C14–S16	-1.54723	2.11973
Sn33–S31–C30–S32	-1.55573	2.12052

Electronic structures of the complexes were examined to describe their prospective reactivity based on electron density distributions of the frontier molecular orbitals (FMOs). The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) electron density isosurfaces of the complexes are shown in Figure 5(a and b). The HOMO electron density for both complexes mainly centered on the S atoms of the dithiocarbamate ligands, while the LUMO electron density is extended to other atoms of the dithiocarbamate ligand. Since the selected iso-value might not reflect contributions below certain percentages in the graphical charge density distribution isosurfaces, numerical values of the percentage contributions of each atom to the HOMO and LUMO were derived from natural bond orbital (NBO) analyzes results interpreted with the aid of Multiwfn [41, 42] modules. The condensed natural atomic orbital (NAO) compositions centered on each atom for the FMOs are listed in Table 2. The results showed that the central Sn atom does not contribute significantly to the FMOs electron density, showing between 1.1 – 1.6 % due to 5s orbital for the HOMO and 1.2–4.4 % due to 5p orbitals for the LUMO. Major contributions to the HOMO and LUMO were due to 3p orbitals of the dithiocarbamate S-atoms and 2s and 2p orbitals of C-atoms of the alkyl co-ligands.

3.3. Biological studies

3.3.1. Antioxidant activities

Antioxidants have the capacity to scavenge free radicals such as ROS found in most biological systems [43]. These radicals have been found to cause oxidation of lipids, proteins, and nucleic acids, which can in turn lead to degenerative diseases such as cancer. Owing to the few data available for the antioxidant activities of organotin(IV) dithiocarbamate complexes, the antioxidant activities cannot simply be evaluated using a single method only. Many systems have been recorded and recommended to establish the authenticity of an antioxidant properties of compounds [44]. Consequently, in this study, radical scavenging assays using 2,2-diphenyl-1-picrylhydrazyl (DPPH), peroxide, nitric oxide were all employed in establishing the antioxidant potential of the synthesized complexes in comparison to ascorbic acid. The IC_{50} of the complexes in all the assays are presented in Table 3, the complexes showed a scavenging property, comparable and somewhat better, especially in the DPPH assay, than the positive control (ascorbic acid). This implies that, the complexes are good donors of hydrogen to radicals which in turn increases their ability to scavenge such radicals [44]. Thus, the reduction of DPPH absorption is suggestive of the ability of the complexes to scavenge free radicals, independent of enzymatic actions due to the capacity of the complexes to break down hydrogen and lipid peroxide. Although, the two complexes showed good activity in the DPPH assay, **[$(C_4H_9)_2$Sn(L(OH))$_2$]** showed best scavenging activity, which is most likely due to the longer butyl chain. This activity agrees well with other

