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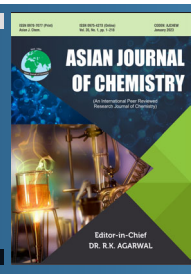

Synthesis, Characterization and Cytotoxic Activity of Organotin(IV) Diisopropyldithiocarbamate Compounds Towards K562 Myeloid Leukaemia Cell Lines

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In this work, two organotin(IV) compounds *viz*. triphenyltin(IV) diisopropyldithiocarbamate (**1**) and dimethyltin(IV) diisopropyldithiocarbamate (**2**) were synthesized *via in situ* method. Both synthesized organotin(IV) complexes were characterized by elemental, FT-IR and ^{1}H, ^{12}C and ^{119}Sn NMR spectroscopies. The single-crystal structure of compound **1** was determined by X-ray single-crystal analysis. The elemental analysis data showed agreement with the suggested formulas of $(C_6H_5)_3Sn[S_2CN(C_3H_7)_2]$ (**1**) and $(CH_3)_2Sn[S_2CN(C_3H_7)_2]_2$ (**2**). The important infrared absorbance peaks, ν(C=N) and ν(C=S), were detected in the ranges 1477-1474 cm^{-1} and 1038-997 cm^{-1} respectively. The chemical shift of carbon in the NCS_2 group for compounds **1** and **2** was observed at 196.97 ppm and 198.11 ppm, respectively. The crystal structure of compound **1** showed that it is 5-coordinated and crystallized in a triclinic, *P*1 space group with the crystal cell parameter: a = 9.7572(1) Å, b = 11.7030(2) Å, c = 11.7602(2)Å, α = 74.419(1)°, β = 80.114(1)°, γ = 67.285(2)° and *R* = 0.002. The cytotoxicity (IC_{50}) of these two compounds against K562 leukaemia cells was 0.25 µM and 4.3 µM, respectively, as assessed using MTT assay. In conclusion, the study demonstrates that both compounds showed potent cytotoxicity towards the K562 cell line tested, with compound **1** displaying a greater effect.

Keywords: Organotin, Dithiocarbamate, Cytotoxicity, Anticancer, Leukaemia cell.

INTRODUCTION

The organotin(IV) compounds have an ability to bind with a sulphur ligand such as thione or dithiocarbamate, which results in the enhancement of the biological activities [1,2]. The studies of the dithiocarbamate compounds of di- and triorganotin(IV) have shown a variety of coordination environments around the central tin atoms, such as their molecular geometry that exists as structures of 4- and 5-coordinated, respectively [3,4]. The number of organic groups, the coordination mode of the CS_2 moiety and the number of ligands attached to the tin atom all influence the geometry of organotin(IV) compounds [1].

The design of new organotin(IV) compounds with a dithiocarbamate ligand may provide useful attributes in various applications, especially in the medicinal area. Due to the lipophilic character demonstrated by the alkyl substituent of dithiocarbamate, the compounds with bioactive metals can reach into the cell membrane [5]. Thus, several organotin(IV) compounds have been subjected to *in vitro* and *in vivo* analysis for their efficacy against cancer cells [6]. In general, the cytotoxicity activity of organotin(IV) compounds is influenced by the organotin moiety, ligand and coordination number of tin atoms, where their toxicity decreases in the order $R_3SnX > R_2SnX_2 > RSnX_3$ [7].

