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Synthesis, spectral characterization and antiproliferative activity of new organotin(IV) dithiocarbamate compounds on K562 cells

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Abstract: Four new organotin(IV) dithiocarbamate compounds with general formulae of $Ph_nSn[S_2CN(CH_2CH_2OCH_2CH_3)]_{4-n}$ for compound 1 and 2; and $Ph_nSn[S_2CN(CH_3)(CH_2CH_2C_6H_5)]_{4-n}$ for compound 3 and 4 were successfully synthesized via in situ insertion method. These compounds namely, diphenyltin(IV)- [1] and triphenyltin(IV) *N*,*N*-bis(2-ethoxyethyl)dithiocarbamate [2], diphenyltin(IV)- [3] and triphenyltin(IV) *N*-methyl-*N*-phenethyldithiocarbamate [4] were each characterized with CHNS elemental analysis, FT-IR and NMR spectroscopies (^{1}H, ^{13}C and ^{119}Sn). The compounds were then assessed for their cytotoxicity against K562 cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazholium bromide (MTT) assay upon 24 h treatment. All compounds produced the essential IR absorption bands and displayed important NCS_2 peak in ^{13}C NMR spectroscopy. From the cytotoxicity studies using MTT assay, the compounds were shown to inhibit cell proliferation in K562 leukemic cells with IC_{50} values ranging from 1.48 to 4.52 μM, and in the manners more cytotoxic compared to standard used imatinib.

Keywords: Organotin(IV) dithiocarbamate, in situ insertion, antiproliferative, cytotoxicity, and K562 cells.

INTRODUCTION

Imatinib was the first drug specifically designed to inhibit BCR-ABL tyrosine kinases, which are commonly found in chronic myeloid leukemia due to abnormality in BCR-ABL genes (Miller *et al.*, 2014). However, tyrosine kinase inhibitor (TKIs) such as imatinib don't seem to entirely cure or make leukemia go away forever, so these drugs need to be taken indefinitely. Apart from that, there are cases reported with imatinib resistance (Perrotti *et al.,* 2010). This issue highlights the need for studies to discover new anti-leukemic agents that might act in a different manner compared to the available tyrosine kinase inhibitors to selectively kill cancer cells.

Following the discovery of cisplatin, countless attempts have been made to study other metal complexes, including organotin(IV) complexes as potential anti-cancer agents (Safari *et al.*, 2013). Organotin compounds have diverse applications in various fields due to their exceptional contribution to the study and understanding of organometallic compounds since 1949 (Adeyemi and Onwudiwe, 2018). Thus, their synthesis and characterization as compounds with ligands containing sulphur (S), oxygen (O) and nitrogen (N) elements have been a continuing subject of interest in recent years (Sirajuddin and Tahir, 2016). Much concentration had been paid to the synthesis and characterization of biological activities for various organotin(IV) derivatives with sulfur ligands such as dithiocarbamate compounds (Pellerito *et al.,* 2006). These complexes possess unique stereo-electronic properties that underline their relevance in the area of medicinal chemistry (Kadu *et al.,* 2015).

Hence, a lot of studies have been conducted to elucidate the potential of organotin(IV) derivatives particularly as anti-cancer agents (Tariq *et al.,* 2013; Girasolo *et al.,* 2014; Khan *et al.,* 2014; Khan *et al.,* 2015). Recently, Kamaludin *et al.* evaluated the potential of organotin(IV) with 2-methoxyethyl-methyldithiocarbamate ligand as anti-leukemic agent owing to the strong cytotoxicity exerted by these compounds on K562 cells leading to apoptosis (Kamaludin *et al.,* 2019). In this study, we synthesized new di- and triphenyltin(IV) derivatives with ligands *N*,*N*-bis(2-ethoxyethyl)dithiocarbamate and *N*-methyl-*N*-phenethyldithiocarbamate and assessed their cytotoxic effects against chronic myelogenous leukemia (CML), K562 cell line.

MATERIALS AND METHODS

All chemicals and solvents were purchased from Sigma Aldrich or Merck and were used without purification. Melting point was determined using an automated melting point apparatus (MPA 120 EZ-Melt). The percentage compositions of the elements (CHNS) for each compound were determined using a Leco CHNS-932 Elemental Analyzer. Infrared (IR) spectra were recorded with potassium bromide disc using a Perkin Elmer Spectrum GX in the range of 4000 to 370 cm^{-1}. The ^{1}H, ^{13}C and

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^{119}Sn nuclear magnetic resonance (NMR) spectra were recorded at room temperature (26-27°C) on Bruker AVANCE 400 lll HD instrument in chloroform ($CDCl_3$) solvent with tetramethylsilane as an internal standard.