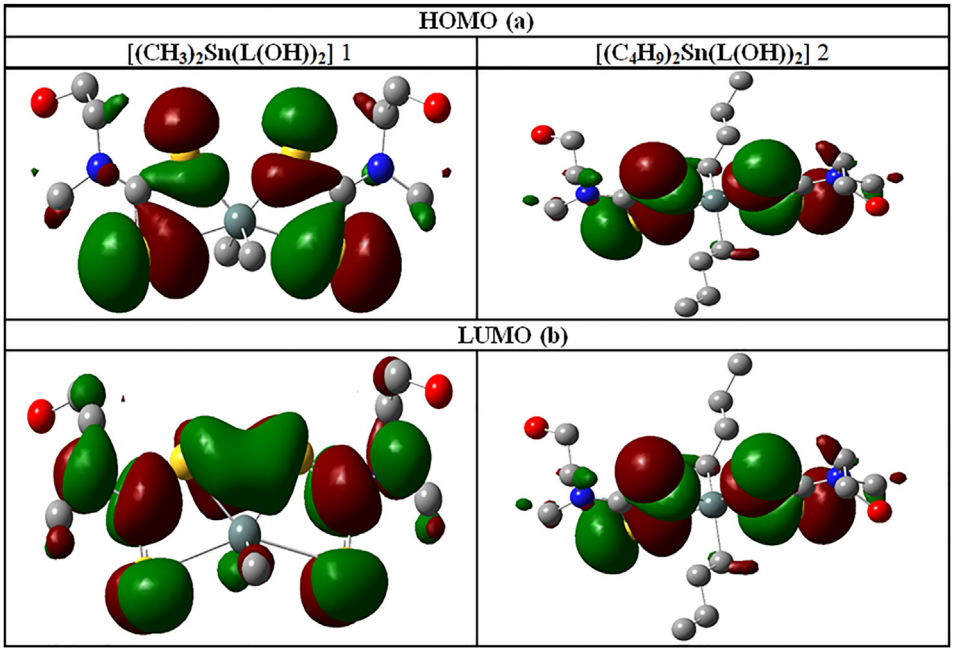

Figure 5. HOMO (a) and LUMO (b) isosurfaces of the alkylptin(IV) dithiocarbamate complexes (Iso-value = 0.020000).

Table 2. Natural atomic orbital compositions of the HOMO and LUMO of complex 1 and complex 2.

Composition (%)				
Atom	$[(CH_3)_2Sn(L(OH))_2]$ 1		$[(C_4H_9)_2Sn(L(OH))_2]$ 2	
	HOMO	LUMO	HOMO	LUMO
C4	-	1.728	-	-
N9	-	-	-	7.124
C10	-	1.063	-	-
C14	2.901	34.172	-	23.244
S15	14.359	14.572	2.300	4.436
S16	8.085	22.819	35.113	9.467
O23	1.180	-	-	-
N25	-	-	-	6.882
C30	3.306	5.507	-	-
S31	12.622	2.320	2.798	4.273
S32	14.385	7.955	42.497	9.115
Sn33	1.609	1.187	1.140	4.381
C34	20.779	4.452	4.776	-
C38	14.848	-	-	-
C47	-	-	4.659	-

Table 3. Antioxidant activities (IC_{50}) of the complexes carried out on DPPH, nitric oxide, reducing power and hydrogen peroxide assays.

Samples	DPPH (IC_{50} μM)	Nitric Oxide (IC_{50} μM)	Reducing power (IC_{50} μM)	Hydrogen Peroxide (IC_{50} μM)
1	3.85 ± 0.04	4.34 ± 0.02	13.97 ± 0.07	3.64 ± 0.01
2	3.65 ± 0.03	3.67 ± 0.03	4.26 ± 0.18	3.2 ± 0.01
Ascorbic acid	4.96 ± 0.01	2.10 ± 0.03	4.09 ± 0.08	3.06 ± 0.04

Each value of the table is represented as mean ± SD (n = 3).

studies in literature [45]. The reducing power test showed the capacity of the complexes to behave like a reductant. Low concentration of nitric oxide has been found to be enough to impose physiological functions of this radical [46]. Nitric oxide is known to carry out many roles as effector molecules in different biological systems such as in vasodilation, neuronal messenger, antimicrobial and antiviral activities [46]. Thus, chronic exposure has been related to many inflammatory condition and carcinomas, and they become more toxic when they interact with superoxide forming a very reactive peroxynitrite anion [46]. Hence, **$[(C_4H_9)_2Sn(L(OH))_2]$** showed a useful capacity comparable with

Table 4. IC_{50} for the as prepared complex and the reference drug (Dox).

Treatment	IC_{50} (μM)					
	A549		Caco-2		KMST-6	
	24 h	48 h	24 h	48 h	24 h	48 h
$[(CH_3)_2Sn(L(OH))_2]$ 1	>100	>100	81.24	83.59	>100	>100
$[(C_4H_9)_2Sn(L(OH))_2]$ 2	3.59	2.70	3.361	3.44	2.80	3.286
Dox	>100	5.059	12.31	17.81	30.13	3.91