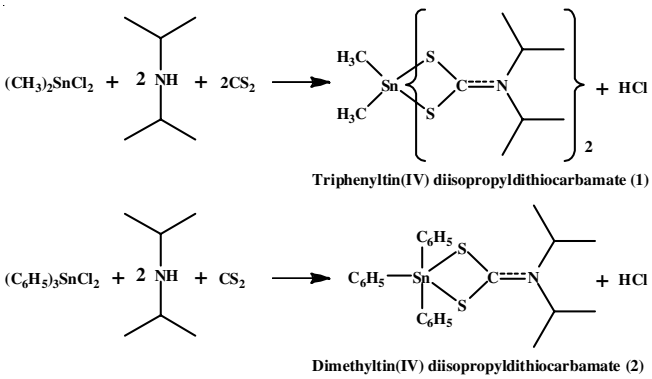
In order to further develop organotin(IV) compounds libraries, two new organotin(IV) dithiocarbamate compounds, triphenyltin(IV) diisopropyldithiocarbamate (**1**) and dimethyltin(IV) diisopropyldithiocarbamate (**2**) have been synthesized. Herein, we report the synthesis, spectral characterization and cytotoxic activity towards K562 myeloid leukaemia cell lines. The X-ray crystallographic study of compound **1** was also carried out.

EXPERIMENTAL

Diisopropylamine, triphenyltin(IV) dichloride, dimethyltin(IV) dichloride, MTT salt, NH_3 solution (25%) and standard imatinib drug were procured from Sigma-Aldrich USA, whereas the solvents *viz*. ethyl alcohol, carbon disulphide, DMSO and chloroform were supplied by Merck. All the received reagents and chemicals were used without further purification.

Physical measurements: The melting point of each compound was measured using the Electrochemical IA 9100. Elemental analyses of carbon, hydrogen, nitrogen and sulphur were performed with the Fison EA 1108. Perkin-Elmer Model GX Spectrophotometer was used to record the infrared spectra using KBr discs. The ^{1}H, ^{12}C & ^{119}Sn spectra were obtained on Joel JNM-LA 400 in $CdCl_3$ using TMS as an internal standard. The X-ray single structure determination was recorded using a Rigaku single crystal X-ray diffractometer.

Synthesis of compounds 1 and 2: Both compounds were synthesized by mixing CS_2 (30 mmol) and ethanolic solution of diisopropylamine (30 mmol). The reaction mixture was then stirred for 2 h at 4 ºC followed by the addition of organotin(IV) [dimethyltin(IV)/triphenyltin(IV)] chloride dissolved in 60 mL of ethanol was added dropwise. The obtained precipitate was filtered and washed with cold ethanol, then dried in a desiccator. A schemetic route of both organotin(IV) diisopropyldithiocarbamate compounds are shown in **Scheme-I**. The physical and analytical data for compounds **1** and **2** are given in Table-1.



Scheme-I: Reaction scheme of diisopropylamine, carbon disulphide, triphenyltin(IV) chloride (**1**) and dimethyltin(IV) chloride (**2**)

Crystallographic study: The slow crystallization at room temperature process was carried out by dissolving the compound with chloroform and ethanol in a 1:1 v/v ratio. An X-ray analysis was used to determine the crystal structures after they had been collected.

Cell and cell culture: Human K562 chronic myeloid leukaemia cell lines were obtained from the American Type Culture Collection (ATCC). Dulbecco's Modified Eagle Medium (DMEM) was used to cultivate K562 cell lines and it was supplemented with 1% penicillin/streptomycin and 10% foetal bovine serum (JR Scientific, USA). The cells were cultured in a humidified environment containing 5% CO_2 at 37 ºC. The cells were sub-cultured using the method described by ATCC.

Cytotoxicity screening: The synthesized compounds were screened against K562 cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) assay [8]. Both compounds were subjected to serial dilution up to seven concentrations, with 10 µM serving as the highest. Imatinib was used as a positive control, whereas non-treated cells were represented as a negative control. The assays were performed three times at each concentration level. The absorbance values at 570 nm were recorded using an ELISA microplate reader to calculate the percentage of viable cells in comparison to the untreated cell population (iMark). The percentage of mean absorbance for each compound concentration and untreated cells was calculated. The graph was plotted as a percentage of viable cells *versus* compound concentrations. The IC_{50} and the Standard Error of the Mean (SEM) were determined using one-way ANOVA analysis (SPSS, version 25).