Cell culture

Human chronic myelogenous leukemia cell line, K562 was purchased from the American Type Culture Collection (ATCC) and were cultured in complete Iscove's Modified Dulbecco's Medium (IMDM) (Sigma-Aldrich, United State) enriched with 10% of fetal bovine serum (FBS) (Tico-Europe, Netherlands). The culture was maintained at 37°C in 5% carbon dioxide (CO_2) atmosphere.

Synthesis of diphenyltin(IV)- and triphenyltin(IV) N,N-bis(2-ethoxyethyl)dithiocarbamate compounds

Compounds were synthesized using a previously reported method with modifications (Awang *et al.*, 2008). The secondary amine, *N*,*N*-bis(2-ethoxyethyl)amine (Merck, Germany) (0.81 mL, 10 mmol) was first dissolved in ethanol (Merck, Germany) (30 mL) and stirred for 30 minutes. Carbon disulphide (CS_2) (Merck, Germany) (0.6 mL, 10 mmol) in cold ethanol was then slowly added and the resulting mixture stirred for the next 2 hours. Ammonia solution (Merck, Germany) (25%) (1-2 mL) was added to generate a basic condition. Diphenyltin(IV) dichloride (Sigma-Aldrich, United State) (1.72 g, 5mmol) and triphenyltin(IV) chloride (Merck, Germany) (3.85 g, 10 mmol) dissolved in ethanol were added dropwise into the previous solution accordingly prior to 2 hours of stirring. All reactions were carried out at <4°C. The precipitate formed was dried and stored for further use.

Synthesis of diphenyltin(IV)- and triphenyltin(IV) N-methyl-N-phenethyldithiocarbamate compounds

Secondary amine, *N*-methyl-*N*-phenethylamine (Sigma-Aldrich, United State) (1.45 mL, 10 mmol) was dissolved in ethanol (Merck, Germany) (30 mL) and stirred for 30 minutes. Later, carbon disulphide (CS_2) (Merck, Germany) (0.6 mL, 10 mmol) in cold ethanol was slowly added and the resulting mixture was stirred for the next 2 hours. Ammonia solution (25 %) (Merck, Germany) (1-2 mL) was added to generate another basic condition. Then, diphenyltin(IV) dichloride (Sigma-Aldrich, United State) (1.72 g, 5 mmol) and triphenyltin(IV) chloride (Merck, Germany) (3.85 g, 10 mmol) dissolved in ethanol were added dropwise into the solution accordingly prior to 2 hours of stirring. All reactions were carried out at <4°C. The precipitate formed was dried and stored for later usage.

MTT cytotoxicity assay

Antiproliferative activity of newly synthesized compounds were determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay which using a principal based on reduction of MTT dye by NAD(P)H-dependent cellular oxidoreductase enzymes to its puprle insoluble formazan that will reflect the number of viable cells present (Mossman, 1983). Cell suspensions of K562 were cultured in 96-well plate at a density of 5 x 10^5 cells per ml and then were treated with different concentrations of the four compounds namely diphenyltin(IV) *N*,*N*-bis(2-ethoxyethyl)dithiocarbamate, triphenyltin(IV) *N*,*N*-bis(2-ethoxyethyl)dithiocarbamate, diphenyltin(IV) *N*-methyl-*N*-phenethyldithiocarbamate and triphenyltin(IV) *N*-methyl-*N*-phenethyldithiocarbamate, in an atmosphere of 5% CO_2 at 37°C for 24 h. After treatment, 20 µL of 5 mg/ml MTT salt (Sigma-Aldrich, United State) was added to each well and incubated for 4 h. Later, 180 µL of the culture medium was removed from each well and replaced with 180 µL dimethyl sulfoxide (DMSO) (Merck, Germany) to dissolve the insoluble purple formazan precipitates produced by MTT reduction. The plate was incubated for 15 minutes to ensure complete dissolution. The cytotoxic activity of the organotin(IV) dithiocarbamate compounds on K562 cells was assessed by measuring the optical density of each well at 570 nm and were determined three times in independent experiments. Finally, mean absorbance for each concentration was expressed as a percentage of untreated cells (negative control) and plotted versus compounds concentrations.

