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Use of Novel Triphenyltin (IV) Dithiocarbamate Compounds in Assessing the Cytotoxicity and Mode of Cell Death of Acute Lymphoblastic Leukemia Cell Lines, CCRF CEM (CCL-119)

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Abstract: Chemotherapy and radiotherapy are often used to treat Acute Lymphoblastic Leukemia (ALL). However, the resistance problem of treatment using the current drug in ALL patients has decreased the effectiveness of such therapy. Therefore, a study needs to be conducted to identify the potential of new anticancer agents. Organotin (IV) dithiocarbamate, an organometallic compound, causes toxic effects on cancer cells *in vitro* and *in vivo*. This study examines the cytotoxic effects and mode of cell death of novel organotin (IV) dithiocarbamate compounds of triphenyltin (IV) diisopropyldithiocarbamate (compound 1), triphenyltin (IV) diallyldithiocarbamate (compound 2) and triphenyltin (IV) diethyldithiocarbamate (compound 3) on the acute lymphoblastic leukemia cell line, CCRF CEM (CCL-119). An MTT assay was used for the determination of the cytotoxicity of the compounds by treating cells with compounds 1-3 at the highest concentration of 10 µm for 24 h. The induction of the mode of cell death for compounds 1, 2, and 3 were identified using Annexin V-FITC/PI assay. From the results, all triphenyltin (IV) dithiocarbamate compounds have substantial cytotoxic effects with IC_{50} values between 0.18-0.20 µm. The chemicals induced apoptosis cell death in CCL-119 cells, based on the determination of cell death mode. However, statistical analysis showed that only apoptotic cell death for treatment with compounds 1-2 is significant compared to negative controls. In conclusion, all these compounds have a high cytotoxicity effect and are able to cause cell death via apoptosis in CCL-119 cells.

Keywords: IC_{50}, Apoptosis, CCL-119, Acute Lymphoblastic Leukemia, Triphenyltin (IV) Dithiocarbamate, MTT Assay

Introduction

Cancer is the second worldwide cause of death, which killed 9.6 million people in 2018, including 16,000 in Malaysia. According to the Malaysia National Cancer Registry Report (MNCRR) 2012-2016, the most prevalent malignancies in children aged 0-14 years are leukemia and spinal cord cancer, while lymphoma cancer is more common in adolescents aged 15-24. The subject of this research is leukemia cancer and according to the Ministry of Health Malaysia, there are two types of leukemia which are acute and chronic. Acute Lymphoblastic Leukaemia (ALL) is the most frequent hematological cancer among children (Sengupta *et al*., 2007; Terwilliger and Abdul-Hay, 2017).

Patients with these types of cancer need intensive care and therapy and treatment using current conventional methods mainly causes various effects. However, the effects, including acute toxicity and slow recovery, have affected the effectiveness of treating cancer (Raetz and Teachey, 2016). Those effects are gastrointestinal toxicity, hepatotoxicity, renal toxicity, peripheral neurotoxicity, myopathy skeletal toxicity, and cardiotoxicity (Zawitkowska *et al*., 2019). As a result, many researchers started their research to evaluate if organometallic can replace the existing anticancer medications (Gasser *et al*., 2011; Zhang and Sadler, 2017).

Organotin compounds have tin atoms covalently bonded to one or more organic substituents (C-Sn), for instance, methyl, ethyl, butyl, propyl, phenyl, and octyl

(Simanjuntak *et al*., 2019). Organotin compounds can be further categorized into four groups depending on the number of carbon tin bonds: Monoorganotin ($RSnX_3$), organotin (R_2SnX_2), tri organotin (R_3SnX), and tetraorganotin (R_4Sn) (Simanjuntak *et al*., 2019). Methyl, butyl, octyl, or phenyl can be the R group in organotin compounds, whereas carboxylate, chloride, fluoride, hydroxide, or oxide can be the X group (Hoch, 2001).

These organotin compounds and their derivatives have the potential as therapeutic agents to treat cancer (Gielen, 2002; Alama *et al*., 2009). Furthermore, a novel study that has been conducted found that triphenyltin (IV) dithiocarbamate compounds are effective against several types of human cancer (Awang *et al*., 2011; 2014). In addition, researchers in the same area stated that this compound has a high potential to be an anticancer agent against cell lines because its IC_{50} is less than 1 µm. The data can be strengthened by most studies conducted on organotin compounds against various types of tumor cells that proved these compounds are useful as antitumor agents (Amir *et al*., 2014; Awang *et al*., 2011; Gleeson *et al*., 2008; Kamaludin *et al*., 2017).

