ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(3):
Pg. 749-757

Elucidating the Suppressive Capabilities of Novel Organotin(IV) Compounds Derived from *N*-Methyl-*N*-benzyl-dithiocarbamate Ligands: Assessing their Cytotoxicity Effects on Human Leukemic Cells (Jurkat E6.1)

NORMAH AWANG[1]*, NURUL AMALINA ABD AZIZ[1], NUR ZAIDATUL SYABIHA SALIHIN[2] and NURUL FARAHANA KAMALUDIN[1]

[1]Center for Toxicology and Health Risk Studies, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia.
[2]Environmental Health and Industrial Safety Program, Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia.
*Corresponding author E-mail: norm@ukm.edu.my

http://dx.doi.org/10.13005/ojc/410306

(Received: February 07, 2025; Accepted: May 01, 2025)

ABSTRACT

Leukemia is a blood cancer characterized by the excessive production of abnormal white cells in both the bone marrow and circulatory system. Effective treatment is often hindered by the development of resistance to chemotherapy. This study evaluates the cytotoxic impact of three newly synthesized organotin(IV) complexes (1-3)-dibutyltin(IV), diphenyltin(IV), and triphenyltin(IV)-derived from *N*-methyl-*N*-benzyldithiocarbamate on Jurkat E6.1 leukemia cells. MTT assays determined IC_{50} values of 0.23 ± 0.01 µM, 0.58 ± 0.05 µM, and 0.28 ± 0.02 µM for Compounds 1, 2, and 3, respectively. Apoptotic morphological changes were observed after 24-hour exposure. Notably, Compound 1 displayed selective toxicity toward Jurkat cells versus normal WIL2-NS cells, suggesting its potential as a lead compound for future anticancer development.

Keywords: Cytotoxicity, Dithiocarbamates, Jurkat E6.1 leukemia, Organotin(IV).

INTRODUCTION

In 2020, leukemia contributed to roughly 2.5% of newly diagnosed cancer cases and was responsible for about 3.1% of global cancer mortality (Sung *et al.,* 2021). Its incidence and death rates vary depending on age, gender, and geographic region (Lim *et al.,* 2014). The peak incidence occurs in young children aged 0–5 years (9.24%) and older adults between 70–74 years (8.92%), while individuals over 60 account for more than half of leukemia-related deaths (57.56%) (Du *et al.,* 2022). Although developed countries show higher diagnosis rates, the mortality burden tends to be greater in developing nations (Tebbi, 2021). Established risk factors include tobacco use, radiation exposure, contact with hazardous chemicals such as benzene, prior chemotherapy treatments, and inherited conditions like Down syndrome (Ansari *et al.,* 2023).

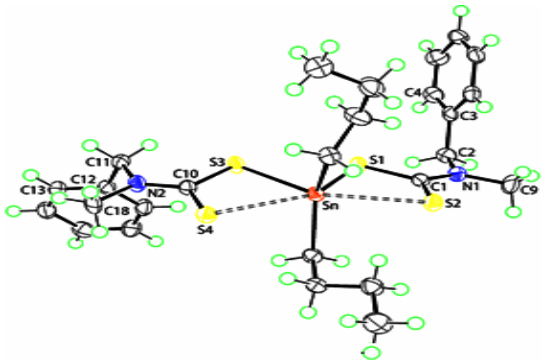
Leukemia encompasses a group of rapidly progressing malignancies that affect the blood

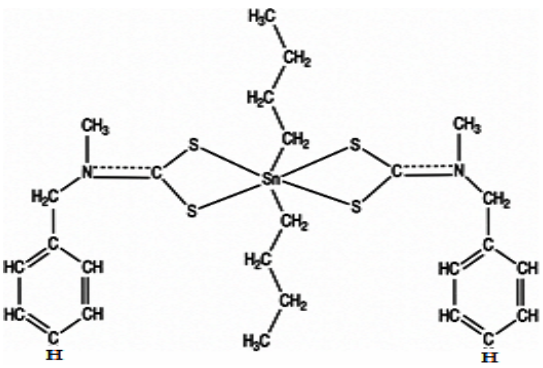
and bone marrow, compromising immune function (Dong *et al.,* 2020). It may present as either acute or chronic, depending on disease progression and prognosis (Ahmed *et al.,* 2019). Leukemia may present as acute or chronic, and is further classified by lymphoid or myeloid lineage, with ALL being the most prevalent pediatric type (Du *et al.,* 2022; Kakaje *et al.,* 2020). Acute lymphoblastic leukemia (ALL) was reported as the most prevalent pediatric cancer, often responds favorably to treatment. It arises from genetic alterations in B or T lymphoid progenitors, resulting in the excessive accumulation of immature blast cells in the bone marrow (Yasuj *et al.,* 2020).