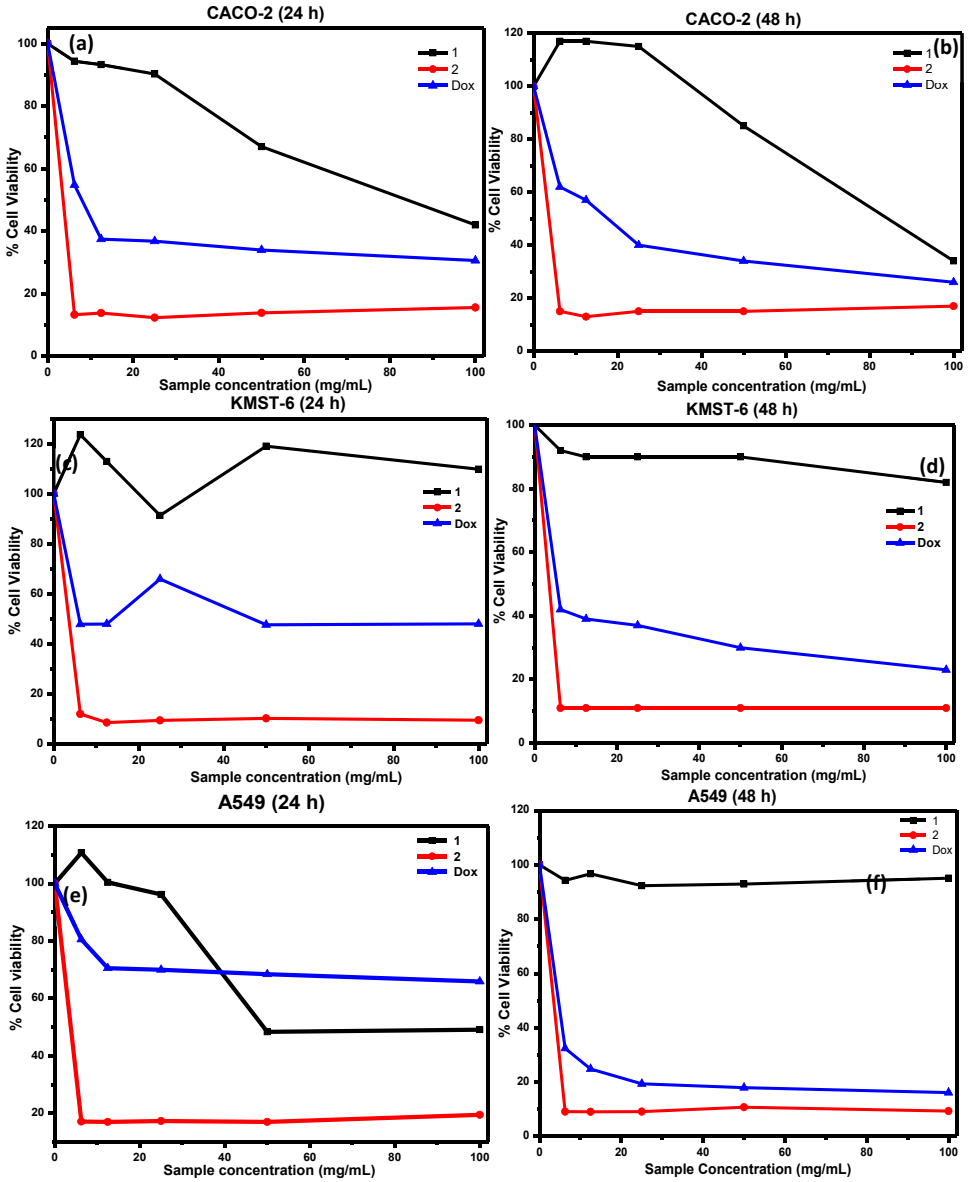

Figure 6. Cytotoxicity effect of the organotin complexes on non-cancer and cancer cells. Cell viability (%) was assessed by MTT assay after 24 h and 48 h (a–f). Complex 1 displayed selective toxicity compared to complex 2.

ascorbic acid to abstract the nitric acid radicals. The observed results, therefore, suggest that the synthesized complexes exhibited good to moderate antioxidant property in all the used assays.