Hence, the assessment of triphenyltin (IV) dithiocarbamate compounds to combat cancer cells and deal with drug resistance in treating ALL is essential. Therefore, this study intends to evaluate the potential of triphenyltin (IV) dithiocarbamate in the inhibitory activity of ALL cancer cells in humans. Currently, there is no study done and tested using this novel triphenyltin (IV) dithiocarbamate compound on ALL cells. Triphenyltin (IV) diisopropyldithiocarbamate, triphenyltin (IV) diallyldithiocarbamate, and triphenyltin (IV) diethyldithiocarbamate (compounds 1-3, respectively) were utilized in this research. This study provides a better understanding of the impact of triphenyltin (IV) dithiocarbamate compounds, particularly on leukemia, which is important in childhood age.

Materials and Methods

Preparation of Stock Compounds

Table 1 shows the important characteristic of compounds 1-3. Approximately 0.0053, 0.0052, and 0.0050 g of compounds 1-3 (Fig. 1-3, respectively) were dissolved in 1 mL of Dimethyl Sulphoxide (DMSO) to prepare 10 mm stock solutions of each compound. After that, the stock solutions were kept at -20°C and diluted to the required concentration before treating the cells. This study employed Menadione (MENA) as a positive control. About 0.0086 g of MENA was dissolved in 1 mL of DMSO to prepare a 50 mm stock solution. All stock solutions were stored at -20°C until treatment took place.

Cell Lines

CCL-119 was acquired from the American Type Culture Collection (ATCC) (Rockville, MD USA), and the cell line was cultivated at the biotechnology laboratory, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur.

Preparation of Cell Culture

CCL-119 cell lines were grown in Roswell Park Memorial Institute (RPMI) 1640 (sigma Aldrich, USA). A sterile laminar flow chamber was used to cultivate the cell lines to avoid any contamination. Then, 10% Foetal Bovine Serum (FBS) was used to enrich the RPMI 1640 media and 1% penicillin streptomycin was added to the media. All incubations in this study were done in an environment of 37°C and 5% carbon dioxide (CO_2). The cell growth, morphology, and confluence of the cell were observed every day using an inverted microscope. After 2-3 days, the subculturing procedure was performed by removing the cell suspension in the respective T75 flask, followed by centrifugation for 5 min at 1,500 rpm. Following the removal of the supernatant, the fresh media containing the suspended cell pellet was transferred into a new labelled T75 flask containing an adequate volume of the medium.

Cell Viability Assessment

The screening of compounds 1-3 was conducted on CCL-119 cell lines in the presence of the MTT assay (i.e., 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Mosmann, 1983). Those compounds used had to undergo a series of serial dilutions where the highest concentration of 10 µm. The positive and negative controls for this assay were MENA and untreated cells, respectively. A 96-well microplate was used for seeding the CCL-119 cell lines at a density of 1×10^6 mL^{-1}, followed by incubation at 37°C in 5% carbon dioxide. After 24 h incubation, each well was added 20 µL of MTT. Next, the plate was kept in an incubator for 4 h. Upon completion, the formazan crystal was thoroughly dissolved by withdrawing 180 µL of supernatant and replacing it with 180 µL of DMSO.

Table 1: Important characteristics of compounds 1, 2 and 3

Compound	Molecular formula	Physical form	Yield (%)	Melting point (°C)
1	$C_{25}H_{29}NS_2Sn$	White powder	47.03	164.6-167.0
2	$C_{25}H_{25}NS_2Sn$	White powder	44.52	181.6-183.0
3	$C_{23}H_{25}NS_2Sn$	White powder	56.50	144.4-145.9

Source: Haezam *et al*. (2020)

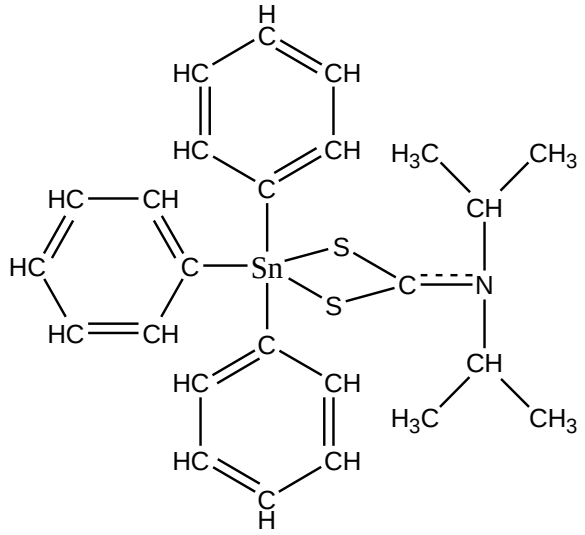

Fig. 1: Chemical structure of triphenyltin (IV) diisopropyldithiocarbamate (compound 1)