ALL treatment generally involves remission induction, consolidation, intensification, and maintenance phases. Chemotherapy is the cornerstone of initial treatment, often supplemented with targeted therapies throughout the process (Aureli *et al.,* 2023). Chemotherapeutic agents disrupt cancer cell division through various mechanisms including DNA cross-linking inhibition, topoisomerase activity interference, and microtubule destabilization during mitosis (Wilkinson and Sumar, 2022). Daunorubicin, a frequently used anthracycline antibiotic, intercalates into DNA and hampers macromolecule synthesis (Al-Aamri *et al.,* 2019). However, its side effects-including nausea, mucositis, hair loss, and diarrhea-can limit its efficacy (Roman Diaz *et al.,* 2024). Moreover, resistance to chemotherapy presents a significant obstacle in treating T-cell acute lymphoblastic leukemia (T-ALL), with relapse rates of 20% in children and 40% in adults, and survival rates under 7% in relapsed cases (Fielding *et al.,* 2007; Pui *et al.,* 2008).

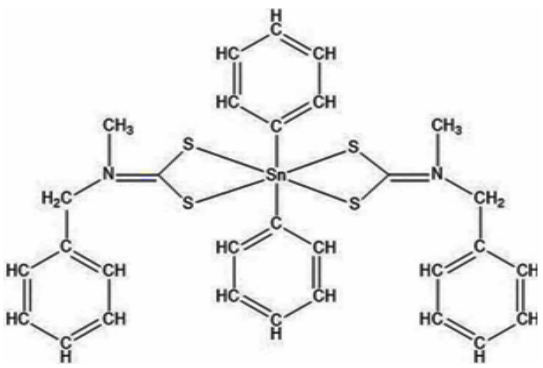
In light of these challenges, organotin(IV) compounds have garnered attention for their potent anticancer properties (Abd Aziz *et al.,* 2023a). These compounds often demonstrate more favorable toxicity profiles compared to conventional platinum agents (Attanzio *et al.,* 2020). Their catalytic and redox capabilities, structural versatility, and ability to interact with biologically active molecules contribute to their effectiveness (Rabiee *et al.,* 2019). The main mechanism of exerting anticancer effects through organotin(IV) compounds is the induction of apoptosis (Jakši, 2012; Stathopoulou *et al.,* 2021; Syed Annuar *et al.,* 2021, 2022). Due to their electrophilic properties, these compounds readily bind to biomolecules rich in electrons, such as phospholipids, ATP, and nucleic acids, disrupting essential cellular processes (Abd Aziz *et al.,* 2023a). Additionally, organotin(IV) compounds can interact with DNA's phosphate backbone, causing structural changes that lead to cell death (Yusof *et al.,* 2019).

Dithiocarbamate ligands have emerged as promising agents in cancer treatment, owing to their capacity to influence critical proteins associated with apoptosis, oxidative stress, transcription, and protein degradation (Sofuoglu and Kosten, 2005). Besides, dithiocarbamates can inhibit catalase activity, leading to an increase in oxidative species and facilitating apoptosis (Fu *et al.,* 2019). This research examines the cytotoxic properties of newly developed organotin(IV) compound derived from *N*-methyl-*N*-benzyldithiocarbamate ligands specifically on Jurkat E6.1 leukemia cells.