3.3.2. Cytotoxicity study

The cytotoxic activity of the complexes was examined against human immortalized non-cancer (KMST-6) and cancer (Caco-2 and A549) cells using MTT assay. For comparison purposes, the cytotoxic potential of the complexes and doxorubicin (Dox) were evaluated under the same conditions. The 50 % inhibition concentration (IC_{50}) estimated from the incubation period of 24 h and 48 h for all the complexes against the used cell lines are summarized in Table 4. The inhibition activity graphs and the effect of the treatments on cellular morphology after 24 h exposure on the used cell lines treated with the highest concentration of complexes, and the vehicle control (1 % DMSO), have been presented in Figures 6 (a–f) and 7 (using a representative images) respectively. These complexes displayed a useful cytotoxic activity, especially for Caco-2. Furthermore, **$[(C_4H_9)_2Sn(L(OH))_2]$** showed an outstanding activity in all tested cell

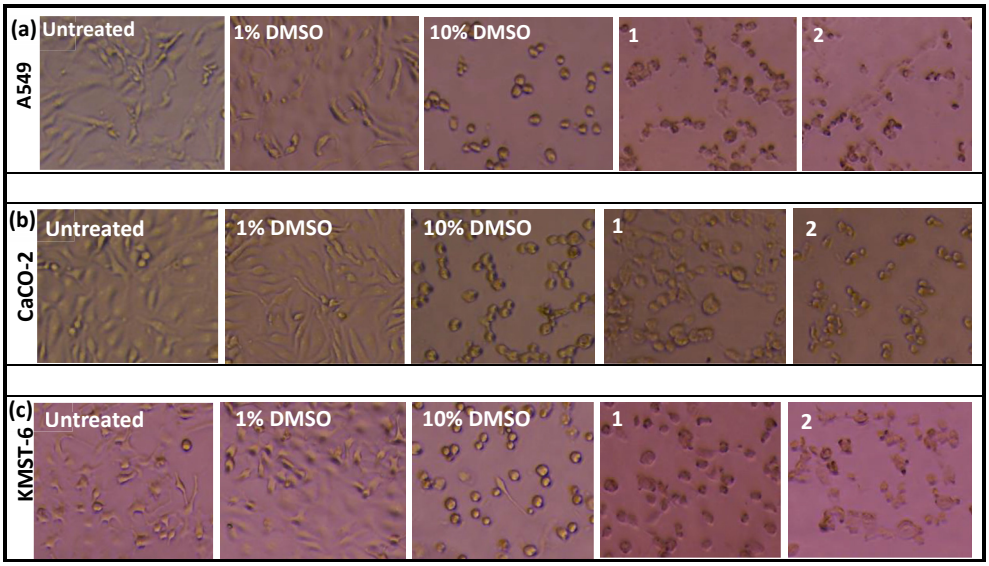

Figure 7. Effect of the treatments on cellular morphology after 24 h exposure. These cells (A549(a), CaCo-2(b) and KMST-6(c) cells) were treated with the highest concentration of complexes, and the vehicle control (1 % DMSO).

lines in comparison to standard anticancer drug (Dox); such that, it was approximately 28 times more effective in the A549 cells; 4 times more effective in the Caco-2 cells; and 15 times more effective in the KMST-6 cells at 24 h as shown in Figure 6. The IC_{50} values for all the complexes against the selected cell lines after 24 h and 48 h treatment are summarized in Table 4. In some cases, **$[(CH_3)_2Sn(L(OH))_2]$** was least toxic to the cells as was the case in the KMST-6 cells and at 48 h for A549. The mode of action in these complexes have already been associated with the length of alkyl group. The synergistic effect observed by both the organotin(IV) and dithiocarbamate ligand have contributed to the significant cytotoxicity in the cell lines tested; in that the ligand served as a carrier and also contributed to the lipophilicity of the complex which in turn facilitates the movement of metal to the location where the cytotoxicity property is exerted [47]. Furthermore, the observed trend of activities in all the cell lines was consistent with most reports studies on the cytotoxic activities of organotin(IV) derivatives [13]. As the alkyl group of the complexes increased, the cytotoxicity also increased [11, 48, 49]. Thus, this study revealed that the alkyl chain played a major role [5]in the observed activity. Although, **$[(C_4H_9)_2Sn(L(OH))_2]$** seemed more active than **$[(CH_3)_2Sn(L(OH))_2]$**, there may be need for a carrier to active sites, since it is not cancer specific as in the case of **$[(CH_3)_2Sn(L(OH))_2]$**, upon further screening and study, **$[(C_4H_9)_2Sn(L(OH))_2]$** may become a useful lead anticancer agent.

