Review

Organotin(IV) Dithiocarbamate Compounds as an Anticancer Agent: A Review of Synthesis and Cytotoxicity Study

Nurul Amalina Abd Aziz , Normah Awang * , Kok Meng Chan , Nurul Farahana Kamaludin , Nur Najmi Mohamad Anuar

Posted Date: 26 May 2023

doi: 10.20944/preprints202305.1910.v1

Keywords: organotin(iv); dithiocarbamate; synthesis; characterisation; cytotoxicity

Review

Organotin(IV) Dithiocarbamate Compounds as an Anticancer Agent: A Review of Synthesis and Cytotoxicity Study

Nurul Amalina Abd Aziz, Normah Awang *, Kok Meng Chan, Nurul Farahana Kamaludin and Nur Najmi Mohamad Anuar

Center for Toxicology and Health Risk Studies, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia; p119419@siswa.ukm.edu.my

* Correspondence: norm@ukm.edu.my; Tel.: +60-392-897-527

Abstract: After Frankland first synthesized organotin compounds for the first time in 1849, their broad range of applications, including in industry and agriculture, resulted in a substantial increase in demand for organotin (IV) compounds after the 1940s. Because of the broad range of coordination numbers and molecular geometry that could result in numerous features, the structural diversity of organotin (IV) compounds is of great interest. Organotin (IV) dithiocarbamate has recently received attention as a therapeutic agent among organotin (IV) compounds. The hybrid complex individual properties of organotin (IV) and the dithiocarbamate moieties form a synergy of action stimulating increased biological activity. Organotin (IV) components have been shown in cytotoxicity studies to play a crucial role in cytotoxicity. Ligands serve to target and react to molecules while preventing unwanted changes in biomolecules. Organotin (IV) dithiocarbamate compounds have also been discovered to exhibit a broad range of cellular, biochemical, and molecular effects, with their toxicity largely determined by their structure. This review discusses the potential cytotoxicity effect of organotin(IV) dithiocarbamate, as well as its synthesis, elemental and spectroscopy analysis.

Keywords: organotin(iv); dithiocarbamate; synthesis; characterisation; cytotoxicity

1. Introduction

Organotin compounds have been used for over 170 years and are still some of the most effective chemicals available. The growing application of organotin derivatives, particularly organotin (IV) compounds, has increased the global production of these compounds. Even though the toxic side effects of organotin (IV) compounds are concerning, but there are some new ways to reduce toxic side effects and improve the compound properties [1]. These compounds are a big industry, with production between 40,000 and 51,000 tons each year [2–4]. Their high catalytic and redox capacities, structural versatility, ligand exchange potential, and broad potential contacts with biologically beneficial properties make organotin (IV) compounds attractive for a wide variety of usage [1,5,6].

Organotin (IV) compounds are often applied as polyvinyl chloride (PVC) stabilizers, industrial and agricultural biocides, and catalysts [7–9]. In addition, organotin(IV) compounds have proven to be effective antibacterial, antimalarial, schizonticidal, and anticancer agents [10–14]. The biological activity of organotin compounds are generally expressed in such order: $RSnX_3$ < R_2SnX_2 <R_4Sn << R_3SnX, with triorganotin (IV) substituents possessing the greatest impacts [8,15–19]. For the anionic X groups, such as chloride, fluoride, oxide, hydroxy, carboxylate, and thiolate [20], it is reported that they have very little effect on the activities [17,19,21]. However, combining two biologically active moieties in the same molecule could enhance their activity [19,22].

As stated by Adeyemi and Onwudiwe, as well as Pellerito et al., the biological effects of organotin compounds can be influenced by the existence of one or more C-Sn bonds, relying on the

 doi:10.20944/preprints202305.1910.v1

amount and type of the alkyl (R) substituents connected to the Sn center [5,23]. The longer the alkyl chain on an organotin compound, the lower its toxicity [17,21], but it also can vary depending on the test organism [17]. Besides that, compounds containing aryl groups were found to be less toxic than those containing alkyl groups [24,25].

Adverse effects and acquired resistance to platinum-based cancer therapies have led to increased research efforts in the search for new platinum-based treatments. Tin complexes have been suggested as potential therapeutic substitutes for cisplatin due to their similar chemical characteristics [26–30]. Even though their precise mode of action is indefinite, these compounds, like cisplatin [8,31], are believed to bind to the external phosphate groups of DNA and interfere with internal phospholipid metabolism [8,32], thereby causing apoptotic cell death. Organotin derivatives show great potential as therapeutic agents for a variety of tumor cells [5,33]. These include those associated with the ovaries, lungs, kidneys, colon, prostate, breast cancer and melanoma [34–36]. They have also shown significant selectivity for a number of cancer cell lines despite the diversity of their ligands [8,32,37,38].

Dithiocarbamate, including organotin(IV), is a class of dithiocarbamate metals that has been substantially investigated for its beneficial biological potential [35,39,40]. These complexes has rare stereoelectronic properties caused by the sulfur atoms of the dithiocarbamate ligand, which assist to transport the molecules to the target sites and prolong the retention time [39], making them widely used in the field of medicinal chemistry [41–43]. The organotin (IV) dithiocarbamate compound has attracted attention as a recent chemotherapy agent due to its capability to stabilize specific stereochemistry and its good anti-proliferative activity noted in in vitro studies [35]. Organotin(IV) dithiocarbamate compounds have shown a cytotoxic effect on various cancer cell lines [28,35,37,44] whereas triorganotin complexes yielded the highest toxicity effects [28,35,45].

Mamba et al., Menezes et al., and Syed Annuar et al. claimed that the individual properties of organotin (IV) and dithiocarbamate constituents may develop synergistic impacts which enhance biological activities [8,46,47]. Metal dithiocarbamate complexes are practically insoluble in water, yet highly soluble in organic solvents. The chelation of tin ions by dithiocarbamate ligands reduces the metal ion polarity, promotes lipophilicity, and increases permeability, resulting in increased biological activity of organotin (IV) dithiocarbamates compounds [12,45,48]. The two sulfur atoms that are present in the molecule provides dithiocarbamates ligands a strong metal-binding ability. They can act as enzyme inhibitors responsible for cancer growth (such as catalase), altering the production of reactive oxygen species or triggering the induction of apoptosis at the mitochondria [49].

The potential of organotin derivatives as pharmacological agents is rapidly emerging. This review summarized a specific methodology useful for synthesizing organotin(IV) dithiocarbamate compounds and their characterization by using elemental and spectroscopy analysis. Besides that, this review also investigated their cytotoxic potential against various cancer cells.

2. Background Chemistry of Organotin(IV) Dithiocarbamate

Tin, a group 14 post-transition metal can exist in two main oxidation states, tin(II) or tin(IV) [1]. Nevertheless, most of the known tin compounds are organotin (IV) derivatives, which are relatively more stable than their +II state, are readily oxidized to their +IV state, and frequently polymerized [50]. Organotin compounds are formed when tin (Sn) bonds with carbon (C) atoms [5,8,51]. A general formula represents these compounds: $R_xSn(L)_{4-x}$ where R represents an alkyl (such as methyl, ethyl, propyl, butyl) or aryl (such as phenyl) group, and L represents an organic or inorganic ligand [20,52]. In addition, organotin compounds can be categorized based on the number of organic moieties on the tin atom: mono-substituted, di-substituted, tri-substituted, and tetra-substituted (Figure **1**) [20,23,34,53].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

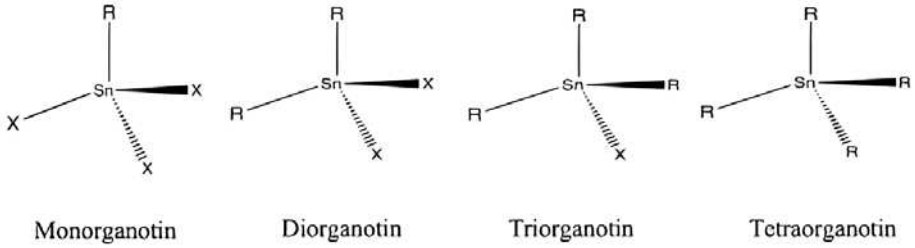


Figure 1. Structure of organotin(IV) compounds.

The dithiocarbamate anions of generic formula $^{-}S_2CNR'R''$ (Figure **2**) are the semi-amides of dithiocarbonic acids and sulfur analogs of carbamates ($R_2NCO_2^-$) [54–57]. Since 1940s, dithiocarbamates have been utilized as non-systemic pesticides to contain various fungal diseases in numerous crops and ornamental plants [58]. Moreover, these compounds and their derivatives are active agents in pharmacology, medicine, and biochemistry, and are extensively used in inorganic and organic chemistry. Its stability and interesting electrochemical and optical properties make it a valuable tool in research [59]. Previous studies reported that the two donor sulfur atoms contribute significantly to the metal binding capabilities of the dithiocarbamate ligand [45,55]. These compounds possess well-known ligands are able to bind firmly and selectively to a wide range of metal ions [55,60], making them extremely useful in a variety of medicinal and industrial applications.

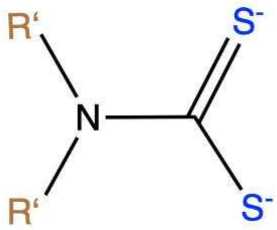


Figure 2. Structure of dithiocarbamate.

The local geometry around the Sn(IV) atom will be affected by the chelation mode and coordination number of the dithiocarbamates [54,61]. Additionally, the binding properties of the metal ions will also determine the structure of the resulting metal complexes [45,62]. The dithiocarbamate is able to coordinate to the tin atom, relying on the the Sn(IV) atom's coordination number ranging from four to seven [54,61]. These compounds are bidentate (two S atoms bonded to the central metal atom or ion), anisobidentate bridging (one S atom bonded to the metal ion while the other S atom bridged to an adjacent molecule, forming dissimilar Sn-S bond distances) or monodentate (one S atom attached to the core of metal atom or ion) (Figure **3**) [5,54,55,59,61,63–65]. Nonetheless, these anions usually behave in a bidentate manner as reported by Awang and colleagues [59].

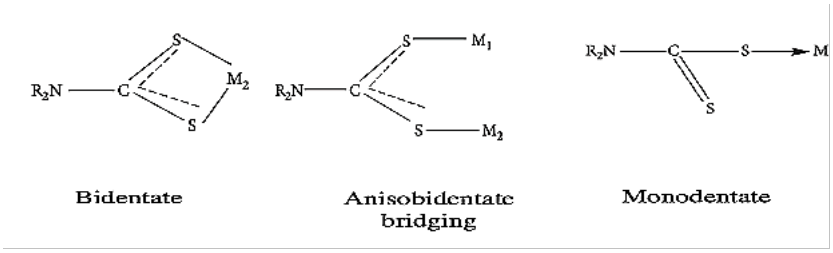


Figure 3. Difference coordination mode of dithiocarbamate [64].

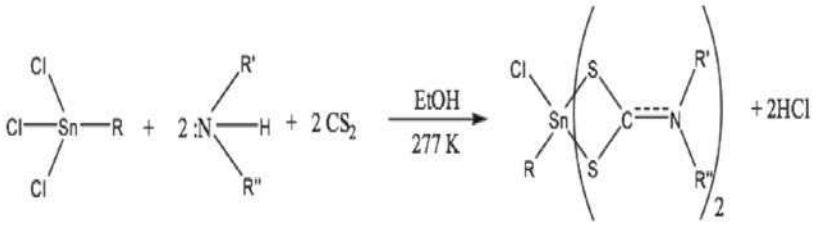
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

3. Synthesis of Organotin(IV) Dithiocarbamate

The general formula of the organotin(IV) dithiocarbamate is represented as $R_nSn(S_2CNR'R'')_{4-n}$ (n = 1, 2, or 3), where R, R', and R'' represent alkyl or aryl groups [66]. Adeyemi and Onwudiwe reported there was no one specific way to prepare organotin(IV) dithiocarbamate complexes; instead, various techniques have been applied [5]. Perry and Geanangle documented that metal dithiocarbamate (DTC) complexes were commonly prepared by two synthetic routes: a) metathetical reactions of alkali-DTC salts with metal compounds, and b) reactions of metal hydroxides with carbon disulfide and the corresponding amines [67]. Several studies, however, have shown that the *in-situ* method is the most effective way to synthesize the organotin(IV) dithiocarbamates compounds [35,44,45,54,66,68–75].

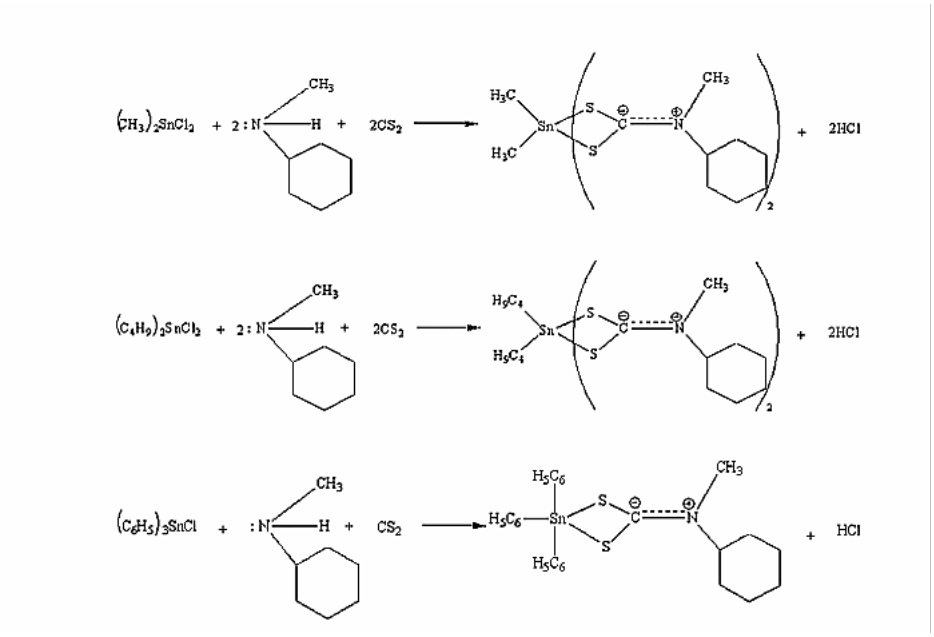
The *in-situ* method has been proposed as the best way to prepare the dithiocarbamate compounds because the ligand cannot be synthesized in solid form at a higher temperature above 4°C [54]. The reaction between carbon disulfide and the secondary amine causes the exothermic reaction (heat release) from the production of dithiocarbamic acid [35,76]. The higher temperature will cause the ligand to break down, causing the formation of carbon dioxide, hydrogen sulfide, and ammonium thiocyanide [54]. Domazetis, Magee, and James (1977) prepared the triphenyltin(IV) dithiocarbamate compounds using the low-temperature method, giving good production and high purity of compounds [63]. This shows that the temperature highly influences the product's form. However, these complexes formed are very sturdy at ambient temperature and start to melt at temperatures exceeding 100°C [54].