STATISTICAL ANALYSIS

Statistical Analysis Statistical evaluations of the percentage of viable cells along with the concentration of compounds used to treat the cells were calculated using Statistical Package for Social Sciences (SPSS) version 23.0 by employing a one-way analysis of variance. A probability of 0.05 or less was deemed statistically significant ($p < 0.05$).

RESULTS

Synthesis of compounds

Compounds 1-4 were synthesized from the corresponding secondary amines namely *N*,*N*-bis(2-ethoxyethyl) amine and *N*-methyl-*N*-phenethylamine , CS_2 and organotin (IV) chloride in ethanol (fig. 1). All four compounds were white in color, stable in air and highly soluble in chloroform and DMSO. The elemental analyses obtained were in good agreement with the calculated theoretical values, thus supporting the proposed molecular formulae, as presented in table 1. The chemical structures of all compounds are illustrated in fig. 2.

Infrared spectroscopy

Solid state infrared spectra of the compounds were recorded in the range of 4000-375 cm^{-1} and the most important bands observed are presented in table 2. All important bands that described organotin(IV) dithiocarba-

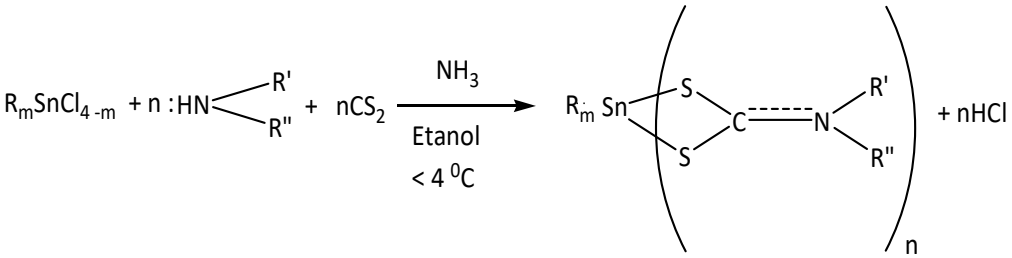
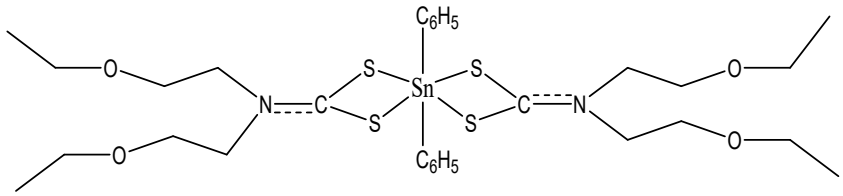
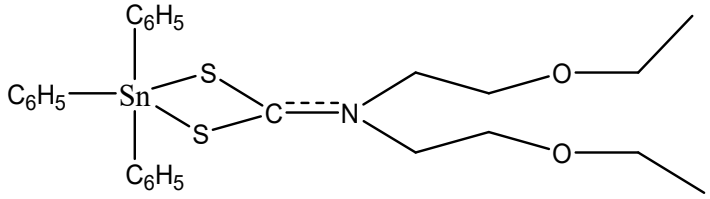


Fig. 2: General equation for the formation of organotin(IV) with different dithiocarbamates ligands

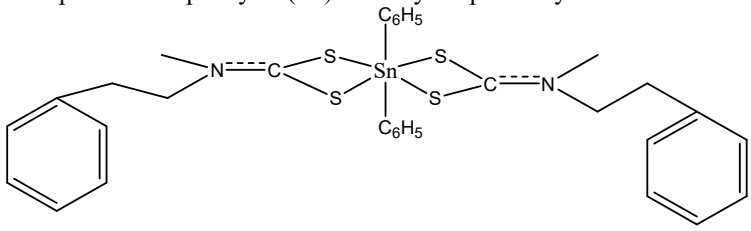
Compound 1: Diphenyltin(IV) *N*,*N*-bis(2- ethoxyethyl)dithiocarbamate