3.3.3. Anti-inflammatory activity

As already established, all anti-cancer agents are desired to show anti-inflammatory activities [50]. Acute and chronic inflammatory diseases remain the leading cause of health concerns in the world today despite the different tested compounds, which were not without acute side effects [51]. Thus, the need to develop new anti-inflammatory agents with little or no side effect continues to remain relevant. Since anti-cancer and anti-inflammatory properties are interrelated, the minimum inhibitory concentration for the anti-inflammatory activities for both complexes have been presented in Table 4 and compared with the Diclofenac. **$[(CH_3)_2Sn(L(OH))_2]$** (2.71 ± 2.12) and 2 (2.29 ± 0.04) showed a better anti-inflammatory activity compared to diclofenac drug (2.94 ± 0.01). The observed trend in the complexes, indicated that longer chain favours anti-inflammatory potentials, which is in agreement with the cytotoxicity study and also agree with other literature reports [50]. The observed better activity for **$[(C_4H_9)_2Sn(L(OH))_2]$**, may be associated with the formation and the ease of transportation of the $[(C_4H_9)_2Sn(IV)]^+$ moiety across the cell membrane [52, 53].

4. Conclusion

New complexes derived from alkyltin(IV) chloride and *N*-methyl-*N*-hydroxyethyl dithiocarbamate ligand have been successful synthesized and characterized. The obtained analytical and computational (molecular and electronic) data confirmed the structure and the composition of the synthesized complexes. The dithiocarbamate ligand coordinated to the tin atomin a bidentate fashion via the two available sulphur atoms, which in turn led to the complexes adopting a distorted octahedral geometry around the metal. The biological studies showed that the complexes possessed a good antioxidant property in all the assays, especially the DPPH assay, which suggest that the complexes can scavenge free radicals, independent of enzymatic actions due to their ability to break down hydrogen and lipid peroxide. Consequently, **$[(C_4H_9)_2Sn(L(OH))_2]$** displayed enhanced and non-selective cytotoxicity against selected cell lines compared to **$[(CH_3)_2Sn(L(OH))_2]$** and Dox. the complexes displayed better anti-inflammatory activity than diclofenac, used as control drug. The study, thus, suggest that the synthesized complexes, especially **$[(CH3)_2Sn(L(OH))_2]$**, are promising candidates as anticancer agents.

Declarations

Author contribution statement

Jerry O. Adeyemi: Performed the experiments; Wrote the paper.

Gbemisola M. Saibu, Lukman O. Olasunkanmi: Performed the experiments; Analyzed and interpreted the data.

Adewale O. Fadaka, Nicole R.S. Sibuyi: Contributed reagents, materials, Analyzed and interpreted the data.

Mervin Meyer: Contributed reagents, materials, analysis tools or data.

Damian C. Onwudiwe, Adebola O. Oyedeji: Contributed reagents, materials, analysis tools or data, Wrote the paper.