Previous studies reported that synthesized compounds using this method yielded greater than 50% [35,44,45,69–71,74]. Through their own research, Awang et al., and Muthalib and Baba noted that the dithiocarbamate ligands were synthesized by nucleophilic addition of carbon disulfide to the corresponding amines in cold ethanol solutions (<4°C) [66,75]. Generally, the order of adding reagents (amines, bases, and carbon disulfide) for the synthesis of dithiocarbamates does not affect the product formed, provided the correct stoichiometric proportions are used [64]. The synthesis of organotin (IV) dithiocarbamate complex is achieved by putting in a defined amount of organotin (IV) chloride dropwise to a stirred mixture of ligands. The white precipitate that developed at end of the process was filtered, washed with ethanol, and vacuum dried in a desiccator over silica gel [66,75]. The purpose of washing the compounds formed with cold ethanol is to remove any unwanted residues from the desired product [64]. The narrow melting point intervals of about 1-2°C indicated that the compound was of good purity [45]. Schemes **1** and **2** show general reaction schemes for synthesized complexes that produce high yields (>70 %).



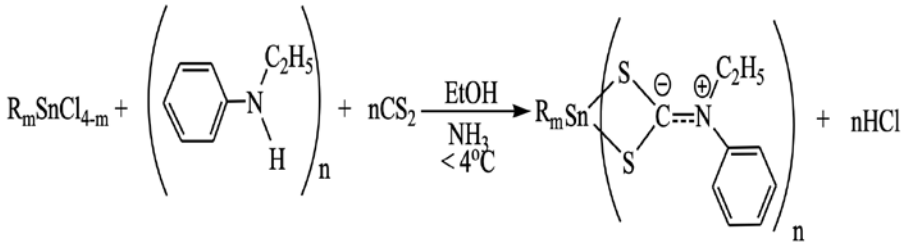
Scheme 1. The general reaction between secondary amine, carbon disulfide, and mono-tin(IV) trichloride [75].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1



Scheme 2. General reactions between *N*-methyl-*N*-cyclohexylamine, carbon disulfide, and organotin(IV) chloride [66].

The labile chloride ion is readily displaced by the dithiocarbamate ligand, and the molar ratio of the dithiocarbamate ligand to the organotin (IV) salt varies with the anions (e.g., Cl^-) exist in the organotin (IV) salt [5]. Kamaludin and Awang (2014) reported complexes with the general formula $RnSn[S_2CN(C_2H_5)(C_6H_5)]_{4-n}$ (where R = Bu and Ph for n = 2; R = Ph for n = 3) derived from the reaction between *N*-ethyl-*N*-phenyldithiocarbamate and corresponding organotin(IV) salts using the different molar ratios of 1:2 for di-organotin(IV) and 1:1 for tri-organotin(IV) compounds [54]. The compounds obtained from the reaction scheme in Scheme 3 yielded a range of yields from 32.0 to 84.5%.



Scheme 3. The schematic reaction between *N*-ethylaniline, carbon disulfide, and organotin(IV) chloride [54].

Some organotin(IV) dithiocarbamate complexes were prepared using a slightly modified procedure. Mohamad, Awang and Kamaludin (2016), Adeyemi, Onwudiwe and Hosten (2018), and Adeyemi et al. (2020) synthesized the ligand by adding ammonia solution to an amine solution prior to adding carbon disulfide [44,69,74]. The ammonia solution added to the reaction provides a basic condition necessary for the reaction to occur [74].

4. Characterization of Organotin(IV) Dithiocarbamate.

4.1. Elemental Analysis of Organotin(IV) Dithiocarbamate (CHNS)

The proportions of carbon, hydrogen, nitrogen, and sulfur in organic compounds can be determined by CHNS analysis. The process of breaking down organic materials results in the release

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

of gases, which can then be analyzed to determine the elements present in a sample [77]. According to the analysis, when all values are within the adequate range and the experimental elemental proportion match the theoretical values, the Sn atom is chelated with the dithiocarbamate group to create neutral compounds [55,72]. Table 1 shows the synthesized organotin (IV) dithiocarbamate complexes' physical and elemental analysis data.

Table 1. Data of organotin (IV) dithiocarbamate complexes' physical and elemental analysis.

Complexes	Yield (%)	Melting point (°C)	Elemental analysis % Found (Calculated)				References
			C	H	N	S	
Dimethyltin(IV) methylcyclohexyldithiocarbamate	89	147.9-148.8	40.66 (41.14)	6.46 (6.48)	5.30 (5.33)	26.43 (24.38)	[66]
Dibutyltin(IV) methylcyclohexyldithiocarbamate	83	122.6-124.0	47.15 (47.29)	8.08 (7.55)	4.62 (4.60)	22.72 (21.02)	
Triphenyltin(IV) methylcyclohexyldithiocarbamate	76	136.8-138.2	57.71 (57.99)	4.98 (5.39)	2.57 (2.60)	11.26 (11.90)	
Diphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	82.1	102.1-104.0	56.15 (56.59)	5.89 (5.31)	3.77 (3.88)	16.81 (17.77)	[45]
Triphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	34.0	101.0 - 102.0	60.54-(60.64)	5.08 (5.09)	2.34 (2.44)	11.31 (11.17)	
Dibutyltin(IV) *N*-ethyl-*N*-phenyldithiocarbamate	84.5	126.9 - 128.2	50.72 (49.92)	7.47 (6.12)	4.22 (4.48)	20.26 (20.50)	[54]
Di-tert-butyltin(IV) *N*-ethyl-*N*-phenyldithiocarbamate	51.6	124.8 - 126.5	48.19 (49.92)	7.34 (6.12)	4.13 (4.48)	20.10 (20.50)	
Diphenyltin(IV) *N*-ethyl-*N*-phenyldithiocarbamate	74.8	70.2-72.9	54.13 (54.14)	4.49 (4.54)	4.27 (4.21)	18.28 (19.27)	
Triphenyltin(IV) *N*-methylbutyldithiocarbamate	78	88.3-90.8	55.70 (56.27)	4.91 (5.31)	2.34 (2.73)	11.91 (12.52)	[55]
Dibutyltin(IV) methoxyethyldithiocarbamate	76	68-69	41.76 (40.77)	6.07 (7.14)	4.91 (4.31)	19.25 (19.75)	[73]
Triphenyltin(IV) methoxyethyldithiocarbamate	89	93-94	54.38 (53.76)	4.38 (5.24)	2.87 (2.51)	12.13 (11.49)	
Dibutyltin(IV) (2-methoxyethyl)methyl dithiocarbamates	66.31	59.7–62.9	40.26 (38.50)	7.33 (6.82)	4.98 (5.04)	23.65 (22.84)	[74]
Diphenyltin(IV) (2-methoxyethyl)methyl dithiocarbamates	78	109.1–111.1	44.70 (43.93)	5.12 (5.03)	4.26 (4.67)	20.24 (21.33)	
Tricyclohexyltin(IV) (2-methoxyethyl)methyl dithiocarbamates	76.39	102.7–104.4	52.40 (51.89)	8.05 (8.14)	2.53 (2.63)	12.47 (12.05)	

 doi:10.20944/preprints202305.1910.v1

Dimethyltin(IV) *N*-ethyl-*N*-phenyl dithiocarbamates	82	167–169	43.90 (44.37)	5.01 (4.84)	4.99 (5.17)	23.99 (23.69)	[69]
Dibuthyltin(IV) *N*-ethyl-*N*-phenyl dithiocarbamates	87	121–122	48.42 (49.92)	5.81 (6.12)	5.48 (4.48)	21.50 (20.50)	

4.2. Fourier Transform Infrared Spectroscopy (FTIR) Analysis

Infrared spectroscopy (FTIR) is a well-known technique used to identify organic materials, including their structure, behavior, and surroundings of molecules in their native environments [78]. Besides that, it is used to determine coordination modes and binding properties of metal complexes [35]. The FTIR spectrum of the sample is often recorded in the 4000-400 cm^{-1} range [79–84]. The presence of a functional group in a molecule or sample that changes its electric dipole moment during vibration has to be a prerequisite to show an infrared spectrum [79]. There are four important absorption regions in the infrared spectrum; υ (C---N), υ (C-S), υ (Sn-C), and υ (Sn-S), indicating the formation of organotin(IV) dithiocarbamate complexes that will be discussed in the review.

Dithiocarbamates can be identified by the distinct infrared spectral bands called the thioureide ν (C---N) and ν (C-S) bands [35,57,74,75,85,86]. These two stretching frequencies are of particular interest in the IR spectra since they can be used to distinguish between mono- and bidentate modes of binding of dithiocarbamate ligands [87]. Besides that, the presence of these two bands confirms that the ligands of dithiocarbamate coordinate to the tin atom via thiol-sulfur [66]. The thioureide band is a combination of ν(C–N) and ν(C=N) [74]. This band is a set of carbon-nitrogen bonds that fall between single bonds at 1250–1350 cm^{-1} and double bonds at 1640–1690 cm^{-1} [85,88,89]. However, these bands are often observed in the spectral range of 1450-1550 cm^{-1} [90,91], which is associated with the vibration of the partial double bond and a polar character [5,92].

The partial double bond character of this thioureide band may be due to the delocalization of electrons in the $–NCS_2$ region [45,74,89]. This band is sensitive to the presence of substituent groups on the tin(Sn) atom. The stretching of the (C---N) bond can be explained by considering that the more electronegative the substituent, the less the electron density on the tin atom and thus, the greater the contribution of the canonical structure (Figure **4**). This will cause a stronger double-bond character to the (C---N) bond [93].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

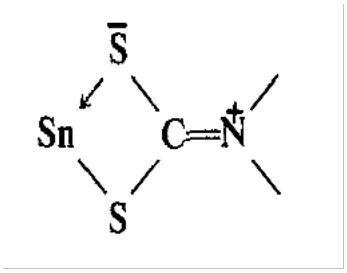


Figure 4. Canonical structure [93].

Besides that, the more electronegative substituent will increase the frequency of vibration [35,74,93,94]. Onwudiwe and colleagues observed an upward shift around 15 cm^{-1} after complexation due to the movement of the electron cloud of the $–NCS_2$ group closer to the metal center [86]. This is in agreement with the results of previous studies which obtained a higher stretching frequency, 1503–1478 cm^{-1}, and 1479-1475 cm^{-1} respectively due to the removal of electrons to the tin center of the compound [35,44].

A study found that the stereochemistry of the complex and the metal's oxidation state influenced the frequency, with the following order: planar > tetrahedral > octahedral [95]. Awang and colleagues observed that the C-N bands shifted down to lower frequencies due to the increase in coordination number [59]. This demonstrates that the geometry of the compound may affect the degree of interaction between the dithiocarbamate ligand and the metal ion, which has resulted in a decreased stretching frequency.

The number of peaks in the υ(C-S) band region can be used to determine the chelation mode of the ligand to the central Sn(IV) atom [45,92]. This υ(C-S) stretching band usually appears in the range of 950-1050 cm^{-1} [54,61,90,91,96]. Apparently, there are two types of υ (C-S) bands, υ (CS_2) asymmetry and υ (CS_2) symmetry, which are found at 1120 – 1131 cm^{-1} and 995 – 1008 cm^{-1}, respectively [87]. A single peak in the spectrum is associated with a bidentate symmetrical bonding while the splitting of this band into a doublet may be attributed to the unsymmetrical monodentate nature of the dithiocarbamate moiety [97]. Previous studies found a single υ(C-S) band at the absorption peak near 1000 cm^{-1}, suggesting a bidentate mode of coordination [35,44,46,66]. The bands split by a difference of 20 cm^{-1} or more within the same region indicated that the ligand coordinated to the central Sn(IV) atom in a monodentate fashion [56,91,92].

Organotin(IV) compounds can be identified by the presence of the two vibrating bands: υ (Sn-C) and υ (Sn-S). Adeyemi et al. indicated that peaks attributed to the Sn-C stretch frequencies were 512-507 cm^{-1} [44]. These results are consistent with studies by Haezam et al. who found vibrational bands of Sn-C in the range 546-556 cm^{-1} within the complex, indicating the stretching frequency for compounds with aryl groups [35]. In contrast, Kamaludin and Awang found that Sn-C stretching occurred for diphenyltin(IV) and triphenyltin(IV) compounds with aryl groups at 256 and 261 cm^{-1}, and for dibutyltin(IV) compounds with alkyl groups at 554 cm^{-1} [54].

Sn-S stretching vibration commonly appears in the far IR region and indicates the presence of metal-ligand bonds and that complexation has occurred. Muthalib and his colleagues reported a strong absorption band attributed to the Sn-S stretching frequencies appearing in the range of 325–386 cm^{-1} [94]. This agrees with previously published data for organotin(IV) dithiocarbamate compounds, with Sn-S stretching vibrations being recorded in the regions of 355-377 cm^{-1}, and 384-390 cm^{-1} [54,98]. Table **2** lists the important infrared absorption bands (cm^{-1}).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

Table 2. Important infrared absorption bands (cm−1).

Compounds	ν(C---N)	ν(C---S)	ν(Sn-C)	ν(Sn-S)	References
$(CH_3)_2Sn[S_2CN(C_7H_7)(iC_3H_7)]_2$	1444	997	-	377	[98]
$(C_4H_9)_2Sn[S_2CN(C_7H_7)(iC_3H_7)]_2$	1427	956	-	355	
$(CH_3)_2Sn[S_2CN(CH_3)\ (C_6H_{11})]_2$	1475	974	554	357	[66]
$(C_4H_9)_2Sn[S_2CN(CH_3)\ (C_6H_{11})]_2$	1459	975	532	359	
$(C_6H_5)_3\ Sn[S_2CN(CH_3)\ (C_6H_{11})]$	1478	979	261	349	
$(C_4H_9)_2Sn[S_2CN(CH_3)(C_6H_{11})]_2$	1478	979	-	375	[57]
$(C_4H_9)_2Sn[S_2CN(iC_3H_7)(C_6H_{11})]_2$	1479	978	-	389	
$(C_4H_9)_2Sn[S_2CN(C_4H_9)(C_6H_5)]_2$	1487.42	951.14	567.97	-	[45]
$(C_6H_5)_2Sn[S_2CN(C_4H_9)(C_6H_5)]_2$	1457.81	996.86	258.69	-	
$(C_6H_5)ClSn[S_2CN(CH_3)(C_2H_5)\ ]_2$	1511	997,957	-	318	[75]
$(CH_3)ClSn[S_2CN(CH_3)(C_2H_5)]\ _2$	1519	995, 957	-	349	
$(C_4H_9)_2Sn[S_2CN(C_2H_5)(C_6H_5)]_2$	1488.72	1003.50	554.14	385.96	[54]
$(C_6H_5)_2Sn[S_2CN(C_2H_5)(C_6H_5)]_2$	1490.73	1000.62	256.21	390.23	
$(C_6H_5)_3Sn[S_2CN(C_2H_5)(C_6H_5)]$	1478.64	996.50	261.09	384.06	
$Bu_2Sn[C_{16}H_{34}NCS_2]_2$	1464	1025,963	563	412	[99]
$Ph_3SnS_2CNC_5H_{12}$	1497	983	605, 567	445	
$C_{20}H_{26}N_2S_4Sn$	1461	1006	551	450	[69]
$C_{26}H_{38}N_2S_4Sn$	1488	1020	553	447	
$C_{30}H_{30}N_2S_4Sn$	1462	1003	552	444	
$(CH_3)_2Sn(L)_2$	1503	981	507	451	[44]
$(C_4H_9)_2Sn(L)_2$	1487	1008	512	440	
$(C_6H_5)_2Sn(L)_2$	1478	996	510	443	
$(C_6H_5)_2Sn[S_2CN(C_3H_5)_2]_2$	1475.54	977.91	545.85	441.70	[35]
$(C_6H_5)_3Sn[S_2CN(C_3H_5)_2]$	1479.40	972.12	555.50	445.56	

4.3. Nuclear Magnetic Resonance (NMR) spectroscopy

NMR spectroscopy is an advanced technique for characterizing most organotin(IV) complexes. This technique provides useful information for predicting the geometry of organotin(IV) complexes.