Compound 2: Triphenyltin(IV) *N*,*N*-bis(2- ethoxyethyl)dithiocarbamate



Compound 3: Diphenyltin(IV)*N*-methyl-*N*-phenethyldithiocarbamate



Compound 4: Triphenyltin(IV) *N*-methyl-*N*-phenethyldithiocarbamate

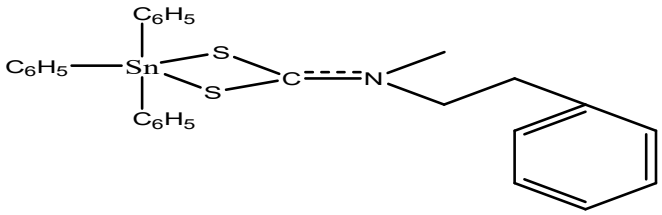


Fig. 2: Chemical structures of compounds 1-4.

mate such as "thioureide band", ν(C-S) , ν(Sn-C) and ν(Sn-S) stretching vibrations were found in the spectrum of compounds at the expected regions.

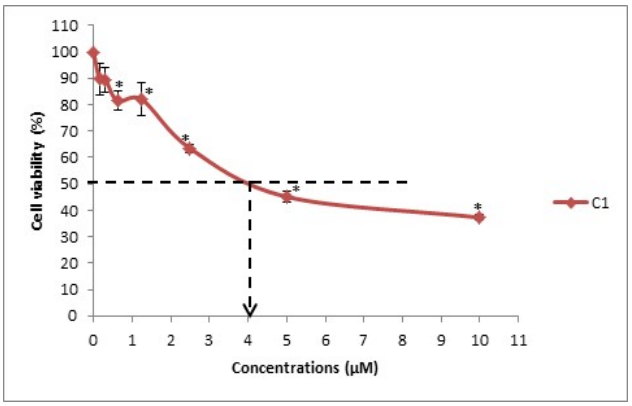


Fig. 3: Graphical representation of cytotoxic activity of compound 1 against K562 cells. The data show the percentage of viable cells (%) ± SEM obtained from three consecutive experiments. *Significant difference ($p<0.05$) from negative control.

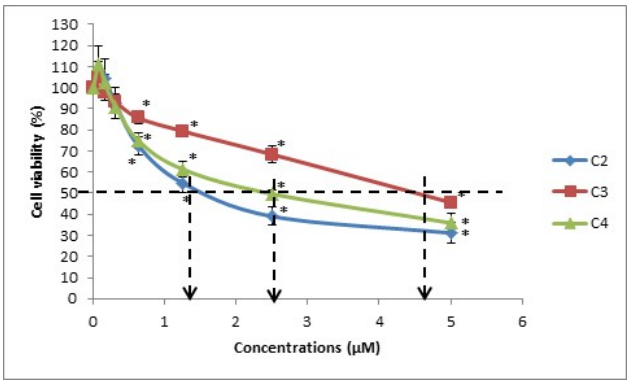


Fig. 4: Graphical representation of cytotoxic activity of compounds 2-4 against K562 cells. The data show the percentage of viable cells (%) ± SEM obtained from three consecutive experiments. *Significant difference ($p<0.05$) from negative control.

NMR Spectroscopy

NMR spectra for all compounds were recorded in deuterated chloroform ($CDCI_3$) solution using tetramethylsilane as an internal standard at room temperature. The chemical shifts in ppm for various protons are presented in table 3. The ^{13}C NMR in table 4 showed the presence of chemical shifts of CS_2 peak from NCS_2 group which is identified as the most significant shift to identify the dithiocarbamate moieties.

Cytotoxicity study

The future of these newly synthesized organotin (IV) dithiocaramate compounds as anticancer agents were preliminary tested in vitro against K562 cells, derived from chronic myelogenous leukemia (CML) cell line. Studies conducted previously by our group demonstrated that organotin(IV) dithiocarbamate compounds have promising potentials to be developed as anticancer agents, particularly against leukemic cell line (Awang *et al.,* 2016; Kamaludin *et al.,* 2017). The IC_{50} values of the compounds against K562 cells were compared using imatinib as positive control and are listed in table 5 and the cell viability curve is depicted in fig. 3 and 4.