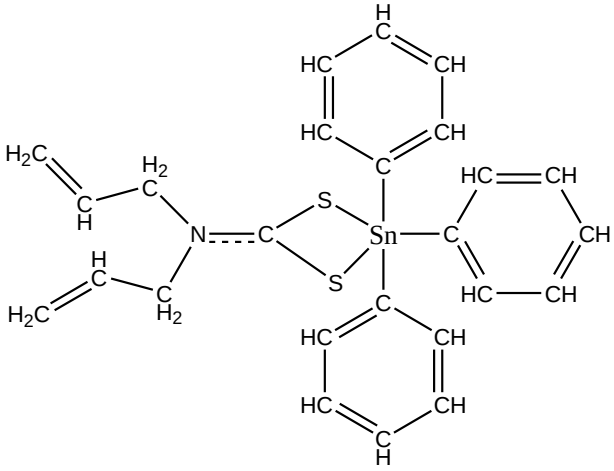

Fig. 2: Chemical structure of triphenyltin (IV) diallyldithiocarbamate (compound 2)

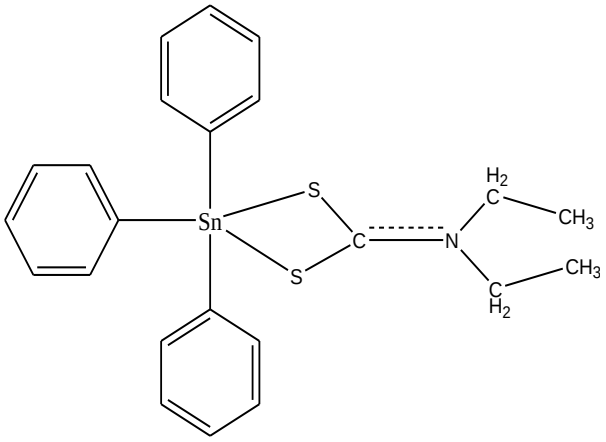

Fig. 3: Chemical structure of triphenyltin (IV) diethyldithiocarbamate (compound 3)

The plate was reincubated for 15 min. Following that, a BIO-RAD microplate reader (iMark) at 570 nm was used to evaluate the results. A plot of the percentage of viable cells (%) against compound concentrations was produced and the IC_{50} values were determined. The IC_{50} values represent the inhibition of 50% in treated cell population activity compared to the negative control.

Mode of Cell Death Determination

The manner of cell death was determined using Annexin V/FITC-PI or the externalization of phosphatidylserine. A six well plate was used for seeding the CCL-119 cell lines at a concentration of 1×10^6 cells/mL, followed by treatment using the three drugs at their respective IC_{50} concentrations. Then, the plate was incubated for 24 h. After harvesting 500 µL of cell suspension and transferring it into a labelled microcentrifuge tube, the sample was subjected to centrifugation for 5 min at 4°C and 2,500 rpm. Upon completion of the first centrifuge process, the supernatant was discarded and replaced with 500 µL cold PBS and the tube was centrifuged again at the same rotation and condition as before. Next, after the removal of the supernatant, the samples were added with 2.0 µL of Annexin V-FITC and 150 µL of Annexin V binding buffer in a dark condition, followed by incubation at room temperature for 15 min. Subsequently, after the addition of 5.0 µL of propidium iodide, the samples were incubated for 2 min at room temperature. Upon completion, the samples were added with 300 µL of Annexin V binding buffer and transferred into falcon tubes. In the final step, a BD-FACS Canto II flow cytometer was used to evaluate the samples.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) software version 26.0 was recruited to analyze the data. All the data were collected in triplicates and expressed as the mean ± Standard Error of Mean (SEM) from three different trials. The statistical differences were examined using a one-way Analysis of Variance (ANOVA). The results can be expressed as a significant difference at a $p<0.05$ value.