Funding statement

This work was supported by North-West University and Walter Sisilu University, South Africa.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] T.K. Komarnisky, L. A, R.J. Christopherson, Sulfur Basu, Its clinical and toxicologic aspects, Nutrition 19 (2003) 54–61.
[2] D.C. Onwudiwe, A.C. Ekennia, Synthesis, characterization, thermal, antimicrobial and antioxidant studies of some transition metal dithiocarbamates, Res. Chem. Intermed. 43 (2017) 1465–1485.
[3] R.M. Sainz, F. Lombo, J.C. Mayo, Radical decisions in cancer: redox control of cell growth and death, Cancers 4 (2012) 442–474.
[4] Y. Yang, M. Hong, L. Xu, J. Cui, G. Chang, D. Li, C.Z. Li, Organotin(IV) complexes derived from Schiff base N'-[(1E)-(2-hydroxy-3-methoxyphenyl)methylidene] pyridine-3-carbohydrazone: synthesis, in vitro cytotoxicities and DNA/BSA interaction, J. Organomet. Chem. 804 (2016) 48–58.
[5] J.O. Adeyemi, D.C. Onwudiwe, Organotin(IV) dithiocarbamate complexes: chemistry and biological activity, Molecules 23 (2018) 2571.
[6] N. Awang, N.A. Nordin, N. Rashid, N.F. Kamaludin, Synthesis and characterisation of phenanthroline adducts of Pb(II) complexes of BisN-alkyl-N-ethyldithiocarbamates, Orient, J. Chem. 31 (2015) 333–339.
[7] D. Cardell, G. Hogarth, S. Faulkner, A dithiocarbamate-stabilized copper(I) cube, Inorg. Chim. Acta. 359 (2006) 1321–1324.
[8] H. Nabipour, S. Ghammamy, S. Ashuri, Z.S. Aghbolagh, Synthesis of a new dithiocarbamate compound and study of its biological properties, Org. Chem. J. 2 (2010) 75–80.
[9] E.A. Hassan, S.E. Zayed, Dithiocarbamates as precursors in organic chemistry; synthesis and uses, phosphorus, sulfur silicon relat, Elements 189 (2014) 300–323.
[10] F. Javed, M. Sirajuddin, S. Ali, N. Khalid, M.N. Tahir, N.A. Shah, Z. Rasheed, M.R. Khan, Organotin(IV) derivatives of o-isobutyl carbonodithioate: synthesis, spectroscopic characterization, X-ray structure, HOMO/LUMO and in vitro biological activities, Polyhedron 104 (2016) 80–90.
[11] J. Adeyemi, D. Onwudiwe, Antimicrobial and cytotoxicity studies of some organotin(IV) N-ethyl-N-phenyl dithiocarbamate complexes, Pol. J. Environ. Stud. 29 (2020) 1–8.
[12] J.O. Adeyemi, D.C. Onwudiwe, M. Singh, Synthesis, characterization, and cytotoxicity study of organotin(IV) complexes involving different dithiocarbamate groups, J. Mol. Struct. 1179 (2019) 366–375.
[13] E.R.T. Tiekink, Tin dithiocarbamates: applications and structures, Appl. Organomet. Chem. 22 (2008) 533–550.
[14] L. Niu, Y. Li, Q. Li, Medicinal properties of organotin compounds and their limitations caused by toxicity, Inorg. Chim. Acta. 423 (2014) 2–13.
[15] R. Kadu, H. Roy, V.K. Singh, Diphenyltin(IV) dithiocarbamate macrocyclic scaffolds as potent apoptosis inducers for human cancer HEP 3B and IMR 32 cells: synthesis, spectral characterization, density functional theory study and in vitro cytotoxicity, Appl. Organomet. Chem. 29 (2015) 746–755.
[16] F.F. Bobinihi, D.C. Onwudiwe, E.C. Hosten, Synthesis and characterization of homoleptic group 10 dithiocarbamate complexes and heteroleptic Ni(II) complexes, and the use of the homoleptic Ni(II) for the preparation of nickel sulphide nanoparticles, J. Mol. Struct. 1164 (2018) 475–485.
[17] P.J. Hay, W.R. Wadt, Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals, J. Chem. Phys. 82 (1985) 299–310.
[18] M.Y. Combariza, R.W. Vachet, Effect of coordination geometry on the gas-phase reactivity of four-coordinate divalent metal ion complexes, J. Phys. Chem. 108 (2004) 1757–1763.