1. ^{1}H NMR spectroscopy

The ^{1}H NMR spectrum of the complex can be assigned to two regions of signals: methyl and methylene proton in dithiocarbamate ligand (3-4 ppm) and organic groups attached to the Sn atoms of aliphatic groups (1-2 ppm), and the phenyl group (7-8 ppm) [74]. Studies by Adeyemi et al. found that ^{1}H NMR chemical shifts of the complexes were observed in the range of δH, 3.94-3.56 ppm and δH 4.16-4.11 ppm, respectively, attributed to methylene protons directly attached to the N atoms of the dithiocarbamate ligands [44,100].

The alkyl groups present within the complex affected the chemical shifts in the ^{1}H NMR spectra of the dithiocarbamate moiety [70]. Onwudiwe and Ajibade [101] observed a downfield by δ = 0.4–0.6 ppm for methyl linked directly to N atoms in contrast with a study by Riveros and colleagues [102] which observed a chemical shift at δH 3.26-3.40 ppm. A downfield shift may contribute to the effect of the electronegativity of the nitrogen atom compared to the alkyl carbon [101,103]. Besides that, the electronegativity of the coordinated dithiocarbamate group is higher than that of the uncoordinated group [104].

Adeyemi and colleagues [70] observed that the proton signals of the methyl group of the *N*-ethyl dithiocarbamate appeared to have lower chemical shifts than the *N*-methyl group at 1.23 ppm and 3.80 ppm, respectively, likely due to the deshielding effect that was reduced as the distance of the alkyl chain from the thioureide bond or metal center increased [105,106]. This result suggests that the resonances of the methyl protons connected to the N atom will be unaffected by the differences in the

 doi:10.20944/preprints202305.1910.v1

organotin used to form each complex as the influence of substituents decreases rapidly with distance [74].

Studies provide compelling evidence that organic groups attached to nitrogen atoms and tin(IV) atoms produce distinct proton signals [44,94]. For example [94], the *N*-methyl protons signal was observed as a singlet at 3.19 - 3.34 while multiplets signals at 1.12 - 1.95 ppm and 4.50 to 4.65 ppm were assigned to N-cyclohexyl protons. For the isopropyl group, multiplet signals of 5.08-5.10 ppm and doublet of 1.21-1.26 ppm were assigned for methyne and methyl protons, respectively. Meanwhile, the chemical shifts of 7.27 to 8.07 ppm indicated the proton aromatic signals of the phenyl group (C_6H_5-N) [45,106].

In addition, Adeyemi et al. [44] reported proton signals in the organotin moiety for the dimethyltin(IV) derivative that appeared in the upfield region as a singlet at 1.53 ppm [66]. For the dibutyltin(IV) derivative, the proton signals were found in the range of 2.35–0.88 ppm, assigned to methylene and methyl protons of the butyl group [107]. A diphenyltin(IV) derivative was found in a range of 8.06 to 7.78 ppm, which was consistent with signals reported for aromatic protons bonded to the Sn atom [68,94]. For the phenyl group, the coupling constants for the protons were difficult to measure because the signals appear as multiplets [54]. The multiplet resonances may be due to the overlapping of proton signals in the aromatic group attributed to the phenyl ring attached to the N-atom of the ligand, and the phenyl group attached to the central Sn(IV) atom [45].

2. 13c NMR spectroscopy

The chemical shift of the CS_2 peak of the thioreide carbon (–NCS_2) group is the most significant shift to characterize the dithiocarbamates complexes. This peak usually occurs between δ 185-220 ppm [108] and the presence of the signal confirms that the coordination of sulfur to the metal atom has occurred [35,59,71]. A study by Onwudiwe and Ajibade (2011) observed weak signals of the ^{13}C NMR spectrum for NCS_2 carbons of the dithiocarbamate complex at 190.51 – 202.10 ppm [101], in line with a previous study (196.8 – 201.9 ppm) [75] and another (197.79-200.82 ppm) [35]. According to Adeyemi, Onwudiwe & Hosten (2019), the presence of the double bond character within the thiouriede group has been linked to the lower values of the NCS_2 peaks [70]. The dithiocarbamate ligands with greater trans-effect have more shielded -CS_2 groups, indicating greater electron density of the ligating group [109].

Furthermore, carbon signals for other carbon-containing substances were also observed in the ^{13}C NMR spectroscopy. Signals attributed to the methylene carbon close to the electronegative nitrogen atom have been observed in the range of δC 55.59-57.05 ppm [73], δC 57.0-59.8 ppm [44] and δC 56.56-57.84 [74]. Recent studies have shown that the methylene-C signal has a downfield shift, which could be attributed to the electronegative effect of the N atoms [45]. The electronegativity effects of the N atom cause a downfield shift in the spectrum 20 times higher at ^{13}C than the ^{1}H chemical shift [45,110].

A study by Adeyemi et al. (2020) reported carbon signals in the alkyl substituents attached to the tin center of dimethyl complex resonated at δ 15.0 ppm [44] which was in agreement with previous studies [66]. For the dibutyl complex, the resonation was observed between δ 31.2 and 13.9 ppm [111]. Meanwhile, the diphenyl complex was found in the region of δ 136.2 to 128.9 ppm consistent with data reported by Haezam et al. [35], which showed resonation at δ 119.0-135.75 ppm. Sometimes, the two signal sets of the aromatic carbon can be seen, indicating that both dithiocarbamate moieties on the adjacent sides of the tin metal are unequal or magnetically unpaired for the aromatic groups [70,106].

3. 119Sn NMR spectroscopy

^{119}Sn NMR spectroscopy usually determines the coordination number of tin [94] and provides information on the geometry of organotin(IV) complexes [111]. The ^{119}Sn shift is found to depend on the nature of the group attached to the Sn. The R substituent of the dithiocarbamate group attached to the Sn atom affects the chemical shift of ^{119}Sn although each compound has the same coordination number [112] due to the sensitivity of the chemical environment of tin [94,113]. Besides that, the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

nature of the chelating ligand (X) in R_nSnX_{4-n} can affect the values of δ (^{119}Sn), with a higher electronegativity of the coordinate ligand causing the δ (^{119}Sn) value to shift downfield [111,114].

The ^{119}Sn NMR spectrum of an organotin(IV) complex often indicates a singlet and is significantly lower in frequency than the corresponding organotin(IV) salts. The lower chemical shifts of ^{119}Sn are mainly due to the presence of electronegative substituents and dπ-pπ bonding effects, which lead to changes in the coordination numbers and bond angles near the tin center [115]. Hence, a lower chemical shift indicates an increase in the coordination number [112,114]. Figure **5** shows a ^{119}Sn chemical shift value (δ) at -335 ppm, indicating a hexacoordinated geometry around the Sn metal [44]. The list below classifies the most common structures of organotin(IV) compounds according to the coordination numbers [5,116–119]:

1. Four-coordinate compounds (δ = 200 to -60 ppm): Distorted Tetrahedral structure
2. Five-coordinate compounds (δ = -90 to -190 ppm): Distorted Trigonal-bipyramidal structure
3. Six-coordinate compounds (δ = -210 to -400 ppm): Distorted Octahedral structure
4. Seven-coordinate compounds (δ = -338 to -446 ppm): Distorted Pentagonal bipyramidal structure

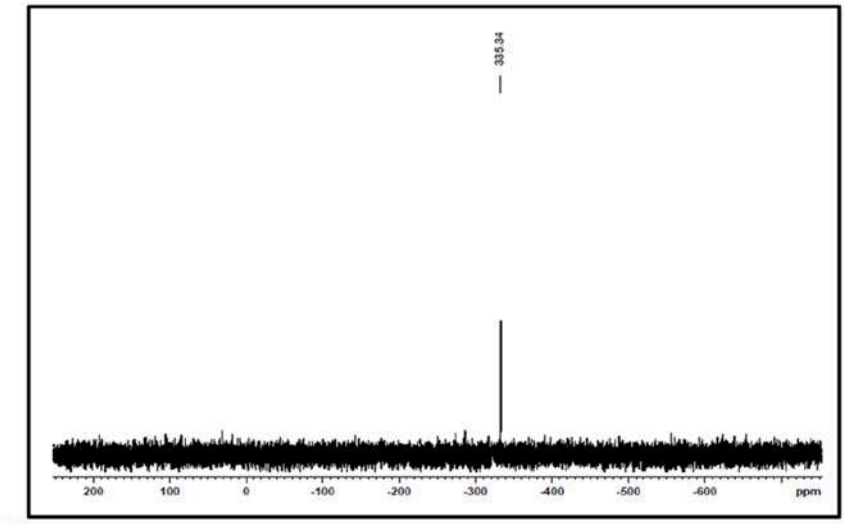


Figure 5. ^{119}Sn NMR (ppm) analysis of the [$(CH_3)_2SnL_2$] complex [44].

4.4. Recrystallization and Crystallography Study

X-ray crystallography can further confirm the structural geometry of organotin(IV) complexes. Generally, a crystallography study involves four important steps: crystallization, data collection, structural elucidation, and refinement/verification [120]. The crystallization of organotin(IV) dithiocarbamate complexes is often done by dissolving the compound in a mixture of an organic solvent such as chloroform:ethanol in the respective ratio of 1:1, 2:1, or 1:3. The mixture is allowed to evaporate for a few days at room temperature before being collected and analyzed using X-ray technology. In previous studies, these methods have obtained colorless crystals [35,54,98].

Deschamps (2010) suggested a similar technique for the crystallization of the small molecule that was used to produce a single crystal suitable for X-ray diffraction experiments [120]**.** Figure **6** shows a different type of crystal formation in which some compounds crystallize as thin plates that stick together or form stacks that appear to be single (a), which is unsuitable for x-ray diffraction. However, careful dissection (such as agglomerations) can yield useful single crystals (d). Besides that, rapid crystal growth often results in many crystals growing from a single nucleation center, forming elongated or acicular crystals (b). These also can be separated to yield useful single crystals (e). Crystal forms that look like glass wool or dust balls (c) are among the least desirable crystal forms. However, careful dissection can separate a single crystal from one of these undesirable forms (f). Crystals that are as small as 5x40x220 microns can be used for data collection [120,121].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

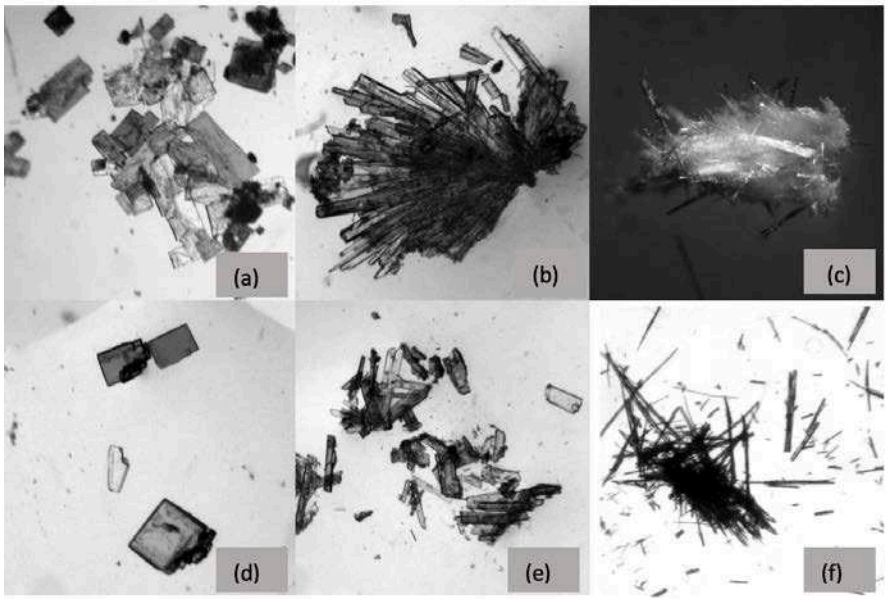
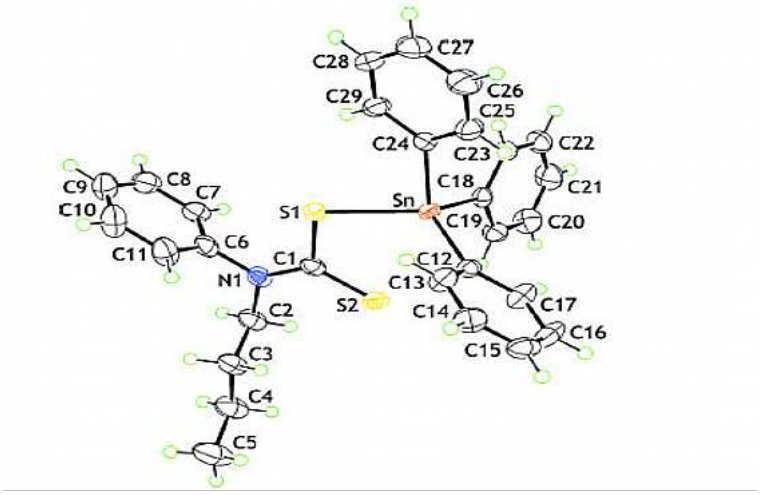


Figure 6. Different types of crystal formation [120].

According to Kim et al. (1987), the coordination geometries of organotin(IV) complexes seem to depend on the bonding mode of dithiocarbamate moiety, which is predominantly monodentate or bidentate [122]. In addition, the overall coordination number at the Sn atom decreases with the number of organic substituents at the Sn atom, which usually occurs when the sulfur donors are asymmetrically coordinated [117]. Therefore, this phenomenon affects the structural geometry of the complex. Organotin(IV) complexes can exist in a variety of structures depending on their coordination environment [1,117,118]. However, distorted tetrahedral, distorted trigonal-bipyramidal structure, and distorted octahedral are the most common geometries of organotin(IV) dithiocarbamates complexes.