Results and Discussion

This study determines the cytotoxic effect induced by compounds 1-3 on CCL-119 using the MTT assay. Based on Figs. 4-6, compounds 1-3 induced cytotoxicity and inhibited the activity of 50% cell population at 0.20, 0.19, and 0.18 µm, respectively. The summary of IC_{50} values for all compounds and MENA is presented in Table 2.

The percentages of viable, apoptotic, and necrotic CCL-119 cells treated with compounds 1-3 and MENA at their respective IC_{50} concentrations are presented in Fig. 7. Based on the results, compound 2 achieved the highest percentage of apoptotic cell death. The percentage of apoptosis was 53.1% after treatment for 24 h. Then

followed by triphenyltin(IV) diisopropyldithiocarbamate (compound 1) which showed an apoptotic percentage of 32.0% and finally, triphenyltin(IV) diethyldithiocarbamate (compound 3) which induced the lowest percentage of apoptotic cell death in the cell population which was at 23.3%.

Haezam *et al*. (2020) synthesized triphenyltin(IV) molecules and dithiocarbamate ligands into a compound that has the potential as an anticancer agent for various types of continuous cells including ALL cancer cells, CCL-119. Recently, many researchers have studied triphenyltin(IV) dithiocarbamate compounds because this compound has the potential to become a new anticancer agent (Awang *et al*., 2015). According to Goodman *et al*. (2019), ligands are used to increase the efficiency of catalysts and accelerate the discovery of new reactivity modes. Moreover, organometallic complexes' structure, properties, and reactivity are also highly dependent on their ligand environment (Movassaghi *et al*., 2018). James *et al*. (1992) also stated that the combination of two biologically active entities in the same molecule could increase toxicity and inhibit the development of species that can tolerate a specific condition. Thus, the presence of lipophilic groups that facilitate transport through lipid membranes is considered as one of the factors for the higher toxicity of organometallic compounds compared to inorganic compounds (Craig, 2003; Markovic *et al*., 2020).

Table 2: IC_{50} values for triphenyltin (IV) diisopropyldithiocarbamate (compound 1), triphenyltin (IV) diallyldithiocarbamate (compound 2), and triphenyltin (IV) diethyldithiocarbamate (compound 3) against CCL-119 cells

Compound	IC_{50} value (IC_{50} ± SEM), µm
Compound 1	0.20±2.78
Compound 2	0.19±5.40
Compound 3	0.18±2.15
MENA	4.10±5.24

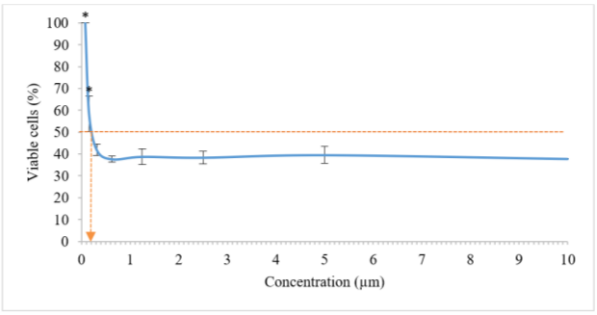

Fig. 4: The IC_{50} value of compound 1 for CCL-119 cell lines after 24 h treatment with the highest concentration of 10.0 µm. The data indicate the percentage of viable cells (%) ± SEM based on three successive experiments. *indicates a significant difference ($p<0.05$) from the negative control

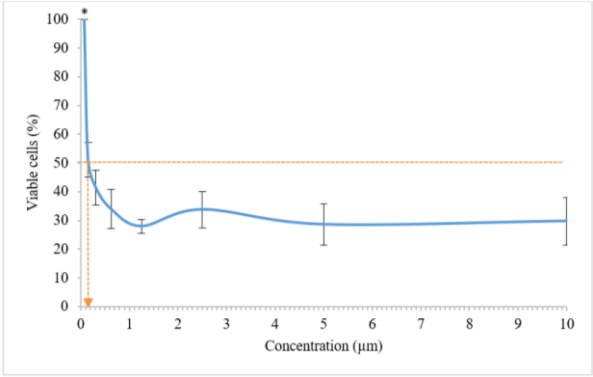

Fig. 5: The IC_{50} value of compound 2 for CCL-119 cell lines after 24 h treatment with the highest concentration of 10.0 µm. The data indicate the percentage of viable cells (%) ± SEM based on three successive experiments. *Indicates a significant difference ($p<0.05$) from the negative control