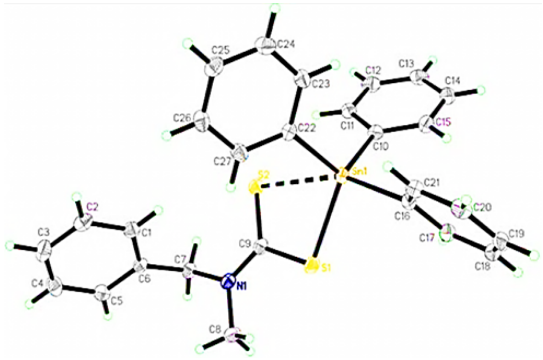




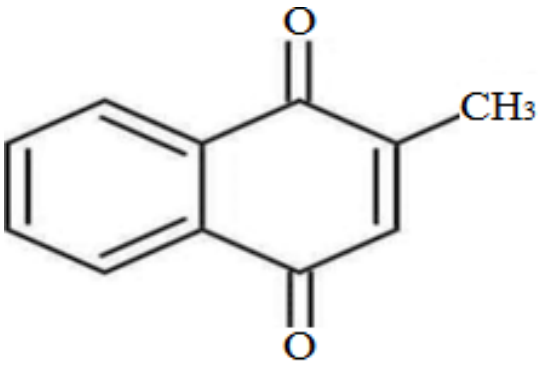
(a)



(b)



(c)



(d)

Fig. 1(a). The crystallographic structure of dibutyltin(IV) *N*-methyl-*N*-benzyldithiocarbamate (Compound 1) (Abd Aziz *et al.,* 2023b), (b) The chemical structure of diphenyltin(IV) *N*-methyl-*N*-benzyldithiocarbamate (Compound 2), (c) The crystallographic representation of triphenyltin(IV) *N*-methyl-*N*-benzyldithiocarbamate

MATERIALS AND METHODS

Stock Solution Preparation

To prepare the stock solutions, precise quantities of each compound were measured: 0.0125 g for Compound 1, 0.0109 g for Compound 3, and 0.0200 g for Compound 2. These were then dissolved in dimethyl sulfoxide (DMSO). Compounds 1 and 3 were each dissolved in 1 mL of DMSO, while Compound 2 required 6 mL of DMSO for complete dissolution. The resulting stock solutions had concentrations of 20 mM for Compounds 1 and 3, and 5 mM for Compound 2. All stock solutions were stored at 4°C to preserve stability and purity until needed. Prior to experimentation, the stock solutions were diluted to the desired concentrations using the appropriate media.

Cell Line and Culture Conditions

Both Jurkat E6.1 and WIL-2NS cell lines were sourced from ATCC and cultured at the Biocompatibility and Biotechnology Laboratory, UKM, Kuala Lumpur. RPMI-1640 medium was used to culture both cells following ATCC guidelines, and incubation was carried out at 37°C under humidified conditions with 5% CO.

MTT Cytotoxicity Assay

MTT assay was employed to evaluate the cytotoxicity of the compounds on leukemic cells (Jurkat E6.1) and non-leukemic cells (WIL-2NS), which were plated at 2×10 cells/mL in 96-well flat-bottom plates. Compounds 1 and 2 were used at 5 µM, whereas Compound 3 was applied at 10 µM, with a 24-h treatment duration. The untreated cells in this experiment served as the negative control, while menadione (20 µM) as the positive control. After treatment, the cells were incubated with the MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] for 4 h, which viable cells reduce to purple insoluble formazan. Subsequently, the insoluble formazan crystals were solubilized using DMSO. The intensity of the color formed was measured (570 nm) to evaluate cell viability, and IC_{50} values were derived from the resulting data.

Cell Morphology Assessment

Jurkat E6.1 cells were treated based on their IC_{50} concentrations determined from the MTT assay, with the objective of inducing approximately 50% cell death (CD_{50}) over a 24-h period. The untreated cells in this experiment served as the negative control, while menadione as the positive control. Cell seeding followed the same protocol as

the MTT assay but was performed in 6-well plates. After incubation, morphological changes associated with cell death were observed under an inverted light microscope at 40× magnification.

Selectivity Index Calculation

The selectivity index (SI) was determined by dividing the IC_{50} value obtained for WIL2-NS cells by the corresponding IC_{50} value for Jurkat E6.1 cells, as measured in the MTT assay. This ratio reflects the compound's preference for targeting cancerous versus normal cells. A higher SI indicates improved selectivity towards cancer cells, whereas a lower SI suggests increased toxicity to normal cells. This parameter helps evaluate the therapeutic potential and safety margin of the tested agents.

Statistical Analysis

SPSS (v26.0) was used for data analysis, with one-way ANOVA employed to identify significant differences in cell viability percentages and compound concentrations among the various treatment groups. The findings were derived from three separate experiments and were deemed statistically significant when p was less than 0.05.