[19] A.C. Ekennia, D.C. Onwudiwe, A.A. Osowole, L.O. Olasunkanmi, E.E. Ebenso, Synthesis, biological, and quantum chemical studies of Zn(II) and Ni(II) mixed-ligand complexes derived from N,N-disubstituted dithiocarbamate and benzoic acid, J. Chem. 2016 (2016) 1–12.
[20] L. Shen, H.-F. Ji, Is antioxidant supplement beneficial? New avenue to explore, Trends Food Sci. Technol. 68 (2017) 51–55.
[21] R. Dennington, T. Keith, J. Millam, GaussView, Version 5, 2009.
[22] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, G.A. Petersson, H. Nakatsuji, Gaussian 16, 2016.
[23] E.D. Glendening, A.E. Reed, J.E. Carpenter, F. Weinhold, Nbo Version 3.1, Tci, Univ. Wisconsin, Madison, 1998, p. 65.
[24] T.O. Elufioye, C.G. Chinaka, A.O. Oyedeji, Antioxidant and anticholinesterase activities of macrosphyra longistyla (DC) hiern relevant in the management of alzheimer's disease, Antioxidants 8 (2019) 400.
[25] M.O. Jimoh, A.J. Afolayan, F.B. Lewu, Antioxidant and phytochemical activities of Amaranthus caudatus L. harvested from different soils at various growth stages, Sci. Rep. 9 (2019) 1–14.
[26] B.I. Okeleye, V. Nongogo, N.T. Mkwetshana, R.N. Ndip, Polyphenolic content and in vitro antioxidant evaluation of the stem bark extract of peltophorum africanum sond (Fabaceae), Afr. J. Tradit., Complementary Altern. Med. 12 (2015) 1–8.
[27] M. Oyaizu, Studies on products of browning reaction. Antioxidative activities of products of browning reaction prepared from glucosamine, Japanese J. Nutr. Diet. 44 (1986) 307–315.
[28] J.O. Adeyemi, D.C. Onwudiwe, A.C. Ekennia, S.N. Okafor, E.C. Hosten, Organotin(IV) N-butyl-N-phenyldithiocarbamate complexes: synthesis, characterization, biological evaluation and molecular docking studies, J. Mol. Struct. 1192 (2019) 15–26.
[29] S. Bhattacharya, S. Chandra, P. Chatterjee, P. Dey, Evaluation of anti-inflammatory effects of green tea and black tea: a comparative in vitro study, J. Adv. Pharm. Technol. Research– (JAPTR) 3 (2012) 136.
[30] Zia-Ur-Rehman, N. Muhammad, S. Ali, I.S. Butler, A. Meetsma, New mononuclear organotin(IV) 4-benzhydrylpiperazine-1-carbodithioates: synthesis, spectroscopic characterization, X-ray structures and in vitro antimicrobial activities, Inorg. Chim. Acta. 373 (2011) 187–194.
[31] Zia-ur-Rehman, N. Muhammad, S. Ali, I.S. Butler, A. Meetsma, Synthesis, spectroscopic properties, X-ray single crystal analysis and antimicrobial activities of organotin(IV) 4-(4-methoxyphenyl)piperazine-1-carbodithioates, Inorg. Chim. Acta. 376 (2011) 381–388.
[32] F. Bonati, S. Cenini, R. Ugo, Organotin and organothallium dithiophosphinates and dithiocarbamates, J. Org. Chem. 9 (1967) 395–402.
[33] N. Awang, N.F. Kamaludin, I. Baba, K.M. Chan, N.F. Rajab, A. Hamid, Synthesis, Characterization and antitumor activity of new organotin (IV) methoxyethyldithiocarbamate complexes, orient, J. Chem. 32 (2016) 101–107.
[34] N. Srinivasan, S. Thirumaran, S. Ciattini, Effect of position of methyl substituent in piperidinedithiocarbamate on the ZnS4N chromophore: synthesis, spectral, valence-bond parameters and single crystal X-ray structural studies on bis(2-methylpiperidinecarbodithioato-S,S′)-(pyridine)zinc(II) and b, J. Mol. Struct. 936 (2009) 234–238.
[35] F. Shaheen, M. Sirajuddin, S. Ali, Zia-ur-Rehman, P.J. Dyson, N.A. Shah, M.N. Tahir, Organotin(IV) 4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine-1-carbodithioates: synthesis, characterization and biological activities, J. Organomet. Chem. 856 (2018) 13–22.