DISCUSSION

Dithiocarbamate ligands showed a tendency to bind with a metal atom through different manners such as monodentately, bidentately or anisobidentely. These binding modes can be identified by means of certain absorbance peaks with predominantly ν(C-N) and ν (C-S). The presence of the "thioureide band" at 1450-1500 cm^{-1} are found in a number of chelated dithiocarbamate that arises from the stretching vibration of the C-N bond with a partial double bond and polar character, $C=N^+$ (Khan *et al.,* 2014; Bonati and Ugo, 1967; Farina *et al.,* 2002). This band arising between the range of C–N single bonds (1250–1360 cm^{-1}) and C=N double bond (1640–1690 cm^{-1}) is an indication of partial double bond character in the C–N bond (Rehman *et al.,* 2009). The infrared spectra of all compounds showed absorptions in the region 1479-1496 cm^{-1} attributable to the thioureide band's vibration.

IR absorption band found at 977-995 cm^{-1} can be assigned to the C-S stretching frequency. There are two types of (C-S) band commonly seen in dithiocarbamate ligands, including the (CS_2)asym that involve both the sulfur atoms, and (CS_2)sym which involving only one sulfur atom in complexation. Both vibrations appear around 1055 cm^{-1} and 961 cm^{-1} respectively (Adeyemi and Onwudiwe, 2018; Sirajuddin and Tahir, 2016). The single band found near 1000 cm^{-1} for our compounds suggested that the $-CS_2$ moiety is asymmetric bidentate (also known as anisobidentate) (Sharma *et al.,* 1981).

Another important peak observed in the infrared spectrum was the signal for ν(Sn-C) that usually occured in the range of 600-500 cm^{-1} (Ferreira *et al.,* 2012). The presences of Sn-C stretching bands for compounds with phenyl moiety were observed at 532-584 cm^{-1}. The peak present at lower frequencies (450-250 cm^{-1}), attributed to the vibration of Sn-S bond (Ferreira *et al.,* 2012) and this peak were observed at 435- 488 cm^{-1} in our compounds. The presence of this ν(Sn-S) band suggesting the complexation of organotin moiety with dithiocarbamate ligands through sulfur atom has been achieved (Sainorudin *et al.,* 2015).

As for ^1H NMR spectra for compound 1 and 2, protons present in the bis(2-ethoxyethyl)dithiocarbamate ligand can be observed through the triplet appearing around 1.2 and 4.1 ppm due to terminal methyl protons and methylene protons attached to nitrogen. Both methylene proton groups bound to oxygen in the ligand structure

Table 4: Elemental analysis and physical data of compounds 1-4

Compound	Yield (%)	Melting point (K)	Elemental analysis found (calc.)(%)			
			C	H	N	S
1	50	331.65- 332.05	46.63 (48.32)	5.72 (6.22)	3.68 (3.76)	16.71 (17.2)
2	61	338.15-339.15	56.61 (55.3)	5.64 (5.67)	2.47 (2.39)	11.27 (10.94)
3	46	383.50-385.50	53.32 (55.41)	4.52 (4.94)	3.73 (4.04)	17.4 (18.5)
4	67	387.45- 388.95	60.68 (60.02)	4.86 (4.86)	2.55 (2.5)	12.21 (11.44)

Table 4: Important Infrared absorption bands of the compounds

Compound	IR spectra (cm^{-1})			
	ν(C-N)	ν(C-S)	ν(Sn-C)	ν(Sn-S)
1	1479	995	549	439
2	1491	991	584	447
3	1496	982	532	435
4	1493	977	532	488

Table 4: ^{1}H and ^{119}Sn NMR data

Compound	^{1}H NMR (ppm)		^{119}Sn NMR (ppm)
	H (Aromatic)	H (Aliphatic)	
1	7.284-7.903 (10H)	N-CH_2= 4.059(2H) C*H*$_2$-O-CH_2= 3.742 (2H) CH_2-O-C*H*$_2$= 3.501(2H) -CH_3= 1.194 (3H)	-494.08
2	7.404-7.751 (15H)	N-CH_2= 4.136(2H) C*H*$_2$-O-CH_2= 3.772 (2H) CH_2-O-C*H*$_2$= 3.515 (2H) -CH_3= 1.204 (3H)	-184.78
3	7.223- 7.944 (20H)	N-CH_3= 3.27 (3H) N-C*H*$_2$$CH_2$-Ar)= 3.987 (2H) N-$CH_2$C*H*$_2$-Ar)= 3.08 (2H)	-323.67
4	7.239-7.777 (20H)	N-CH_3= 3.361 (3H) N-C*H*$_2$$CH_2$-Ar)= 4.069(2H) N-$CH_2$C*H*$_2$-Ar)= 3.091 (2H)	-183.84