RESULTS AND DISCUSSION

The synthesized compounds **1** and **2** are highly soluble in chloroform and stable at room temperature. The C, H, N and S elemental analysis data showeda good agreement between the experimental and theoretical values based on the suggested general formula.

Infrared spectra: The key absorbance peaks data obtained from the FT-IR spectrophotometer for compounds **1** and **2** are shown in Table-2. Compounds **1** and **2** has strong absorptions in the 1477 cm^{-1} and 1474 cm^{-1} region, which is characteristic thioureido band of ν(C⋯N) vibration [9]. This band is caused due to the vibration of C-N bond with a partial double bond. Compounds **1** and **2** have medium vibrations of ν(C⋯S) of 997 cm^{-1} and 1038 cm^{-1}, respectively. The presence of a single band in the ν(C⋯S) region suggested the bidentate bonding of the dithiocarbamate ligand. In addition to peaks at 582-583 cm^{-1}, which indicate the presence of the Sn-C stretching bands for the compounds with phenyl or methyl moiety, the ν(Sn-C) peak is a key one observed only in organotin(IV) compounds due to the stretching between C, N and S elements. Absorptions of medium intensity at 443 and 415 cm^{-1} suggested that tin metal was coordinated with the sulphur atom in diisopropyldithiocarbamate, confirm the existence of Sn-sulphur coordination [10].

^{1}H NMR spectra: The chemical shifts (ppm) of the various observed protons are presented in Table-3. The aromatic protons of phenyl groups directly attached to the Sn atom in compound **1** were observed at δ 7.468-8.098 ppm. In addition, the proton

TABLE-1
PHYSICAL AND ELEMENTAL ANALYSIS DATA OF COMPOUNDS **1** AND **2**

Compounds	Colour	Yield (%)	m.p.	Elemental analysis (%): Found (calcd.)			
				C	H	N	S
$(C_6H_5)_3Sn[S_2CN(C_3H_7)_2]$ (**1**)	White	47.30	164.6-165.0	57.39 (57.07)	5.31 (5.51)	2.48 (2.66)	11.26 (12.19)
$(CH_3)_2Sn[S_2CN(C_3H_7)_2]_2$ (**2**)	White	62.15	81.3-84.8	37.74 (38.35)	6.00 (6.78)	4.08 (5.59)	23.67 (25.59)

TABLE-2
IMPORTANT INFRARED ABSORPTION BANDS OF COMPOUND **1** AND **2**

Compound	Wavenumber (cm^{-1})					
	ν(C-H)	ν(C------N)	ν(N–C)	ν(C------S)	ν(Sn–C)	ν(Sn–S)
1	2972	1477	1141	997	582	443
2	2972	1474	1194	1038	583	415

TABLE-3
NMR SPECTRAL DATA OF COMPOUNDS **1** AND **2**

Compounds	Chemical shifts, δ (ppm)							
	^{1}H NMR			^{13}C NMR				^{119}Sn NMR
	CH_3	N-CH	Sn-R (R=CH_3, C_6H_5)	N-CS2	Sn-R (R=CH_3, C_6H_5)	N-CH	CH_3	
1	1.744	3.429	7.468, 7.493, 7.514, 8.075, 8.098	196.97	128.75, 130.05, 135.79, 142.24	47.50	19.34	-206.91
2	1.644	5.459	7.284	198.11	15.60	58.04	19.94	-327.09

of compound **1** showed a chemical shift at δ 3.429 ppm, which was assigned to the methyl proton of the isopropyl group attached to a nitrogen atom. In ^{1}H NMR spectrum of compound **2** was observed at δ 7.284 ppm, which indicates the methyl groups directly attached to the Sn atom.