The triorganotin(IV) complexes are often seen as tetrahedral or trigonal bipyramidal symmetry with distortions regardless of the nature of the ligands attached to the Sn atoms [123]. The distortion arises as a result of the distance of the second uncoordinated sulfur which forms a "pendant-like" structure [5]. As shown in Figure **7** and **8**, the complexes exhibit a distorted tetrahedral geometry around the tin center [45,54]. The dithiocarbamate ligands coordinate to the Sn atom in a monodentate manner due to the large disparity in the C–S bond distances. Consistently, Sn-S bond distances are also non-equivalent for both complexes. The C–S bond angles for complex $(C_6H_5)_3Sn[S_2CN(C_4H_9)(C_6H_5)$ are S1–C1=1.758(2) Å and S2–C1=1.675(2) Å while complex $(C_6H_5)_3Sn[S_2CN(C_2H_5)(C_6H_5)$ with two independent molecules in the asymmetric unit have bond angles of S1-C1 = 1.759(2) Å; S2-C1 = 1.680 (2) Å; S3-C28 = 1.7496 (19) Å, S4-C28 = 1.6862 (19) Å.



Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

Figure 7. ORTEP plot of compound $(C_6H_5)_3Sn[S_2CN(C_4H_9)(C_6H_5)$ with distorted tetrahedral geometry at a 50 % probability level [45].

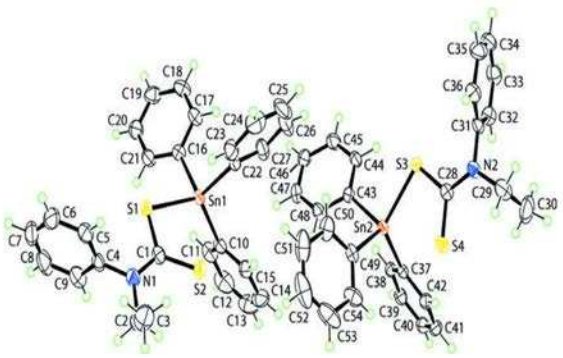


Figure 8. ORTEP plot of compound $(C_6H_5)_3Sn[S_2CN(C_2H_5)(C_6H_5)$ with distorted tetrahedral geometry at 50 % probability level [54].

The covalent Sn–S bond distances are unequal for both complexes with Sn-S1 (2.4772 (5) Å) and Sn-S2 (3.1048 (5) Å) for triphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate while Sn1-S2 = 3.1477 (6) A°, and Sn2-S4 = 2.9970 (5) A° for triphenyltin(IV) *N*-ethyl-*N*-phenyldithiocarbamate. The longer bond distance (3.1048 (5) Å and 3.1477 (6) A°) is less than the sum of the van der Waal radii of two atoms (4.0 Å), indicating weak interaction for the Sn1–S2 bond [5]. The wider angles between the bond distance also cause deviation in the tetrahedral angles from the ideal tetrahedral geometry (109.5°) which is attributed to the influence of the proximity of the non-coordinating thione sulfur atoms in the complexes [45,124].

The bond length of C-N also known as thioureide distance indicates the formation of the dithiocarbamate group. This bond is usually found in the bond length of mean value 1.45 Å [45,125]. However, the thioureide distance in both complexes was shorter as compared to the normal bond length in which C1-N1=1.337(2) Å for triphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate while for triphenyltin(IV) *N*-ethyl-*N*-phenyldithiocarbamate the C1-N1 and C28-N2 is 1.342 (2) A° and 1.333 (2) A°, respectively. Therefore, the bonds formed impose a partial double bond feature as found in most dithiocarbamate complexes [45,54,76,126].

Six coordinated or octahedral geometry around the tin atom are most common for diorganotin(IV) complexes. This geometry is usually formed through bidentate coordination of dithiocarbamate ligand with its two sulfur atoms to the tin center [117]. Awang & Baba (2012) reported an anisobidentate coordination of the dithiocarbamate ligand to the tin atom through four Sn-S bonds, forming a six-coordinated geometry (Figure **9**) [57]. The covalent Sn–S bonds were Sn(1)-S(1) = 2.9255(11) A°; Sn(1)-S(3) = 2.8922(9) A°; Sn(1)-S(2) = 2.5419(10) A°; and Sn(1)-S(4) = 2.5293(10) A°). The longer Sn-S distances are significantly lower as compared to the sum of the van der Waals radii (4.0 A°) [127]. Therefore, these bonds may be considered weak [81].

The C-S bond distances [S(2)-C(9) = 1.746(3) A°, S(4)-C(18) = 1.743(4)] and [C(9)-S(1) = 1.692(4), C(18)-S(3) = 1.692(4)] of this complex are reported almost similar to the dithiocarbamate complexes found by Rehman et al. [128], thus confirming the considerable double bond character associated with the C-S bonds. The short thioureide distance (C(9)−N(1) = 1.328(4) Å and C(18)−N(2) = 1.331(4) Å) showed that the π-electron density was delocalized over the S_2CN moiety and had a partial double bond character [45,54].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

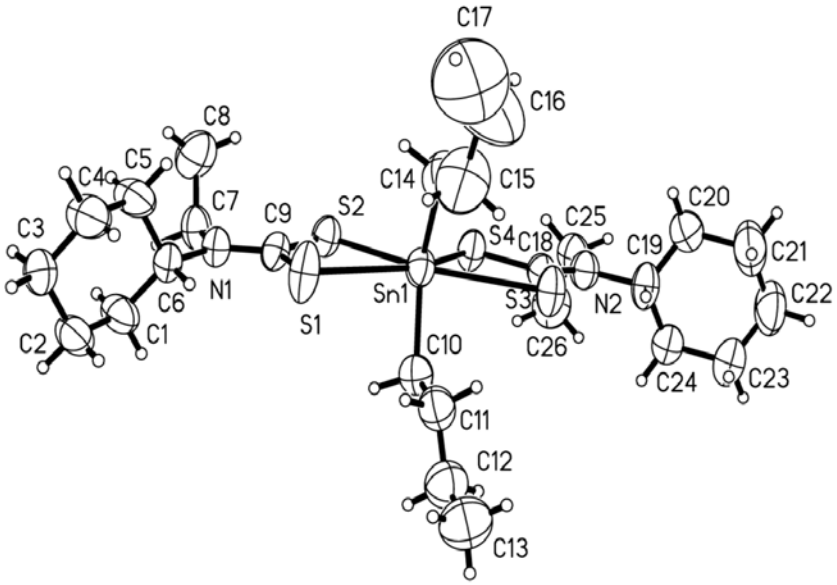


Figure 9. ORTEP plot of *N*-alkyl-*N*- cyclohexyldithiocarbamato)dibutyltin(IV) at 50% probability level [57].

Haezam et al. (2021) and Adeyemi, Onwudiwe & Hosten (2019) reported the octahedral environment around the tin atom resulting from two bidentate coordination of sulfur atoms in ligand dithiocarbamate to the tin atom in the organotin(IV) complex as shown in Figure **10** and **11** [35,70]. Sulfur atoms in the structure form unequal distances from tin atoms, forming one short Sn-S and long Sn-S bond. This suggests that the dithiocarbamate ligand coordinated with the tin atom asymmetrically, forming a distortion of the regular octahedral geometry. Adeyemi and colleagues reported that the Sn-S distances in dimethyltin(IV) *N,N*-methyl phenyl-*N,N*-ethyl phenyl dithiocarbamate were higher than the sum of usual Sn-S covalent radii (2.42 Å), but significantly less than the sum of the van der Waals radii (3.97 Å) [129], making them a true bond. The distortion around the metal center and asymmetrical nature of ligand dithiocarbamate suggests this complex has a skew trapezoidal-bipyramidal geometry [70].

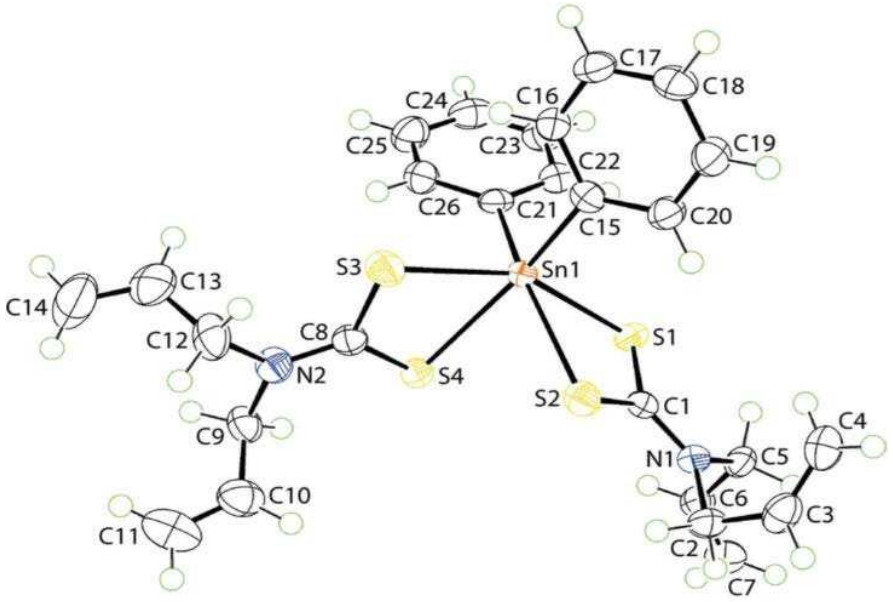


Figure 10. ORTEP plot of compound $(C_6H_5)_2Sn[S_2CN(C_3H_5)_2]_2$ at 50% probability level [35].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

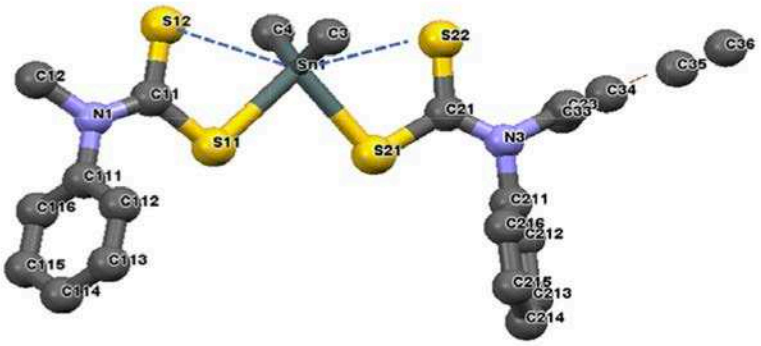


Figure 11. A structure of dimethyltin(IV) *N,N*-methyl phenyl-*N,N*-ethyl phenyl dithiocarbamate complex $[(CH_3)_2SnL^1L^3]$ [70].

A crystal structure of the 1,1-Dibutyl-1,1-bis[(4-methyl-1-piperidinyl)dithiocarbamato)]tin(IV) **(**Figure **12)** in the asymmetric unit with four coordination number of the tin atom has been reported [81]. Ligand dithiocarbamate bonds to the Sn atom through sulfur atoms (1) and (3), with Sn-S (1) = 2.534 (12) A° and Sn-S (3) = 2.536 (11) A°. The structural data suggest that the ligand is coordinated in a monodentate fashion, which is unusual for di-organotin(IV) substituents [5]. The Sn-S (2) and Sn-S (4) bond distances, which are 2.918 (14) and 2.919 (13) A°, respectively, are too long to be strong covalent bonds and are considered weak due to shorter than the sum of the van der Waals radii for these atoms [98,130].

The bond distance is considered as weak maybe because the steric interaction of the two butyl groups and the four-membered chelating ring may prevent the formation of the Sn(1)-S(2) and Sn(1)-S(4) bonds [81,98]. The geometry is distorted from a regular tetrahedron due to the bond angle of C(15)-Sn-C(19) being 135.3 (16)° which is larger than the expected angle for a tetrahedron (109.5°) [5,45]. Another important distortion is caused by the asymmetric Sn-S bond lengths which the angle S(1)-Sn(1)-S(3) of 83.03 (14)°, is not consistent with true tetrahedral geometry. Thus, the coordination geometry for this complex is described as distorted tetragonal.

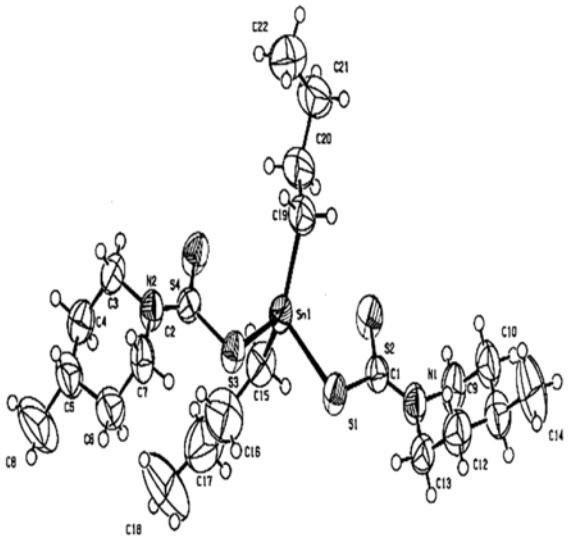


Figure 12. ORTEP drawing of 1,1-dibutyl-1,1-bis[(4-methyl-1-piperidinyl)dithiocarbamato)]tin(IV) with atomic numbering scheme [81].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

Monorganotin(IV) complex exhibits only distorted octahedral geometries with the little exception being the pentagonal pyramid geometry [117]. Muthalib and Baba [75] reported the structure of monorganotin(IV) complex with the formula of $PhSnCl[S_2CN(Et)(i\text{-}Pr)]_2$ (compound 5), $MeSnCl[S_2CN(Me)(Cy)]_2$ (compound 11) and $MeSnCl[S_2CN(i\text{-}Pr)(CH_2Ph)]_2$ (compound 17) (Figure **13**). These molecules have a distorted octahedral geometry attributed to the bonding between the tin atom and the $CClS_4$ donor atom from the two chelating dithiocarbamate ligands. These three compounds have short Sn-S bond distances (from 2.5 to 2.7 Å) which indicate symmetric coordination modes [131]. The shortest Sn-S bond lengths (Sn-S1= 2.5191(11) Å) observed in compound 5 might be due to the higher electronegative effect of the phenyl substituent.

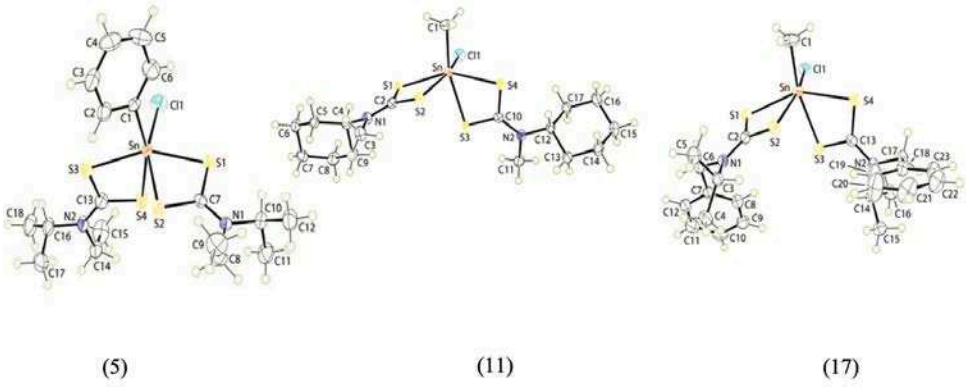


Figure 13. ORTEP plot of compound compounds 5, 11, and 17 with distorted octahedral geometry at a 50% probability level [75].