[36] M. Sirajuddin, S. Ali, V. McKee, S. Zaib, J. Iqbal, Organotin (<scp>iv</scp>) carboxylate derivatives as a new addition to anticancer and antileishmanial agents: design, physicochemical characterization and interaction with Salmon sperm DNA, RSC Adv. 4 (2014) 57505–57521.
[37] V. Barba, B. Arenaza, J. Guerrero, R. Reyes, Synthesis and structural characterization of diorganotin dithiocarbamates from 4-(ethylaminomethyl) pyridine, Heteroat, Inside Chem. 23 (2012) 422–428.
[38] J.O. Adeyemi, D.C. Onwudiwe, E.C. Hosten, Synthesis, characterization and the use of organotin(IV) dithiocarbamate complexes as precursor to tin sulfide nanoparticles by heat up approach, J. Mol. Struct. 1195 (2019) 395–402.
[39] M.I. Azócar, G. Gómez, P. Levín, M. Paez, H. Muñoz, M.I. Azócar, G. Gómez, P. Levín, M. Paez, H. Muñoz, Review : antibacterial behavior of carboxylate silver (I) complexes, J. Coord. Chem. 67 (2014) 3843–3856.
[40] M.A. Carvajal, J.J. Novoa, S. Alvarez, Choice of coordination number in d 10 complexes of group 11 metals, J. Am. Chem. Soc. 126 (2004) 1465–1477.
[41] 分子轨道成分的计算 卢天陈飞武, 化学学报, 2011, p. 2393, 69.
[42] T. Lu, F. Chen, Multiwfn : A Multifunctional Wavefunction Analyzer, 2011.
[43] S. Ali, S. Shahzadi, Anticarcinogenicity and toxicity of organotin (IV) Complexes:, Iran, J. Sci. Technol. Trans. A Sci. 42 (2018) 505–524.
[44] C. Ye, D. Dai, W. Hu, Antimicrobial and antioxidant activities of the essential oil from onion (Allium cepa L .), Food Contr. 30 (2013) 48–53.
[45] E. Khan, U.A. Khan, A. Badshah, M.N. Tahir, A.A. Altaf, Supramolecular dithiocarbamatogold(III) complex a potential DNA binder and antioxidant agent, J. Mol. Struct. 1060 (2014) 150–155.
[46] F. Boora, E. Chirisa, S. Mukanganyama, Evaluation of Nitrite Radical Scavenging Properties of Selected Zimbabwean Plant Extracts and Their Phytoconstituents, 2014, p. 2014.
[47] N.F. Kamaludin, N. Awang, I. Baba, A. Hamid, C.K. Meng, Synthesis, characterization and crystal structure of organotin(IV) N-Butyl-N-phenyldithiocarbamate compounds and their cytotoxicity in human leukemia cell lines, Pakistan J. Biol. Sci. 16 (2013) 12–21.
[48] C. Pellerito, L. Nagy, L. Pellerito, A. Szorcsik, Biological activity studies on organotin(IV)n+ complexes and parent compounds, J. Organomet. Chem. 691 (2006) 1733–1747.
[49] D. Ray, K. Das Sarma, A. Antony, Differential effects of tri-n-butylstannyl benzoates on induction of apoptosis in K562 and MCF-7 cells, IUBMB Life 49 (2000) 519–525.
[50] M. Nath, M. Vats, P. Roy, Mode of action of tin-based anti-proliferative agents: biological studies of organotin(IV) derivatives of fatty acids, J. Photochem. Photobiol. B Biol. 148 (2015) 88–100.
[51] R.S. Saxena, B. Gupta, K.K. Saxena, R.C. Singh, D.M. Prasad, Study of anti-inflammatory activity in the leaves of Nyctanthes arbor tristis Linn. — an Indian medicinal plant, J. Ethnopharmacol. 11 (1984) 319–330.
[52] M. Nath, S. Pokharia, G. Eng, X. Song, A. Kumar, New triorganotin (IV) derivatives of dipeptides as anti-inflammatory – antimicrobial agents, Eur. J. Med. Chem. 40 (2005) 289–298.
[53] M. Nath, M. Vats, P. Roy, Tri- and diorganotin (IV) complexes of biologically important orotic acid : synthesis , spectroscopic studies , in vitro anti-cancer , DNA fragmentation , enzyme assays and in vivo anti-in fl ammatory activities, Eur. J. Med. Chem. 59 (2013) 310–321.