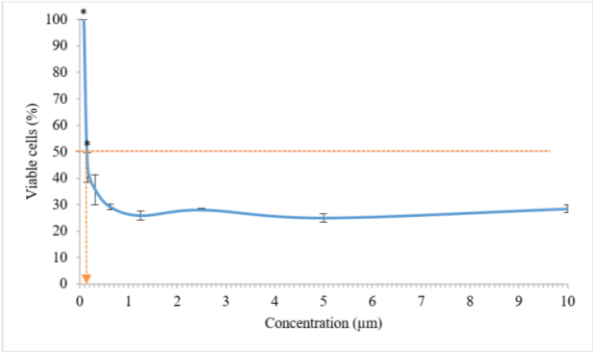

Fig. 6: The IC_{50} value of compound 3 for CCL-119 cell lines after 24 h treatment with the highest concentration of 10.0 µm. The data indicate the percentage of viable cells (%) ± SEM based on three successive experiments. *Indicates a significant difference ($p<0.05$) from the negative control

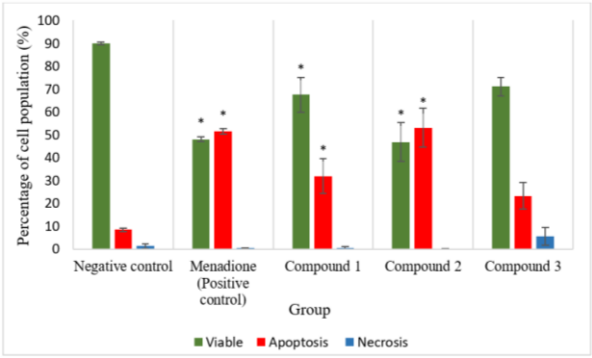

Fig. 7: The percentage of viable, apoptotic, and necrotic cells in CCL-119 cells treated with compounds 1-3 at IC_{50} concentrations for 24 h. The data indicate the mean (% ± SEM) based on three successive experiments. *Indicates a significant difference ($p<0.05$) from the negative control

The MTT experiment indicated that compound 3 was more cytotoxic to CCL-119 cells than compounds 1 and 2 based on the lower IC_{50} value of compound 3 (0.18 μm) than compounds 1 and 2 (0.20 and 0.19 μm, respectively). This study was similar to Syed Annuar *et al*. (2021), who observed that ethyl compounds had superior cytotoxic activity against human lung epithelial cells (A549) and human breast adenocarcinoma (MCF7) cells than other ligands. Koch *et al*. (2009) also observed that compounds having a shorter alkyl substituent group were more cytotoxic, highlighting the importance of this feature for determining their cytotoxicity.

The toxicity potential of organotin compounds depends on strong cell membrane adherence, in which their lipophilic nature determines the mechanism of action (Hanana *et al*., 2014). Its ability to cross membranes allows the compound to penetrate cells easily. According to Iqbal *et al*. (2016); Jan (2019), triorganotin compounds are stimulants to apoptosis in various cell types and there are two main pathways of cell death by apoptosis due to cytokines and mechanisms that affect mitochondrial activity.

Based on the results, compounds 1-3 caused CCL-119 cell cytotoxicity within 24 h. The respective cell line's IC_{50} values were less than 1.0 μm for those substances, indicating strong cytotoxic effects. Moreover, triphenyltin (IV) dithiocarbonate compounds could induce apoptosis at their respective IC_{50} concentrations after 24 h treatment.

Conclusion

In conclusion, this study found that organotin (IV) dithiocarbamate derivative compounds (compounds 1-3) induced cytotoxic effects on ALL cell lines (CCL-119) within 24 h of treatment. All of these compounds have high cytotoxic effects. This is because the concentration required to inhibit the activity of leukemia cells is very low which was less than 1.0 μm. All compounds influenced cell death within 24 h of treatment based on the mode of cell death through the apoptosis assay. The findings of this study have shown that triphenyltin(IV) diallyldithiocarbamate (compound 2) is the compound with the highest cytotoxic properties among the three compounds as it was able to cause the highest cell death of 53.1% of cell populations at a concentration of 0.19 μm.

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Author's Contributions

Normah Awang: Contributed to the written of the manuscript.

Nur Hidayah Hasrin, Rasyiqin Rasli and Sharifah Nadhira Syed Annuar: Participated in all experiments.

Nurul Farahana Kamaludin: Coordinated the data analyzed.

Asmah Hamid: Designed the research plan and organized the study.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all authors have read and approved the manuscript and that there are no ethical issues.

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