5. Anticancer Effect Of Organotin(IV) Dithiocarbamate

The FDA's approval of cisplatin, **Pt1** for the treatment of testicular cancer in 1978 caused a surge of interest in clinical metallodrugs and marked the beginning of medicinal inorganic chemistry [132]. However, cisplatin is known to have significant side effects, including nephrotoxicity, hepatotoxicity, gastrotoxicity, myelosuppression, neurotoxicity, cardiotoxicity, and ototoxicity [133,134]. Therefore, this led researchers to turn their attention to non-platinum chemotherapy drugs with few side effects [17,27].

Recently, the organotin(IV) dithiocarbamate complex has been receiving much attention due to its therapeutic potential. Both organotin and dithiocarbamate moieties have been found to play a significant role in the cytotoxic activities of various cancerous cell lines [44]. Organotin compounds hold potential as a non-platinum chemotherapeutic drug due to their ability to exhibit fewer side effects, greater excretion abilities, higher antiproliferative activities, and low toxicity than other platinum-based drugs [8,28,32,135]. A study by Varela-Ramirez et al. [29] reported that even though organotin have been implicated in important deleterious ecological effects, it is possible that by chemical modification these compound can be generated with low toxic side effects and higher antitumor activity. For this reason, more stable tin-based compounds with different ligands have been synthesized and are starting to be tested as potential cancer treatments.

Kamaludin et al. (2013) and Muhammad et al. (2022) claim that the toxicity of organotin(IV) is directly correlated with the number and nature of the organic moiety [45,136]. Highly substituted organotin compounds are more toxic while shorter alkyl substituents enhance the cytotoxic effect of compounds [137–139]. On the contrary, according to Adeyemi et al. (2020), longer chains of alkyl or aryl groups in organotin complexes cause more cytotoxicity than shorter chain counterparts. However, this trend can be a hindrance due to selectivity toward the used cell lines [44]. This could be that the toxicity trend based on the length/nature of the substituents depends on the employed target.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

The organotin(IV) compounds with trialkyl and triaryl substitutions are reported to be more toxic than those with di-alkyl and aryl substitutions [26,28,35,66,68,73,140]. Compared to the cytotoxic activity of the mono-substituted derivatives, the di-substituted alkyl or aryltin(IV) groups showed a better cytotoxic effect [39,68,96,131]. However, mono-substituted alkyl or aryltin complexes may have good activity, especially for butyl and phenyl derivatives [39] possibly because the complexes have exceptional cytotoxic capabilities. Table **3** shows the cytotoxicity of the organotin(IV) dithiocarbamate complexes against various human tumor cell lines (IC_{50} values). The compounds are considered to be highly toxic if their IC_{50} values are lower than 5.0 μg cm^{-3} (< 8.70 μM) [45,141] (Table **4**).

Table 3. In vitro cytotoxicity of the complexes against various human tumor cell lines (IC_{50}).

Compounds	IC_{50} values (μM)	Tumor Cell Lines	References
Dibutyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	0.8	Jurkat E6.1	[45]
Diphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	1.3		
Triphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	0.4		
Doxorubicin hydrochloride (control)	0.1		
Dibutyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	5.3	K-562	
Diphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	9.2		
Triphenyltin(IV) *N*-butyl-*N*-phenyldithiocarbamate	1.9		
Doxorubicin hydrochloride (control)	11.0		
Triphenyltin(IV) benzylisopropyldithiocarbamate	0.18	Jurkat E6.1	[26]
Triphenyltin(IV) methylisopropyldithiocarbamate	0.03		
Triphenyltin(IV) ethylisopropyldithiocarbamate	0.42		
Etoposide (control)	0.12		
$MeSnClL_2$	>4000	HeLa	[39]
$BuSnClL_2$	8.12		
$PhSnClL_2$	4.37		
Me_2SnL_2	12.30		
Bu_2SnL_2	11.75		
Ph_2SnL_2	0.01		
5-Fluorouracil (control)	40		
Dimethyltin(IV)benzyldithiocarbamate	40	Hela	[44]
Dibutyltin(IV)benzyldithiocarbamate	0.019		
Diphenyltin(IV)benzyldithiocarbamate	330		
5-Fluorouracil (control)	40		

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 May 2023 doi:10.20944/preprints202305.1910.v1

Dimethyltin(IV)benzyldithiocarbamate	185	MCF-7	
Dibutyltin(IV)benzyldithiocarbamate	57.3		
Diphenyltin(IV)benzyldithiocarbamate	20		
5-Fluorouracil (control)	56.2		
Diphenyltin(IV) diallyldithiocarbamate	2.36	HT-29	[35]
Triphenyltin(IV) diallyldithiocarbamate	0.39		

Table 4. Categories of toxicity levels of chemical compounds [141].

Categories	IC_{50} value (μg cm^{-3})
Very toxic	< 5.0
Moderately toxic	5.0 ≤ 10.0
Less toxic	10.0 – 25.0
Non-toxic	> 25.0

The lipophilicity of metal complexes is often affected by the nature of the alkyl or aryl group on the metal core of tin. For instance, the phenyl group in an organotin molecule can facilitate π-π interaction with biomolecules [42], which also contribute to enhanced lipophilicity [39]. Previous research has shown that compounds containing phenyl groups have the highest cytotoxicity activity compared to the other series of complexes being studied with the lowest IC_{50} value of 0.01 μM [28,39,44,98].

Additionally, the cytotoxicity of the organotin(IV) complex can be influenced by the ligand dithiocarbamate. The ligand system has been reported to play a significant role in the lipophilicity and stability of metal complexes [142]. The presence of sulfur donor atoms in the ligand dithiocarbamate aids in the transport of metal complexes. The chelation effect due to the polarity of the tin metal enhances biological activities [39] by increasing lipophilicity and facilitating the transportation of molecules to the targeted sites [44,45,48]. Therefore, the interaction of organotin(IV) compounds with cellular and cytoplasmic membranes can occur [143].

Previous studies found that the activity of organotin(IV) antitumor compounds was influenced by several factors: the stability of ligand-Sn bonds (such as Sn-N, Sn-S, and Sn-O), their slow hydrolytic decomposition [144], the structure of the molecule, and the coordination number of the tin(IV) atoms [145]. Metal complexes formed by bidentate ligands such as dithiocarbamate form quite stable molecules because of the "chelate effect" and the fact that the decomposition and loss of ligand dithiocarbamate are impossible to occur. In addition, the presence of a chelating dithiocarbamate should make the coordination of additional S-donor ligands (e.g., methionine and cysteine residues) *trans* to the -NCSS moiety less favorable because of the strong *trans*-influencing effect of the dithiocarbamate sulfur atoms. This may prevent further interactions of the metal center with other thiol-containing biomolecules that likely to cause severe side effects such as nephrotoxicity [146,147]. A study by Kadu and colleagues found that sulfur-containing compounds had better therapeutic indices in acidic environments, in which slightly acidic conditions were typically seen in solid tumors induced by the anaerobic fermentation of glucose-secreting lactic acid in the tumor tissue [42].

Organotin-induced apoptosis may be the primary mechanism of cell death for organotin(IV) complexes [8,28,32,35,148]. Jakšić (2012) [149] proposed that organotins might be responsible for inducing apoptosis by causing changes to the cytoskeleton and disruption of mitochondrial functions. The apoptotic pathway is initiated by the interaction of organotins with cellular components, which can lead to perturbation of intracellular Ca^{2+} homeostasis, and increased [Ca^{2+}] uptake that leads to harmful effects for the mitochondrion itself, such as loss of ΔΨm, increased ROS production, followed by MPT and membrane depolarization. The final ΔΨm degradation by MPT

 doi:10.20944/preprints202305.1910.v1

promotes the release of cytochrome c from mitochondria into the cytosol, formation of the apoptosome, and subsequent activation of initiator caspase-9 and executioner caspase-3, which executes the final steps of apoptosis.

The interaction of organotin compounds with biomolecular proteins is influenced by their coordination geometry, biological properties, and presence of the functional group. It has been reported that compounds with a lower coordination number of tin atoms (i.e., four) are more exposed to interaction with the donor atoms of the biomolecule of the target cell. Therefore, this complex has higher anticancer activity [136]. Besides that, organotin(IV) compounds exhibit electrophile properties that enhance the interaction with electron-donating groups of biomolecules [53], a trait similar to the aquated form of cisplatin, a potent electrophile that reacts with a variety of nucleophiles, including nucleic acids and sulfhydryl groups of proteins [150]. The interaction of this compound with phosphorus-containing biomolecules such as phospholipids, ATP, and nucleic acids inhibits the synthesis of phospholipids and intracellular transport of these biomolecules, hence inducing the antiproliferative activity of the organotin(IV) derivative complex [53].

Organotin(IV) compounds have been found to cause DNA damage by binding to the phosphate backbone of DNA, leading to DNA contraction and a change in DNA conformation [151,152]. The interaction of the organotin complex with DNA is different from the interaction of cisplatin with DNA, which can bind to DNA via cross-linking [5]. Studies have shown that the planar complex can easily intercalate into DNA base pairs in the cell lines [153]. Therefore, this complex may possess high cytotoxicity activity. This argument is supported when phenyl-substituted compounds show higher cytotoxicity than butyl- and methyl-substituted compounds 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 [39]. Besides that, organotin can inhibit cell division and proliferation by interacting with nitrogenous bases of nucleotides of nucleic acids, interfering with the replication and transcription of DNA molecules, or affecting the multienzyme complexes responsible for the replication and transcription of DNA [154]. Hence, these complexes may be targeting DNA according to findings in the literature [8,32,39,66,68].

Conclusions

In this review, we have described the synthesis of organotin(IV) dithiocarbamate complexes by using the in-situ method in different molar ratios. Besides that, we have highlighted the different coordination modes of dithiocarbamates to the tin(IV) atom; monodentate, bidentate, and anisobidentate. Depending on the coordination modes, the structural geometry of organotin(IV) dithiocarbamate may exist in the tetrahedral, trigonal-bipyramidal, octahedral, and pentagonal bipyramidal structures. The organotin(IV) constituents play a critical role in inducing cytotoxicity, with the ligands being involved in transporting and addressing the molecule to the target while avoiding unwanted changes within the biomolecules [155]. The presence of a functional group R on the Sn(IV) atom is believed to affect the anticancer activities of these complexes [35]. The stabilization of a drug by coordination to the metal centers known as metal-drug synergy also enhances the activity of the organic drug [146,156]. Therefore, the organotin(IV) dithiocarbamate complex may be a potential anticancer agent, but more research is needed to understand the mechanism of cell death caused by this complex.

Funding: We would like to thank the Malaysian Ministry of Higher Education for the financial support (Grant: FRGS/1/2021/STG04/UKM/02/5) and the Faculty of Health Sciences, Universiti Kebangsaan Malaysia for supporting this study.

Acknowledgments: We would like to acknowledge the Faculty of Health Sciences, Universiti Kebangsaan Malaysia for the facilities used to carry out this studies.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rabiee, N.; Safarkhani, M.; Amini, M.M. Investigating the Structural Chemistry of Organotin(IV) Compounds: Recent Advances. *Reviews in Inorganic Chemistry* **2019**, *39*, doi:10.1515/revic-2018-0014.
2. Ahmed, A.; El-Hiti, G.A.; Hadi, A.G.; Ahmed, D.S.; Baashen, M.A.; Hashim, H.; Yousif, E. Photostabilization of Poly(Vinyl Chloride) Films Blended with Organotin Complexes of Mefenamic Acid for Outdoor Applications. *Applied Sciences (Switzerland)* **2021**, *11*, doi:10.3390/app11062853.
3. Graf, G.G. Tin, Tin Alloys, and Tin Compounds. In *Ullmann's Encyclopedia of Industrial Chemistry*; 2000.
4. M. Graisa, A.; A. Husain, A.; H. Al-Mashhadani, M.; S. Ahmed, D.; Adil, H.; Yousif, E. The Organotin Applications in Biological, Industrial and Agricultural Sectors: A Systematic Review. *Jurnal Serambi Engineering* **2021**, *7*, doi:10.32672/jse.v7i1.3825.
5. Adeyemi, J.O.; Onwudiwe, D.C. Organotin(IV) Dithiocarbamate Complexes: Chemistry and Biological Activity. *Molecules* 2018, *23*.
6. Gasser, G.; Metzler-Nolte, N. The Potential of Organometallic Complexes in Medicinal Chemistry. *Curr Opin Chem Biol* 2012, *16*.
7. Ross, A. INDUSTRIAL APPLICATIONS OF ORGANOTIN COMPOUNDS. *Ann N Y Acad Sci* **1965**, *125*, doi:10.1111/j.1749-6632.1965.tb45382.x.
8. Syed Annuar, S.N.; Kamaludin, N.F.; Awang, N.; Chan, K.M. Cellular Basis of Organotin(IV) Derivatives as Anticancer Metallodrugs: A Review. *Front Chem* 2021, *9*.
9. Yousif, E. A Review of Organotin Compounds: Chemistry and Applications. *Archives of Organic and Inorganic Chemical Sciences* **2018**, *3*, doi:10.32474/aoics.2018.03.000161.
10. Awang, N.; Jumat, H.; Ishak, S.A.; Kamaludin, N.F. Evaluation of the Ex Vivo Antimalarial Activity of Organotin (IV) Ethylphenyldithiocarbamate on Erythrocytes Infected With Plasmodium Berghei Nk 65. *Pakistan Journal of Biological Sciences* **2014**, *17*, 836–842, doi:10.3923/pjbs.2014.836.842.
11. Awang, N.; Mokhtar, N.; Zin, N.M.; Kamaludin, N.F. Antibacterial Activity of Organotin(IV) Methyl and Ethyl Cylohexyldithiocarbamate Compounds. *Available online www.jocpr.com Journal of Chemical and Pharmaceutical Research* **2015**, *7*, 379–383.
12. Javed, F.; Sirajuddin, M.; Ali, S.; Khalid, N.; Tahir, M.N.; Shah, N.A.; Rasheed, Z.; Khan, M.R. Organotin(IV) Derivatives of o-Isobutyl Carbonodithioate: Synthesis, Spectroscopic Characterization, X-Ray Structure, HOMO/LUMO and in Vitro Biological Activities. *Polyhedron* **2016**, *104*, doi:10.1016/j.poly.2015.11.041.
13. Sadiq-ur-Rehman; Ali, S.; Badshah, A.; Mazhar, M.; Song, X.; Eng, G.; Khan, K.M. Synthesis, Spectroscopic Characterization: (IR, Multinuclear NMR, 119mSn Mössbauer and Mass Spectrometry), and Biological Activity (Antibacterial, Antifungal, and Cytotoxicity) of Di- and Triorganotin(IV) Complexes of (E)-3-(4-Chlorophenyl)-2-Phenylpropenoic Acid. *Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry* **2004**, *34*, doi:10.1081/SIM-200026257.
14. Saeed, A.; Channar, P.A.; Larik, F.A.; Jabeen, F.; Muqadar, U.; Saeed, S.; Flörke, U.; Ismail, H.; Dilshad, E.; Mirza, B. Design, Synthesis, Molecular Docking Studies of Organotin-Drug Derivatives as Multi-Target Agents against Antibacterial, Antifungal, α-Amylase, α-Glucosidase and Butyrylcholinesterase. *Inorganica Chim Acta* **2017**, *464*, doi:10.1016/j.ica.2017.05.036.
15. Niu, L.; Li, Y.; Li, Q. Medicinal Properties of Organotin Compounds and Their Limitations Caused by Toxicity. *Inorganica Chim Acta* 2014, *423*.
16. Sirajuddin, M.; Ali, S.; McKee, V.; Sohail, M.; Pasha, H. Potentially Bioactive Organotin(IV) Compounds: Synthesis, Characterization, in Vitro Bioactivities and Interaction with SS-DNA. *Eur J Med Chem* **2014**, *84*, doi:10.1016/j.ejmech.2014.07.028.
17. Hadi, A.G.; Jawad, K.; Ahmed, D.S.; Yousif, E. Synthesis and Biological Activities of Organotin (IV) Carboxylates: A Review. *Systematic Reviews in Pharmacy* **2019**, *10*, doi:10.5530/srp.2019.1.5.
18. Song, X.; Zapata, A.; Eng, G. Organotins and Quantitative-Structure Activity/Property Relationships. *J Organomet Chem* 2006, *691*.
19. Hadjikakou, S.K.; Abdellah, M.A.; Hadjiliadis, N.; Kubicki, M.; Bakas, T.; Kourkoumelis, N.; Simos, Y. v.; Karkabounas, S.; Barsan, M.M.; Butler, I.S. Synthesis, Characterization, and Biological Studies of Organotin(IV) Derivatives with o- or p-Hydroxybenzoic Acids. *Bioinorg Chem Appl* **2009**, *2009*, doi:10.1155/2009/542979.
20. Sunday, A.O.; Alafara, B.A.; Oladele, O.G. Toxicity and Speciation Analysis of Organotin Compounds. *Chemical Speciation and Bioavailability* **2012**, *24*, doi:10.3184/095422912X13491962881734.
21. van der Kerk, G.J.M.; Luijten, J.G.A. Investigations on Organo-Tin Compounds. IV. The Preparation of a Number of Trialkyl- and Triaryltin Compounds. *Journal of Applied Chemistry* **1956**, *6*, 49–55, doi:https://doi.org/10.1002/jctb.5010060201.
22. James, B.D.; Gioskos, S.; Chandra, S.; Magee, R.J.; Cashion, J.D. Some Triphenyltin(IV) Complexes Containing Potentially Bidentate, Biologically Active Anionic Groups. *J Organomet Chem* **1992**, *436*, doi:10.1016/0022-328X(92)85043-V.
23. Pellerito, C.; Nagy, L.; Pellerito, L.; Szorcsik, A. Biological Activity Studies on Organotin(IV)N+ Complexes and Parent Compounds. *J Organomet Chem* 2006, *691*.