Table 4: ^{13}C NMR data of compounds 1-4

Compound	^{13}C NMR (ppm)		
	S_2*C*N	C (Aromatic)	C (Aliphatic)
1	199.99	127.8-134.26	N-CH_2= 56.96 *C*H_2-O-CH_2= 67.53 CH_2-O-*C*H_2= 66.66 -CH_3= 15.2
2	197.05	128.23- 142.39	N-CH_2= 57.29 *C*H_2-O-CH_2= 67.66 CH_2-O-*C*H_2= 66.67 -CH_3= 15.21
3	199.64	126.76-137.84	N-CH_3= 32.94 N-C*H*$_2$$CH_2$-Ar)= 60.03 N-$CH_2$C*H*$_2$-Ar)= 44.45
4	196.61	126.79- 142.33	N-CH_3= 33.12 N-C*H*$_2$$CH_2$-Ar)= 60.25 N-$CH_2$C*H*$_2$-Ar)= 44.51

Table 5: IC_{50} values of tested compounds against K562 cells

Compound	IC_{50} value ± S.E.M (μM)	IC_{50} value (μg/ cm^3)
1	4.1 ± 0.31	3.08
2	1.48 ± 0.26	0.87
3	4.52 ± 0.19	3.13
4	2.65 ± 0.35	1.49
Imatinib	83 ± 3.5	415

resonated as quartet and triplet around 3.5 and 3.7 ppm respectively. The aromatic protons of phenyl group attached to the metal center observed resonated in the range of 7.3-7.9 ppm for diphenyltin compound and 7.4-7.8 ppm for triphenyltin compound respectively.

Conversely, protons present in *N*-methyl-*N*-phenethyldithiocarbamate ligand resonated as singlet and triplet at around 3.3 and 4 ppm for both terminal methyl and methylene protons attached to the nitrogen. The methylene protons next to phenyl group of the ligand appeared at ~3.1 ppm. All peaks were observed to appear at the same range for both diphenyltin and triphenyltin compounds, indicating that the addition of another phenyl group at the tin center did not cause any significant effect on the proton resonance. As for the aromatic protons in both compounds 3 and 4, the signals appeared at 7.2-7.9 and 7.2 -7.8 ppm respectively.

^{119}Sn NMR chemical shift can be used to give preliminary information on the environment around tin atom. The coordination numbers of the central tin atoms can be defined based on the values of δ(^{119}Sn). Values in the ranges of 200 to -60 ppm, -90 to-190 ppm, -210 to -400 and -440 to -540 ppm of the δ(^{119}Sn) are all attributed to four-, five-, six- and seven-coordinate compounds respectively (Rehman *et al.,* 2008). However, ^{119}Sn chemical shift is also strongly dependent on other factors, such as electronegativity of the ligands, temperature and concentration employed in the experiments (Sirajuddin and Tahir, 2016). For compound 1 and 3, the geometry of both is expected to be six-coordinate, however, the ^{119}Sn NMR values suggested hepta-coordination of the tin atom centre for compound 1. This higher chemical shift values for compound 1 is most likely due to the presence of dissociated-electronegative chlorine (s) in compound that originated from metal salts, which can shift the resonance to a lower frequency (Sirajuddin and Tahir, 2016). As for triphenyltin(IV) compounds which are compound 2 and 4, the value of ^{119}Sn NMR lies in the range of five-coordinated compound as expected. The data are shown in table 3.

The ^{13}C NMR spectra of compound 1 and 2 exhibited signals for terminal carbon (CH_3) and methylene carbon (N-CH_2) at 15.2 and 57 ppm respectively, whilst both of the methylene carbons bound to oxygen atom resonated around 66 and 67 ppm accordingly. It is well known that the most notable shift for identification of dithiocarbamate moieties is the chemical shifts of the CS_2 peak originated from the NCS_2 group. This peak normally resonates in the range of 185-220 ppm (Van Gaal *et al.,* 1979). According to Adeyemi *et al.,* NCS_2 resonance is normally found at higher field above 205 ppm in free dithiocarbamate ligands, whereas it is shifted downfield in compounds as indication of tin chelation (Khan *et al.,* 2014; Adeyemi *et al.,* 2018). This downfield shift is due to the contribution of $R_2N^+{=}CS_2^{2-}$ resonance form in these compounds (Adeyemi *et al.,* 2018). The signal for NCS_2 carbon in both diphenyltin(IV)- and triphenyltin(IV) bis (2-ethoxyethyl) dithiocarbamate was found at 199.99 and 197.05 ppm respectively. Meanwhile, the aromatic carbons were found to resonate at 127.8-134.26 ppm in diphenyltin compound and at 128.23-142.39 ppm for triphenyltin compound respectively.