^{13}C NMR and ^{119}Sn spectra: The ^{13}C NMR and ^{119}Sn spectra of compounds **1** and **2** are given in Table-3. The ^{13}C NMR spectra of both compounds **1** and **2** exhibited a signal for methyl carbon in the isopropyl group at δ 19.34 ppm and δ 19.94 ppm, respectively, while the chemical shifts for carbon directly attached to the N atom were found at δ 47.50 ppm and δ 58.04 ppm, respectively. The chemical shifts of the CS_2 peak from the NCS_2 group were identified as the most significant shifts to identify the dithiocarbamate moieties. This peak normally resonates in the range of δ 185-220 ppm [11]. In compounds **1** and **2**, the chemical shifts of CS_2 were observed at δ 196.97 ppm and 198.11 ppm, respectively.

The values of δ (^{119}Sn) define the regions where the core tin atoms have varied coordination numbers [12]. The values in the range of +200 to -60 ppm, -90 to -190 ppm and -210 to -400 ppm of δ (^{119}Sn) are attributed to four-, five- and six-coordinated compounds, respectively [13]. Based on the ^{119}Sn chemical shifts for both compounds, single crystal X-ray structures provide further confirmation that compound **1** exists as 5-coordinated molecule with the bidentate nature of dithiocarbamate ligands, while compound **2** is confirmed to exist as 4-coordinated compound.

Crystal structure of $(C_6H_5)_3Sn[S_2CN(C_3H_7)_2]$: For X-ray crystallographic studies, suitable crystals of compound **1** were obtained by slow evaporation of chloroform:ethanol mixture at room temperature. Table-4 provides the crystallographic information and refinement parameters for compound **1**, while Table-5 provides a selection of geometric parameters. The ligand was successfully coordinated with organotin through Sn-S1 and Sn-S2 bonds. The Sn-S bonds Sn-S1 2.479 Å and Sn-S2 2.926 Å suggests that the Sn-S2 interaction is considered weak and the Sn-S2 bond distance is too long to be strong covalent bonds. Due to its strong electron-withdrawing properties, isopropyl (*i*-C_3H_7) will decrease the electron density on the S atom at C-S, reducing its ability to form a coordinated complex with the tin atom [14]. The coordination of the central tin atom in compound **1** is best described as tetrahedral based on the S1-Sn-C31 bond and the C11-Sn-C21 bond based on Fig. 1. It is concluded that triphenyltin(IV) diisopropyldithiocarbamate (**1**) is a 5-coordinated compound.

TABLE-4
CRYSTALLOGRAPHIC DATA AND
REFINEMENT PARAMETERS FOR COMPOUND **1**

Triphenyltin(IV) diisopropyldithiocarbamate, $Ph_3Sn(iPr_2Dtc)$	
Empirical formula	$Sn(C_6H_5)_3(C_7H_{14}NS_2)$
Formula weight	526.30
a (Å)	9.7572 (1)
b (Å)	11.7030 (2)
c (Å)	11.7602 (2)
α (°)	74.419 (1)
β (°)	80.114 (1)
γ (°)	67.285 (2)
V (Å)	1189.71 (4)
MoKα (Å)	Cu Kα
Z	2
D/Mgm^{-3}	1.469 Mg m^{-1}
μ (mm^{-1})	0.12 × 0.11 × 0.08
F (000)	536
Colours	Not available
Crystal size(mm^{-1})	10.25
Temperature (K)	100
Range θ (°)	3.9-76.3
Index ranges (±h, ±k, ±l)	-11/11, -13/13, -13/14
Reflection collected	28219
Independent reflections	4248
Data collection	4231
Refinement parameters	266
Largest and small peak (e Å^{-3})	0.36, -0.44

TABLE-5
SELECTED BOND LENGTHS (Å)

Bond	Bond length (Å)	Bond	Bond length (Å)
Sn-S1	2.4792 (4)	C1-S1	1.7587 (15)
Sn- S2	2.9264 (4)	C1-S2	1.7006 (16)
Sn-C11	2.1446 (14)	C1-N1	1.336 (2)
Sn-C21	2.1349 (15)	C5-N1	1.495 (2)
Sn-C31	2.1754 (15)	C2-N1	1.497 (2)