24. Mushak, P.; Krigman, M.R.; Mailman, R.B. Comparative Organotin Toxicity in the Developing Rat: Somatic and Morphological Changes and Relationship to Accumulation of Total Tin. *Neurobehav Toxicol Teratol* **1982**, *4*.
25. Doctor, S. v.; Fox, D.A. Effects of Organotin Compounds on Maximal Electroshock Seizure (Mes) Responsiveness in Mice. i.Tri(n-Alkyl)Tin Compounds. *J Toxicol Environ Health* **1982**, *10*, doi:10.1080/15287398209530229.
26. Awang, N.; Yousof, N.S.A.M.; Rajab, N.F.; Kamaludin, N.F. In Vitro Cytotoxic Activity of New Triphenyltin (IV) Alkyl-Isopropyldi-Thiocarbamate Compounds on Human Acute T-Lymphoblastic Cell Line. *J Appl Pharm Sci* **2015**, *5*, 7–11, doi:10.7324/JAPS.2015.54.S2.
27. Gielen, M. Organotin Compounds and Their Therapeutic Potential: A Report from the Organometallic Chemistry Department of the Free University of Brussels. In Proceedings of the Applied Organometallic Chemistry; 2002; Vol. 16.
28. Hamid, A.; Azmi, M.A.; Rajab, N.F.; Awang, N.; Jufri, N.F. Cytotoxic Effects of Organotin(IV) Dithiocarbamate Compounds with Different Functional Groups on Leukemic Cell Line, K-562. *Sains Malays* **2020**, *49*, doi:10.17576/jsm-2020-4906-20.
29. Varela-Ramirez, A.; Costanzo, M.; Carrasco, Y.P.; Pannell, K.H.; Aguilera, R.J. Cytotoxic Effects of Two Organotin Compounds and Their Mode of Inflicting Cell Death on Four Mammalian Cancer Cells. *Cell Biol Toxicol* **2011**, *27*, doi:10.1007/s10565-010-9178-y.
30. Awang, N.; Kamaludin, N.F.; Hamid, A.; Mokhtar, N.W.N.; Rajab, Z.F. Cytotoxicity of Triphenyltin(IV) Methyl- and Ethylisopropyldithiocarbamate Compounds in Chronic Myelogenus Leukemia Cell Line (K-562). *Pakistan Journal of Biological Sciences* **2012**, *15*, doi:10.3923/pjbs.2012.833.838.
31. Fuertes, M.; Castilla, J.; Alonso, C.; Pérez, J. Cisplatin Biochemical Mechanism of Action: From Cytotoxicity to Induction of Cell Death Through Interconnections Between Apoptotic and Necrotic Pathways. *Curr Med Chem* **2012**, *10*, doi:10.2174/0929867033368484.
32. Attanzio, A.; D'Agostino, S.; Busà, R.; Frazzitta, A.; Rubino, S.; Girasolo, M.A.; Sabatino, P.; Tesoriere, L. Cytotoxic Activity of Organotin(IV) Derivatives with Triazolopyrimidine Containing Exocyclic Oxygen Atoms. *Molecules* **2020**, *25*, doi:10.3390/molecules25040859.
33. Szorcsik, A.; Nagy, L.; Gajda-Schrantz, K.; Pellerito, L.; Nagy, E.; Edelmann, F.T. Structural Studies on Organotin(IV) Complexes Formed with Ligands Containing {S,N,O} Donor Atoms. *J Radioanal Nucl Chem* **2002**, *252*, doi:10.1023/A:1015802820423.
34. Carraher, C.E.; Roner, M.R. Organotin Polyethers as Biomaterials. *Materials* 2009, *2*.
35. Haezam, F.N.; Awang, N.; Kamaludin, N.F.; Mohamad, R. Synthesis and Cytotoxic Activity of Organotin(IV) Diallyldithiocarbamate Compounds as Anticancer Agent towards Colon Adenocarcinoma Cells (HT-29). *Saudi J Biol Sci* **2021**, *28*, doi:10.1016/j.sjbs.2021.02.060.
36. Khan, N.; Farina, Y.; Mun, L.K.; Rajab, N.F.; Awang, N. Syntheses, Characterization, X-Ray Diffraction Studies and in Vitro Antitumor Activities of Diorganotin(IV) Derivatives of Bis(p-Substituted-N-Methylbenzylaminedithiocarbamates). *Polyhedron* **2015**, *85*, doi:10.1016/j.poly.2014.08.063.
37. Awang, N.; Aziz, Z.A.; Kamaludin, N.F.; Chan, K.M. Cytotoxicity and Mode of Cell Death Induced by Triphenyltin (IV) Compounds in Vitro. *Online J Biol Sci* **2014**, *14*, doi:10.3844/ojbsci.2014.84.93.
38. Girasolo, M.A.; Tesoriere, L.; Casella, G.; Attanzio, A.; Capobianco, M.L.; Sabatino, P.; Barone, G.; Rubino, S.; Bonsignore, R. A Novel Compound of Triphenyltin(IV) with N-Tert-Butoxycarbonyl-L-Ornithine Causes Cancer Cell Death by Inducing a P53-Dependent Activation of the Mitochondrial Pathway of Apoptosis. *Inorganica Chim Acta* **2017**, *456*, doi:10.1016/j.ica.2016.11.012.
39. Adeyemi, J.O.; Onwudiwe, D.C. Antimicrobial and Cytotoxicity Studies of Some Organotin(Iv) n-Ethyl-n-Phenyl Dithiocarbamate Complexes. *Pol J Environ Stud* **2020**, *29*, doi:10.15244/pjoes/111231.
40. Baul, T.S.B. Antimicrobial Activity of Organotin(IV) Compounds: A Review. *Appl Organomet Chem* **2008**, *22*, doi:10.1002/aoc.1378.
41. Awang, N.; Zakri, N.H.; Zain, N.M. Antimicrobial Activity of Organotin(IV) Alkylisopropildithiocarbamate Compounds. *Available online www.jocpr.com Journal of Chemical and Pharmaceutical Research* **2016**, *8*.
42. Kadu, R.; Roy, H.; Singh, V.K. 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* **2015**, *29*, doi:10.1002/aoc.3362.
43. Awang, N.; Mohktar, S.M.; Zin, N.M.; Kamaludin, N.F. Evaluation of Antimicrobial Activities of Organotin (IV) Alkylphenyl Dithiocarbamate Compounds. *Asian Journal of Applied Sciences* **2015**, *8*, doi:10.3923/ajaps.2015.165.172.
44. Adeyemi, J.O.; Adeyemi, J.O.; Onwudiwe, D.C.; Onwudiwe, D.C.; Nundkumar, N.; Singh, M. Diorganotin(Iv) Benzyldithiocarbamate Complexes: Synthesis, Characterization, and Thermal and Cytotoxicity Study. *Open Chem* **2020**, *18*, doi:10.1515/chem-2020-0037.

45. Kamaludin, N.F.; Awang, N.; Baba, I.; Hamid, A.; Meng, C.K. Synthesis, Characterization and Crystal Structure of Organotin(IV) N-Butyl-N-Phenyldithiocarbamate Compounds and Their Cytotoxicity in Human Leukemia Cell Lines. *Pakistan Journal of Biological Sciences* **2013**, *16*, doi:10.3923/pjbs.2013.12.21.
46. Mamba, S.M.; Mishra, A.K.; Mamba, B.B.; Njobeh, P.B.; Dutton, M.F.; Fosso-Kankeu, E. Spectral, Thermal and in Vitro Antimicrobial Studies of Cyclohexylamine-N-Dithiocarbamate Transition Metal Complexes. *Spectrochim Acta A Mol Biomol Spectrosc* **2010**, *77*, doi:10.1016/j.saa.2010.06.002.
47. Menezes, D.C.; Vieira, F.T.; de Lima, G.M.; Porto, A.O.; Cortés, M.E.; Ardisson, J.D.; Albrecht-Schmitt, T.E. Tin(IV) Complexes of Pyrrolidinedithiocarbamate: Synthesis, Characterisation and Antifungal Activity. *Eur J Med Chem* **2005**, *40*, doi:10.1016/j.ejmech.2005.07.008.
48. Cvek, B.; Dvorak, Z. Targeting of Nuclear Factor-κB and Proteasome by Dithiocarbamate Complexes with Metals. *Curr Pharm Des* **2007**, *13*, doi:10.2174/138161207782110390.
49. Ajiboye, T.O.; Ajiboye, T.T.; Marzouki, R.; Onwudiwe, D.C. The Versatility in the Applications of Dithiocarbamates. *Int J Mol Sci* 2022, *23*.
50. Ali, M.; Yousif, E. Chemistry and Applications of Organotin(IV) Complexes: A Review. *Res J Pharm Biol Chem Sci* **2016**, *7*.
51. Iqbal, H.; Ali, S.; Shahzadi, S. Antituberculosis Study of Organotin(IV) Complexes: A Review. *Cogent Chem* **2015**, *1*, doi:10.1080/23312009.2015.1029039.
52. AYANDA, O.S.; FATOKI, O.S.; ADEKOLA, F.A.; XIMBA, B.J. Fate and Remediation of Organotin Compounds in Seawaters and Soils. *Chem Sci Trans* **2012**, *1*, doi:10.7598/cst2012.177.
53. Awang, N.; Kamaludin, N.F.; Ghazali, A.R. Cytotoxic Effect of Organotin(IV) Benzylisopropyldithiocarbamate Compounds on Chang Liver Cell and Hepatocarcinoma HepG2 Cell. *Pakistan Journal of Biological Sciences* **2011**, *14*, doi:10.3923/pjbs.2011.768.774.
54. Kamaludin, N.F.; Awang, N. Synthesis and Characterisation of Organotin(IV) Nethyl- N-Phenyldithiocarbamate Compounds and the Crystal Structures of Dibutyl- And Triphenyltin(IV) Nethyl-N-Phenyldithiocarbamate. *Res J Chem Environ* **2014**, *18*.
55. Sainorudin, M.H.; Sidek, N.M.; Ismail, N.; Rozaini, M.Z.H.; Harun, N.A.; Tuan Anuar, T.N.S.; Azmi, A.A.A.R.; Yusoff, F. Synthesis, Characterization and Biological Activity of Organotin(IV) Complexes Featuring Di-2-Ethylhexyldithiocarbamate and N-Methylbutyldithiocarbamate as Ligands. *GSTF Journal of Chemical Sciences (JChem)* **2015**, *2*, doi:10.7603/s40837-015-0002-3.
56. Sharma, R.; Kaushik, N.K. Thermal Studies on Some Organotin(IV) Complexes with Piperidine and 2-Aminopyridine Dithiocarbamates. *J Therm Anal Calorim* **2004**, *78*, 953–964, doi:10.1007/s10973-004-0461-0.
57. Awang, N.; Baba, I. Diorganotin(IV) Alkylcyclohexyldithiocarbamate Compounds: Synthesis, Characterization and Biological Activities. *Sains Malays* **2012**, *41*.
58. Fanjul-Bolado, P.; Fogel, R.; Limson, J.; Purcarea, C.; Vasilescu, A. Advances in the Detection of Dithiocarbamate Fungicides: Opportunities for Biosensors. *Biosensors (Basel)* **2021**, *11*, doi:10.3390/bios11010012.
59. Awang, N.; Baba, I.; Yamin, B.M.; Halim, A.A. Preparation, Characterization and Antimicrobial Assay of 1,10-Phenanthroline and 2,2′-Bipyridyl Adducts of Cadmium(II) N-Sec-Butyl-N- Propyldithiocarbamate: Crystal Structure of Cd[S2CN(i-C4H9)(C3H7)]2(2,2′-Bipyridyl). *World Appl Sci J* **2011**, *12*, 1568–1574.
60. Nabipour, H.; Ghammamy, S.; Ashuri, S.; Aghbolagh, Z.S. Synthesis of a New Dithiocarbamate Compound and Study of Its Biological Properties. *Org. Chem. J* **2010**, *2*.
61. Jung, O.-S.; Sohn, Y.-S. Coordination Chemistry of Organotin(IV) Dithiocarbamate Complexes. *Bull Korean Chem Soc* **1988**, *9*.
62. Xu, L.Z.; Zhao, P.S.; Zhang, S.S. Crystal Structure and Characterization of Pd(II) Bis(Diisopropyldithiocarbamate) Complex. *Chin J Chem* **2001**, *19*, doi:10.1002/cjoc.20010190422.
63. Domazetis, G.; Magee, R.J.; James, B.D. Synthesis and Structure of Some Triphenyltin(IV) Dithiocarbamate Compounds. *J Organomet Chem* **1977**, *141*, doi:10.1016/S0022-328X(00)90667-3.
64. Odularu, A.T.; Ajibade, P.A. Dithiocarbamates: Challenges, Control, and Approaches to Excellent Yield, Characterization, and Their Biological Applications. *Bioinorg Chem Appl* 2019, *2019*.
65. Onwudiwe, D.C.; Ajibade, P.A. Synthesis and Characterization of Metal Complexes of N-Alkyl-N-Phenyl Dithiocarbamates. *Polyhedron* **2010**, *29*, doi:10.1016/j.poly.2010.01.011.
66. Awang, N.; Baba, I.; Yamin, B.M.; Othman, M.S.; Kamaludin, N.F. Synthesis, Characterization and Biological Activities of Organotin (IV) Methylcyclohexyldithiocarbamate Compounds. *Am J Appl Sci* **2011**, *8*, doi:10.3844/ajassp.2011.310.317.
67. Perry, D.; Geanangle, R.A. The Preparation of Tin(II) Dithiocarbamates from Ammonium Dithiocarbamate Salts. *Inorganica Chim Acta* **1975**, *13*, doi:10.1016/S0020-1693(00)90196-8.
68. Adeyemi, J.O.; Onwudiwe, D.C.; Ekennia, A.C.; Okafor, S.N.; Hosten, E.C. Organotin(IV)N-Butyl-N-Phenyldithiocarbamate Complexes: Synthesis, Characterization, Biological Evaluation and Molecular Docking Studies. *J Mol Struct* **2019**, *1192*, doi:10.1016/j.molstruc.2019.04.097.