RESULTS AND DISCUSSION

The three compounds studied are novel derivatives of organotin(IV) *N*-methyl-*N*-benzyldithiocarbamate. The synthesis method used in this study follows the procedure previously described for Compound 1 in our earlier work (Abd Aziz *et al.,* 2023b). As the focused of this study is to elucidate the cytotoxic effects of these compounds on K562 cells, we provide only a brief summary of their key spectroscopic features (^{1}H and ^{13}C NMR) to support their novelty and confirmed their structures. The ^{1}H NMR spectra showed expected singlets for methylene protons (δ 5.060–5.148 ppm) and aromatic multiplets (δ 7.249–8.000 ppm) (Haezam *et al.,* 2021). Signals for protons bound to Sn(IV) were observed in the ranges of δ 0.972–2.127 ppm (Compound 1), δ 7.270–7.522 ppm (Compound 2), and δ 7.247–7.491 ppm (Compound 3) (Mohamad *et al.,* 2016). The ^{13}C NMR spectra supported these findings, with the thioureide carbon resonating at δ 197–202 ppm, methylene carbon at δ 59.95–61.64 ppm, and methyl carbon at δ 41.77–42.90 ppm. Aromatic carbons appeared in the range of δ 127–151 ppm (Abd Aziz *et al.,* 2023a). Additionally, the crystallographic data of Compound 1 confirmed a skewed trapezoidal bipyramidal geometry (Abd Aziz *et al.,* 2023b), whereas Compound 3 exhibited a trigonal bipyramidal geometry. Full crystallographic data and detailed structural interpretation will be reported in a separate publication focused on the synthesis and molecular characterization of these compounds.

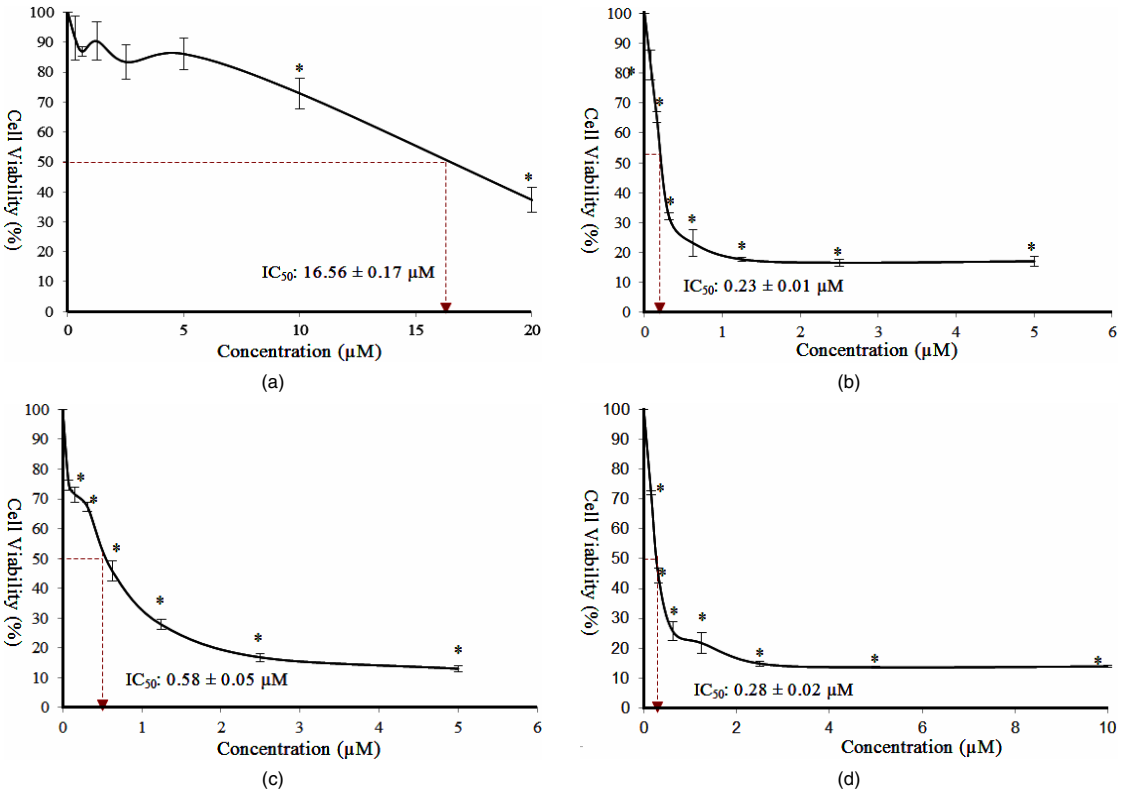
The cytotoxic impacts of these compounds on Jurkat E6.1 and WIL2-NS cells are illustrated in Fig. 2. The median inhibitory concentrations (IC_{50}) for Compound 1 to 3 for both cell lines are detailed in Tables 1 and 2. Each of the compounds significantly reduced cell viability at concentrations of 5 µM and 10 µM after a 24-h exposure. The MTT assay revealed IC_{50} values of 0.23 µM, 0.58 µM, and 0.28 µM for Compounds 1, 2, and 3 in Jurkat E6.1 cells, respectively. For WIL2-NS cells, the IC_{50} values were found to be 0.86 µM for Compound 1, 0.49 µM for Compound 2, and 0.39 µM for Compound 3. Bich-Loan *et al.,* (2021) classified these compounds as highly toxic, supported by their low IC_{50} values. These low IC_{50} values classify the compounds as highly cytotoxic (Bich-Loan *et al.,* 2021), suggesting they exert strong biological effects.