Cytotoxic screening: The efficiency of the synthesized triphenyltin(IV) and dimethyltin(IV) diisopropyldithiocarbamate as potential anticancer agents against K562 leukaemia

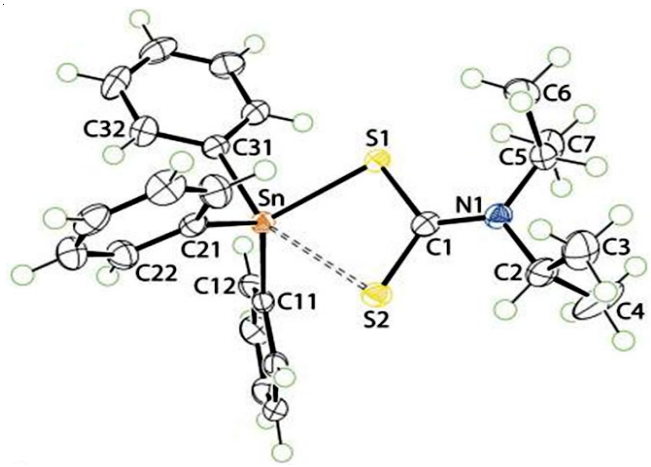


Fig. 1. ORTEP plot of compound **1**

cell lines were tested preliminary *in vitro*. The results of the *in vitro* cytotoxic activity of both compounds were compared using imatinib as a positive control. Organotin(IV) compounds have been demonstrated to be highly promising for use as novel anticancer drugs in past [15-17]. The values are expressed as IC_{50}, *i.e.* the concentration of compound (μM) that inhibits the proliferation rate of cancer cells by 50% as compared to untreated cells as a control. Compound **1** (IC_{50} = 0.32 μM) was found to have significant cytotoxic activity with a lower IC_{50} value than compound **2** (IC_{50} = 4.30 μM). The reason is attributed due to the fact that compound **1** was derived from triphenyltin(IV), which was more active than diorganotin(IV) (**2**) (Fig. 2). Hence, the cytotoxic activity of organotin(IV) obtained in this study could be arranged as triorganotin(IV) > diorganotin(IV). Analysis using one-way ANOVA showed that the trend percentage of the viable cell for both compounds was significant ($p < 0.05$).

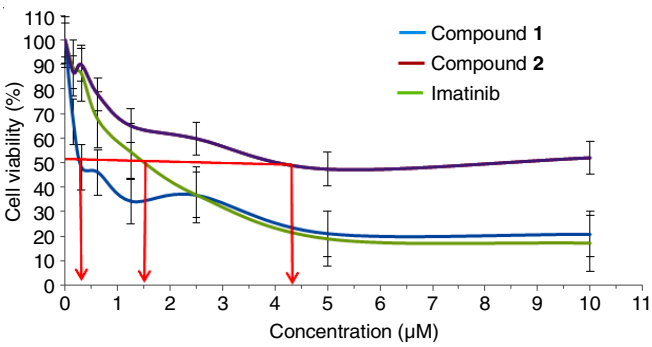


Fig. 2. The cytotoxic activity of compounds **1** and **2** and Imatinib against K562 cell lines. The red line indicates 50% of the viable cells population

Conclusion

The synthesis and characterization of dibutyltin(IV) and triphenyltin(IV) diisopropyldithiocarbamate compounds was carried out successfully. The thioureide bands, ν(C=N) and the Sn-S stretchings in both compounds confirmed the formation of dithiocarbamate groups and bonding between the Sn(IV) and the dithiocarbamate ligands, respectively. Compound **1** was found to have an X-ray crystal structure with distorted tetrahedral geometry and isobidentate coordination. The ^{13}C NMR peaks for NCS_2 provided an additional evidence for the dithiocarbamate formation. The cytotoxicity assay of compound **1** results for the K562 cell lines were much higher than those for compound **2**. It is suggested that additional *in vitro* and *in vivo* studies be conducted on this prospective drug.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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