As for compound 3 and 4, the ^{13}C NMR spectra showed signals around 33 and 60 ppm for terminal methyl carbon and methylene carbon bound to nitrogen (N-CH_2) whilst the signals for methylene carbon next to phenyl ring in the ligand resonated at 44.5 ppm. The carbon in NCS_2 moiety for both diphenyltin(IV)- and triphenyltin(IV) *N*-methyl-*N*-phenethyldithiocarbamate compounds were found at 199.64 and 196.61 ppm respectively. The aromatic carbons of phenyl groups were conversely observed at 126.8-137.8 and 126.8-142.3 ppm for both compounds respectively. All data are presented in table 4.

The cytotoxicity study showed that our tested compounds induced antiproliferative effect towards K562 cells upon 24 h treatment in concentration-dependent manner. All compounds tested can be classified as very toxic as the IC_{50} values were less than 5μg/ cm^3 (How *et al.,* 2008). These organotin(IV) dithiocarbamate compounds are highly soluble in organic solvents such as DMSO, which has high lipophilic characters that facilitate the transportation of these compounds through the cell membrane (Huang *et al.,* 2009).

Comparing the IC_{50} values, triphenyltin(IV) derivatives exhibited higher cytotoxic effects compared to diorganotin(IV) derivatives when treated at various concentrations. It is well known that organotin(IV) toxicity is directly associated with the number of the

organic moieties present, whereby the highly substituted organotin compounds are more toxic than the low substituted compounds (Cooney and Wuertz, 1989). Besides, such higher cytotoxic activity of triphenyltin(IV) derivatives might also be related to the existence of free coordination sites around tin(IV) atoms given that Sn(IV) are five-coordinated compared to six-coordinated in diphenyltin compounds (Hadjikakou and Hadijiliadis, 2009). The relatively stable ligand-Sn bonds, e.g., Sn–N and Sn-S and their slow hydrolytic decomposition also play as contributing factors that characterized the structures of all organotin-antiproliferative active compounds (Hadjikakou and Hadijiliadis, 2009). It ensures the perfect timing for the compounds to reach their targeted site.

The present findings produced here are preliminary; therefore, warrants further mechanistic study on the anti-leukemic activities of these compounds. Determination of the mode of cell death either through apoptosis or necrosis should be conducted further, as inducing apoptosis is a vital character for good anticancer agent. Targeting apoptosis is also effective regardless the type of cancer, as apoptosis evasion is a hallmark of cancer (Pfeffer and Singh, 2018). There are many anticancer drugs that target various stages in both the intrinsic as well as extrinsic pathways (Lin and Zhu, 2017). Any stage in the pathways can be targeted for treatment; however, there is no indication of which target is most effective. As more apoptosis-inducing anticancer drugs are designed, the most effective targets will be determined (Pfeffer and Singh, 2018). Besides that, in this study we limited the antiproliferative study on K562 leukemic cells, thus it is recommended to screen the effects of compounds against different panels of human cells lines such as breast cancer (MCF7), colon cancer (HT-29), and cervical cancer (HeLa) cell lines as the compounds might express different cytotoxicity towards different cancer types.

CONCLUSION

Four new organotin(IV) dithiocarbamate compounds namely diphenyltin(IV)- and triphenyltin(IV) *N*, *N*-bis(2-ethoxyethyl)dithiocarbamate and diphenyltin(IV)- and triphenyltin(IV) *N*-methyl-*N*-phenethyldithiocarbamate were successfully synthesized and characterized. These compounds which were then tested against K562 cells for their antiproliferative activity showed a very promising potential as they were able to induce cytotoxicity against leukemic cell line at low concentration and were classified as very toxic with IC_{50} less than 5 µg/cm^3. The cytotoxicity elicited by these compounds was also relatively better than the commercial drug, imatinib. However, in-depth studies are still obligatory to investigate the underlying mechanism of action induced by these new organotin(IV) dithiocarbamate compounds.

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