69. Adeyemi, J.O.; Onwudiwe, D.C.; Hosten, E.C. Organotin(IV) Complexes Derived from N-Ethyl-N-Phenyldithiocarbamate: Synthesis, Characterization and Thermal Studies. *Journal of Saudi Chemical Society* **2018**, *22*, doi:10.1016/j.jscs.2017.08.004.
70. Adeyemi, J.O.; Onwudiwe, D.C.; Hosten, E.C. Synthesis, Characterization and the Use of Organotin(IV) Dithiocarbamate Complexes as Precursor to Tin Sulfide Nanoparticles by Heat up Approach. *J Mol Struct* **2019**, *1195*, doi:10.1016/j.molstruc.2019.05.115.
71. Adli, H.K.; Sidek, N.M.; Ismail, N.; Khairul, W.M. Several Organotin (IV) Complexes Featuring 1-Methylpiperazinedithiocarbamate and N-Methylcyclohexyldithiocarbamate as Ligands and Their Anti-Microbial Activity Studies. *Chiang Mai Journal of Science* **2013**, *40*.
72. Awang, N.; Baba, I.; Yamin, B.; Othman, M.; Halim, A.; Muda, J.; Aziz, A.; Lumpur, K.; Malaysia Synthesis, Characterization and Crystal Structure of Triphenyltin(IV) N-Alkyl-N-Cyclohexyldithiocarbamate Compounds. *World Appl Sci J* **2011**, *12*, 630–635.
73. Awang, N.; Kamaludin, N.F.; Baba, I.; Chan, K.M.; Rajaajab, N.F.; Hamid, A. Synthesis, Characterization and Antitumor Activity of New Organotin(IV) Methoxyethyldithiocarbamate Complexes. *Oriental Journal of Chemistry* **2016**, *32*, doi:10.13005/ojc/320110.
74. Mohamad, R.; Awang, N.; Farahana Kamaludin, N. Synthesis and Characterisation of New Organotin (IV)(2-Methoxyethyl)-Methyldithiocarbamate Complexes. *Res J Pharm Biol Chem Sci* **2016**, *7*.
75. Muthalib, A.F.A.; Baba, I. New Mono-Organotin (IV) Dithiocarbamate Complexes. In Proceedings of the AIP Conference Proceedings; 2014; Vol. 1614.
76. Baba, I.; Raya, I. Kompleks Praseodimium Ditiokarbamat 1,10 Fenantrolin. *Sains Malays* **2010**, *39*.
77. Fadeeva, V.P.; Tikhova, V.D.; Nikulicheva, O.N. Elemental Analysis of Organic Compounds with the Use of Automated CHNS Analyzers. *Journal of Analytical Chemistry* **2008**, *63*, doi:10.1134/S1061934808110142.
78. Edington, S.C.; Liu, S.; Baiz, C.R. Infrared Spectroscopy Probes Ion Binding Geometries. In *Methods in Enzymology*; 2021; Vol. 651.
79. Kumar, A.; Khandelwal, M.; Gupta, S.K.; Kumar, V.; Rani, R. Fourier Transform Infrared Spectroscopy: Data Interpretation and Applications in Structure Elucidation and Analysis of Small Molecules and Nanostructures. In *Data Processing Handbook for Complex Biological Data Sources*; 2019.
80. Sonia, T.A.; Sharma, C.P. Experimental Techniques Involved in the Development of Oral Insulin Carriers. In *Oral Delivery of Insulin*; 2014.
81. Zia-ur-Rehman; Shahzadi, S.; Ali, S.; Badshah, A.; Jin, G.X. Crystal Structure of 1,1-Dibutyl-1,1-Bis[(4-Methyl-1-Piperidinyl) Dithiocarbamato] Tin(IV). *Journal of the Iranian Chemical Society* **2006**, *3*, doi:10.1007/BF03245943.
82. Win, Y.F.; Teoh, S.G.; Tengku-Muhammad, T.S.; Ha, S.T.; Sivasothy, Y. Synthesis and Structural Characterization of Organotin (IV) Complexes Derived of 4- (Diethylamino) Benzoic Acid: Cytotoxic Assay on Human Liver Carcinoma Cells (HepG2). *Aust J Basic Appl Sci* **2010**, *4*.
83. Chaber, R.; Łach, K.; Szmuc, K.; Michalak, E.; Raciborska, A.; Mazur, D.; Machaczka, M.; Cebulski, J. Application of Infrared Spectroscopy in the Identification of Ewing Sarcoma: A Preliminary Report. *Infrared Phys Technol* **2017**, *83*, doi:10.1016/j.infrared.2017.05.006.
84. Dominguez, G.; McLeod, A.S.; Gainsforth, Z.; Kelly, P.; Bechtel, H.A.; Keilmann, F.; Westphal, A.; Thiemens, M.; Basov, D.N. Nanoscale Infrared Spectroscopy as a Non-Destructive Probe of Extraterrestrial Samples. *Nat Commun* **2014**, *5*, doi:10.1038/ncomms6445.
85. Kartina, D.; Wahab, A.W.; Ahmad, A.; Irfandi, R.; Raya, I. In Vitro Antibacterial and Anticancer Activity of Zn(II)Valinedithiocarbamate Complexes. In Proceedings of the Journal of Physics: Conference Series; 2019; Vol. 1341.
86. Onwudiwe, D.C.; Hrubaru, M.; Ebenso, E.E. Synthesis, Structural and Optical Properties of TOPO and HDA Capped Cadmium Sulphide Nanocrystals, and the Effect of Capping Ligand Concentration. *J Nanomater* **2015**, *2015*, doi:10.1155/2015/143632.
87. Yin, H.D.; Xue, S.C. Synthesis and Characterization of Organotin Complexes with Dithiocarbamates and Crystal Structures of (4-NCC6H4CH2) 2Sn(S2CNEt2)2 and (2-ClC 6H4CH2)2 Sn(Cl)S 2CNBz2. *Appl Organomet Chem* **2006**, *20*, doi:10.1002/aoc.1048.
88. Odola, A.J.; Woods, J.A.O. New Nickel(II) Mixed Ligand Complexes of Dithiocarbamates with Schiff Base. *J Chem Pharm Res* **2011**, *3*.
89. Alverdi, V.; Giovagnini, L.; Marzano, C.; Seraglia, R.; Bettio, F.; Sitran, S.; Graziani, R.; Fregona, D. Characterization Studies and Cytotoxicity Assays of Pt(II) and Pd(II) Dithiocarbamate Complexes by Means of FT-IR, NMR Spectroscopy and Mass Spectrometry. *J Inorg Biochem* **2004**, *98*, doi:10.1016/j.jinorgbio.2004.03.011.
90. Nomura, R.; Takabe, A.; Matsuda, H. Facile Synthesis of Antimony Dithiocarbamate Complexes. *Polyhedron* **1987**, *6*, doi:10.1016/S0277-5387(00)81000-1.
91. Brown, D.A.; Glass, W.K.; Burke, M.A. The General Use of i.r. Spectral Criteria in Discussions of the Bonding and Structure of Metal Dithiocarbamates. *Spectrochim Acta A* **1976**, *32*, doi:10.1016/0584-8539(76)80060-8.

92. Bonati, F.; Ugo, R. Organotin(IV) N,N-Disubstituted Dithiocarbamates. *J Organomet Chem* **1967**, *10*, doi:10.1016/S0022-328X(00)93085-7.
93. Honda, M.; Komura, M.; Kawasaki, Y.; Tanaka, T.; Okawara, R. *INFRA-RED AND PMR SPECTRA OF SOME ORGANO-TIN(IV) N,N-DIMETHYLDITHIOCARBAMATES*; 1968; Vol. 30;.
94. Muthalib, A.F.A.; Baba, I.; Farina, Y.; Samsudin, M.W. SYNTHESIS AND CHARACTERIZATION OF DIPHENYLTIN(IV) DITHIOCARBAMATE COMPOUNDS (Sintesis Dan Pencirian Sebatian Difenilstanum(IV) Ditiokarbamat). *The Malaysian Journal of Analytical Sciences* **2011**, *15*.
95. Cotton, F.A.; McCleverty, J.A. Dimethyl- and Diethyldithiocarbamate Complexes of Some Metal Carbonyl Compounds. *Inorg Chem* **1964**, *3*, doi:10.1021/ic50020a012.
96. Adeyemi, J.O.; Onwudiwe, D.C.; Singh, M. Synthesis, Characterization, and Cytotoxicity Study of Organotin(IV) Complexes Involving Different Dithiocarbamate Groups. *J Mol Struct* **2019**, *1179*, 366–375, doi:10.1016/j.molstruc.2018.11.022.
97. Khan, S.; Nami, S.A.A.; Siddiqi, K.S. Mononuclear Indolyldithiocarbamates of SnCl4 and R2SnCl2: Spectroscopic, Thermal Characterizations and Cytotoxicity Assays in Vitro. *J Organomet Chem* **2008**, *693*, doi:10.1016/j.jorganchem.2007.12.026.
98. Awang, N.; Baba, I.; Mohd Yousof, N.S.A.; Kamaludin, N.F. Synthesis and Characterization of Organotin(IV) N-Benzyl-N-Isopropyldithiocarbamate Compounds: Cytotoxic Assay on Human Hepatocarcinoma Cells (HepG2). *Am J Appl Sci* **2010**, *7*, doi:10.3844/ajassp.2010.1047.1052.
99. Sainorudin, M.H.M.H.S.N.M.S.N.I.M.Z.H.R.N.A.H.T.N.S.T.A.A.A.A.R.A. ,Farhanini Y. Synthesis, Characterization and Biological Activity of Organotin(IV) Complexes Featuring Di-2-Ethylhexyldithiocarbamate and N-Methylbutyldithiocarbamate as Ligands. **2015**, doi:10.7603/s40837-015-0002-3.
100. Adeyemi, J.O.; Saibu, G.M.; Olasunkanmi, L.O.; Fadaka, A.O.; Meyer, M.; Sibuyi, N.R.S.; Onwudiwe, D.C.; Oyedeji, A.O. Synthesis, Computational and Biological Studies of Alkyltin(IV) N-Methyl-N-Hydroxyethyl Dithiocarbamate Complexes. *Heliyon* **2021**, *7*, doi:10.1016/j.heliyon.2021.e07693.
101. Onwudiwe, D.C.; Ajibade, P.A. Synthesis, Characterization and Thermal Studies of Zn(Ii), Cd(II) and Hg(II) Complexes of N-Methyl-N-Phenyldithiocarbamate: The Single Crystal Structure of [(C 6H 5)(CH 3)NCS 2]4Hg 2. *Int J Mol Sci* **2011**, *12*, doi:10.3390/ijms12031964.
102. Riveros, P.C.; Perilla, I.C.; Poveda, A.; Keller, H.J.; Pritzkow, H. Tris(Dialkyldithiocarbamato)Diazenido(1-) and Hydrazido(2-) Molybdenum Complexes: Synthesis and Reactivity in Acid Medium. *Polyhedron* **2000**, *19*, doi:10.1016/S0277-5387(00)00496-4.
103. Arul Prakasam, B.; Ramalingam, K.; Bocelli, G.; Cantoni, A. NMR and Fluorescence Spectral Studies on Bisdithiocarbamates of Divalent Zn, Cd and Their Nitrogenous Adducts: Single Crystal X-Ray Structure of (1,10-Phenanthroline)Bis(4-Methylpiperazinecarbodithioato) Zinc(II). *Polyhedron* **2007**, *26*, doi:10.1016/j.poly.2007.06.008.
104. Yin, H.D.; Zhai, J.; Sun, Y.Y.; Wang, D.Q. Synthesis, Characterizations and Crystal Structures of New Antimony (III) Complexes with Dithiocarbamate Ligands. *Polyhedron* **2008**, *27*, doi:10.1016/j.poly.2007.10.019.
105. Prakasam, B.A.; Ramalingam, K.; Baskaran, R.; Bocelli, G.; Cantoni, A. Synthesis, NMR Spectral and Single Crystal X-Ray Structural Studies on Ni(II) Dithiocarbamates with NiS2PN, NiS2PC, NiS2P2 Chromophores: Crystal Structures of (4-Methylpiperazinecarbodithioato)(Thiocyanato-N)(Triphenylphosphine)Nickel(II) and Bis(Triphenylphosphine)(4-Methylpiperazinecarbodithioato)Nickel(II) Perchlorate Monohydrate. *Polyhedron* **2007**, *26*, doi:10.1016/j.poly.2006.10.006.
106. Ajibade, P.A.; Onwudiwe, D.C.; Moloto, M.J. Synthesis of Hexadecylamine Capped Nanoparticles Using Group 12 Complexes of N-Alkyl-N-Phenyl Dithiocarbamate as Single-Source Precursors. *Polyhedron* **2011**, *30*, doi:10.1016/j.poly.2010.10.023.
107. Ahmad, M.S.; Hussain, M.; Hanif, M.; Ali, S.; Qayyum, M.; Mirza, B. Di- and Triorganotin(IV) Esters of 3,4-Methylenedioxyphenylpropenoic Acid: Synthesis, Spectroscopic Characterization and Biological Screening for Antimicrobial, Cytotoxic and Antitumor Activities. *Chem Biol Drug Des* **2008**, *71*, doi:10.1111/j.1747-0285.2008.00668.x.
108. VAN GAAL, H.L.M.; DIESVELD, J.W.; PIJPERS, F.W.; VAN DER LINDEN, J.G.M. ChemInform Abstract: CARBON-13 NMR SPECTRA OF DITHIOCARBAMATES. CHEMICAL SHIFTS, CARBON-NITROGEN STRETCHING VIBRATION FREQUENCIES AND Π-BONDING IN THE NCS2 FRAGMENT. *Chemischer Informationsdienst* **1980**, *11*, doi:10.1002/chin.198008093.
109. Sovilj, S.P.; Vučković, G.; Babić, K.; Sabo, T.J.; Macura, S.; Juranić, N. Mixed-Ligand Complexes of Cobalt(III) with Dithiocarbamates and a Cyclic Tetradentate Secondary Amine. *J Coord Chem* **1997**, *41*, doi:10.1080/00958979708027954.
110. Macomber, R.S. Proton-Carbon Chemical Shift Correlations. *J Chem Educ* **1991**, *68*, doi:10.1021/ed068p284.

111. Sirajuddin, M.; Ali, S.; McKee, V.; Zaib, S.; Iqbal, J. Organotin(Iv) Carboxylate Derivatives as a New Addition to Anticancer and Antileishmanial Agents: Design, Physicochemical Characterization and Interaction with Salmon Sperm DNA. *RSC Adv* **2014**, *4*, doi:10.1039/c4ra10487k.
112. Otera, J. 119Sn Chemical Shifts in Five- and Six-Coordinate Organotin Chelates. *J Organomet Chem* **1981**, *221*, doi:10.1016/S0022-328X(00)81028-1.
113. Jung, O.S.; Hwa Jeong, J.; Soo Sohn, Y. Preparation, Properties and Structures of Estertin(IV) Sulphides. *Polyhedron* **1989**, *8*, doi:10.1016/S0277-5387(00)81156-0.
114. Ahmad, F.; Ali, S.; Parvez, M.; Munir, A.; Mazhar, M.; Khan, K.M.; Ali Shah, T. Synthesis, Characterization, and Biological Studies of Tri- and Diorganotin(Iv) Complexes with 2′, 4′-Difluoro-4-Hydroxy-[1, 1′]-Biphenyle-3-Carbolic Acid: Crystal Structure of [(CH3)3Sn(C13H7O3F2)]. *Heteroatom Chemistry* **2002**, *13*, doi:10.1002/hc.10057.
115. Sedaghat, T.; Shokohi-Pour, Z. Synthesis and Spectroscopic Studies of New Organotin(IV) Complexes with Tridentate N- and O-Donor Schiff Bases. *J Coord Chem* **2009**, *62*, doi:10.1080/00958970903180103.
116. Sirajuddin, M.; Ali, S.; Tahir, M.N. Pharmacological Investigation of Mono-, Di- and Tri-Organotin(IV) Derivatives of Carbodithioates: Design, Spectroscopic Characterization, Interaction with SS-DNA and POM Analyses. *Inorganica Chim Acta* **2016**, *439*, doi:10.1016/j.ica.2015.10.017.
117. Shahzadi, S.; Ali, S. Iranian Chemical Society Structural Chemistry of Organotin(IV) Complexes. *Journal of the* **2008**, *5*.
118. Tiekink, E.R.T. Structural Chemistry of Organotin Carboxylates: A Review of the Crystallographic Literature. *Appl Organomet Chem* 1991, *5*.
119. Chans, G.M.; Nieto-Camacho, A.; Ramirez-Apan, T.; Hernandez-Ortega, S.; Alvarez-Toledano, C.; Gomez, E. Synthetic, Spectroscopic, Crystallographic, and Biological Studies of Seven-Coordinated Diorganotin(IV) Complexes Derived from Schiff Bases and Pyridinic Carboxylic Acids. *Aust J Chem* **2016**, *69*, doi:10.1071/CH15344.
120. Deschamps, J.R. X-Ray Crystallography of Chemical Compounds. *Life Sci* 2010, *86*.
121. Francisco, M.E.Y.; Burgess, J.P.; George, C.; Bailey, G.S.; Gilliam, A.F.; Seltzman, H.H.; Thomas, B.F. Structure Elucidation of a Novel Ring-Constrained Biaryl Pyrazole CB 1 Cannabinoid Receptor Antagonist. *Magnetic Resonance in Chemistry* **2003**, *41*, doi:10.1002/mrc.1174.
122. Kim, K.; Ibers, J.A.; Jung, O.S.; Sohn, Y.S. Structure of Di(Tert-Butyl)Bis(N,N-Dimethyldithiocarbamato)Tin(IV). *Acta Crystallogr C* **1987**, *43*, doi:10.1107/s0108270187087924.
123. Abbas, S.M.; Ali, S.; Hussain, S.T.; Shahzadi, S. Review: Structural Diversity in Organotin(IV) Dithiocarboxylates and Carboxylates. *J Coord Chem* 2013, *66*.
124. Khan, N.; Farina, Y.; Mun, L.K.; Rajab, N.F.; Awang, N. Syntheses, Spectral Characterization, X-Ray Studies and in Vitro Cytotoxic Activities of Triorganotin(IV) Derivatives of p-Substituted N-Methylbenzylaminedithiocarbamates. *J Mol Struct* **2014**, *1076*, doi:10.1016/j.molstruc.2014.08.015.
125. Sieber, K.; Kutschabsky, L.; Kulpe, S. The Molecular and Crystal Structure of Bis-Dimethyl Pentamethine Cyanine Perchlorate, C9H17N2Cl04. *Kristall und Technik* **1974**, *9*, doi:10.1002/crat.19740091006.
126. Fuentes-Martínez, J.P.; Toledo-Martínez, I.; Román-Bravo, P.; García, P.G. y.; Godoy-Alcántar, C.; López-Cardoso, M.; Morales-Rojas, H. Diorganotin(IV) Dithiocarbamate Complexes as Chromogenic Sensors of Anion Binding. *Polyhedron* **2009**, *28*, doi:10.1016/j.poly.2009.09.010.
127. Shahzadi, S.; Ali, S.; Fettouhi, M. Synthesis, Spectroscopy, in Vitro Biological Activity and X-Ray Structure of (4-Methylpiperidine-Dithiocarbamato-S,S′)Triphenyltin(IV). *J Chem Crystallogr* **2008**, *38*, doi:10.1007/s10870-007-9295-5.
128. Rehman, Z.U.; Shahzadi, S.; Ali, S.; Jin, G.X. Preparation, Spectroscopy, Antimicrobial Assay, and X-Ray Structure of Dimethyl Bis-(4-Methylpiperidine Dithiocarbamato-S,S′)-Tin(IV). *Turk J Chem* **2007**, *31*.
129. Yadav, R.; Trivedi, M.; Chauhan, R.; Prasad, R.; Kociok-Köhn, G.; Kumar, A. Supramolecular Architecture of Organotin(IV) 4-Hydroxypiperidine Dithiocarbamates: Crystallographic, Computational and Hirshfeld Surface Analyses. *Inorganica Chim Acta* **2016**, *450*, 57–68, doi:https://doi.org/10.1016/j.ica.2016.05.028.
130. Bondi, A. Van Der Waals Volumes and Radii. *Journal of Physical Chemistry* **1964**, *68*, doi:10.1021/j100785a001.
131. Tiekink, E.R.T. Tin Dithiocarbamates: Applications and Structures. *Appl Organomet Chem* **2008**, *22*, doi:10.1002/aoc.1441.
132. Anthony, E.J.; Bolitho, E.M.; Bridgewater, H.E.; Carter, O.W.L.; Donnelly, J.M.; Imberti, C.; Lant, E.C.; Lermyte, F.; Needham, R.J.; Palau, M.; et al. Metallodrugs Are Unique: Opportunities and Challenges of Discovery and Development. *Chem Sci* **2020**, *11*, doi:10.1039/d0sc04082g.
133. Oun, R.; Moussa, Y.E.; Wheate, N.J. The Side Effects of Platinum-Based Chemotherapy Drugs: A Review for Chemists. *Dalton Transactions* 2018, *47*.
134. Dasari, S.; Bernard Tchounwou, P. Cisplatin in Cancer Therapy: Molecular Mechanisms of Action. *Eur J Pharmacol* 2014, *740*.
135. Gómez-Ruiz, S.; Kaluderović, G.N.; Prashar, S.; Hey-Hawkins, E.; Erić, A.; Žižak, Ž.; Juranić, Z.D. Study of the Cytotoxic Activity of Di and Triphenyltin(IV) Carboxylate Complexes. *J Inorg Biochem* **2008**, *102*, doi:10.1016/j.jinorgbio.2008.07.009.

136. Muhammad, N.; Ahmad, M.; Sirajuddin, M.; Ali, Z.; Tumanov, N.; Wouters, J.; Chafik, A.; Solak, K.; Mavi, A.; Muhammad, S.; et al. Synthesis, Characterization, Biological Activity and Molecular Docking Studies of Novel Organotin(IV) Carboxylates. *Front Pharmacol* **2022**, *13*, doi:10.3389/fphar.2022.864336.
137. Koch, B.; Basu Baul, T.S.; Chatterjee, A. P53-Dependent Antiproliferative and Antitumor Effect of Novel Alkyl Series of Diorganotin(IV) Compounds. *Invest New Drugs* **2009**, *27*, doi:10.1007/s10637-008-9176-6.
138. Ray, D.; das Sarma, K.; Antony, A. Differential Effects of Tri-n-Butylstannyl Benzoates on Induction of Apoptosis in K562 and MCF-7 Cells. *IUBMB Life* **2000**, *49*, doi:10.1080/15216540050167061.
139. Wada, O.; Manabe, S.; Iwai, H.; Arakawa, Y. Recent Progress in the Study of Analytical Methods, Toxicity, Metabolism and Health Effects of Organotin Compounds. *Japanese Journal of Industrial Health* **1982**, *24*, doi:10.1539/joh1959.24.24.
140. Nath, M. Toxicity and the Cardiovascular Activity of Organotin Compounds: A Review. *Appl Organomet Chem* 2008, *22*.
141. How, F.N.F.; Crouse, K.A.; Tahir, M.I.M.; Tarafder, M.T.H.; Cowley, A.R. Synthesis, Characterization and Biological Studies of S-Benzyl-β-N-(Benzoyl) Dithiocarbazate and Its Metal Complexes. *Polyhedron* **2008**, *27*, doi:10.1016/j.poly.2008.07.022.
142. Galanski, M.; Jakupec, M.; Keppler, B. Update of the Preclinical Situation of Anticancer Platinum Complexes: Novel Design Strategies and Innovative Analytical Approaches. *Curr Med Chem* **2005**, *12*, doi:10.2174/0929867054637626.
143. Iqbal, H.; Ali, S.; Shahzadi, S. Anti-Inflammatory and Acute Toxicity Study of Organotin (IV) Complexes : A Review.; 2016.
144. Iqbal, M.; Ali, S.; Haider, A.; Khalid, N. Therapeutic Properties of Organotin Complexes with Reference to Their Structural and Environmental Features. *Reviews in Inorganic Chemistry* 2017, *37*.
145. Shah, S.; Ashfaq, M.; Waseem, A.; Ahmed, M.; Najam, T.; Shaheen, S.; Rivera, G. Synthesis and Biological Activities of Organotin(IV) Complexes as Antitumoral and Antimicrobial Agents. A Review. *Mini-Reviews in Medicinal Chemistry* **2015**, *15*, doi:10.2174/1389557515050150408142958.
146. Adokoh, C.K. Therapeutic Potential of Dithiocarbamate Supported Gold Compounds. *RSC Adv* 2020, *10*.
147. Cattaruzza, L.; Fregona, D.; Mongiat, M.; Ronconi, L.; Fassina, A.; Colombatti, A.; Aldinucci, D. Antitumor Activity of Gold(III)-Dithiocarbamato Derivatives on Prostate Cancer Cells and Xenografts. *Int J Cancer* **2011**, *128*, doi:10.1002/ijc.25311.
148. Kamaludin, N.F.; Ismail, N.; Awang, N.; Mohamad, R.; Pim, N.U. Cytotoxicity Evaluation and the Mode of Cell Death of K562 Cells Induced by Organotin (IV) (2-Methoxyethyl) Methyldithiocarbamate Compounds. *J Appl Pharm Sci* **2019**, *9*, doi:10.7324/JAPS.2019.90602.
149. Jakšić, Ž. Mechanisms of Organotin-Induced Apoptosis. In *Biochemical and Biological Effects of Organotins*; 2012.
150. Basu, A.; Krishnamurthy, S. Cellular Responses to Cisplatin-Induced DNA Damage. *J Nucleic Acids* 2010, *2010*.
151. Yusof, E.N.M.; Latif, M.A.M.; Tahir, M.I.M.; Sakoff, J.A.; Simone, M.I.; Page, A.J.; Veerakumarasivam, A.; Tiekink, E.R.T.; Ravoof, T.B.S.A. O-Vanillin Derived Schiff Bases and Their Organotin(Iv) Compounds: Synthesis, Structural Characterisation, in-Silico Studies and Cytotoxicity. *Int J Mol Sci* **2019**, *20*, doi:10.3390/ijms20040854.
152. Arjmand, F.; Parveen, S.; Tabassum, S.; Pettinari, C. Organo-Tin Antitumor Compounds: Their Present Status in Drug Development and Future Perspectives. *Inorganica Chim Acta* 2014, *423*.
153. Liu, K.; Yan, H.; Chang, G.; Li, Z.; Niu, M.; Hong, M. Organotin(IV) Complexes Derived from Hydrazone Schiff Base: Synthesis, Crystal Structure, in Vitro Cytotoxicity and DNA/BSA Interactions. *Inorganica Chim Acta* **2017**, *464*, doi:10.1016/j.ica.2017.05.017.
154. Shaheen, F.; Sirajuddin, M.; Ali, S.; Zia-ur-Rehman; Dyson, P.J.; Shah, N.A.; Tahir, M.N. Organotin(IV) 4-(Benzo[d][1,3]Dioxol-5-Ylmethyl)Piperazine-1-Carbodithioates: Synthesis, Characterization and Biological Activities. *J Organomet Chem* **2018**, *856*, doi:10.1016/j.jorganchem.2017.12.010.
155. Alama, A.; Tasso, B.; Novelli, F.; Sparatore, F. Organometallic Compounds in Oncology: Implications of Novel Organotins as Antitumor Agents. *Drug Discov Today* 2009, *14*.
156. Navarro, M. Gold Complexes as Potential Anti-Parasitic Agents. *Coord Chem Rev* 2009, *253*.