Compounds 1 and 3 exhibited significant toxicity to Jurkat E6.1 cells across all tested concentrations: 0.08 µM to 5.00 µM for Compound 1 and 0.16 µM to 10.00 µM for Compound 3. Compound 2 showed significant toxicity from 0.16 µM to 5.00 µM. For WIL2-NS cells, Compound 1 was notably toxic at 0.63 µM and higher, while Compound 2 showed consistent toxicity across all concentrations tested. Compound 3's toxicity was significant from 0.16 µM up to 10.00 µM. Among the three, Compound 1 exhibited the most potent cytotoxicity towards Jurkat E6.1 cells, reflected in

its lowest IC_{50} value of 0.23 µM. This heightened effect is attributed to its shorter alkyl chain on the tin(IV) atom, which enhances antioxidant activity and cytotoxic regulation (Koch, Basu Baul, and Chatterjee, 2009). Studies indicate that shorter alkyl chains improve both antioxidant properties and cytotoxicity (Verma *et al.,* 2016). Similarly, Kamaludin *et al.,* (2013) reported significant cytotoxic effects of dibutyltin(IV) butylphenyldithiocarbamate on Jurkat E6.1 and K562 cells, with IC_{50} values falling below 5 µg/mL (<8.70 µM). In their research, the IC_{50} values for Jurkat E6.1 cells treated with dibutyltin(IV) butylphenyldithiocarbamate ranged from 0.50 to 0.80 µM, while for K562 cells, they varied from 3.90 to 5.30 µM.

In contrast, Compound 3 showed greater cytotoxicity compared to Compound 2, likely due to its increased number of phenyl groups, which enhances lipophilicity. Increased lipophilicity facilitates stronger interactions with biological membranes, which are primarily composed of lipids, thereby promoting cellular uptake and amplifying cytotoxic effects (Hussain *et al.,* 2015; Javed *et al.,* 2016). This property also improves compound permeability across physiological barriers, such as the gastrointestinal epithelium, and enhances interaction with cellular lipids and proteins, potentially increasing bioavailability (Riley *et al.,* 2001; Alavijeh *et al.,* 2005). Such characteristics are crucial in drug development, where optimizing lipophilicity can improve therapeutic efficacy and minimize adverse effects.

While variations in the alkyl and aryl substituents influence lipophilicity and steric hindrance, the tin(IV) center itself plays a crucial role in the cytotoxic mechanism. Organotin(IV) compounds are recognized for their ability to interact with thiol-containing biomolecules, impairing cellular respiration, producing oxidative species, and activating apoptotic pathways. Notably, triorganotin(IV) compounds, such as Compound 3, may exert stronger biological activity due to their higher coordination flexibility and greater exposure of the Sn(IV) center, which enhances interactions with intracellular targets (Abd Aziz *et al.,* 2023a; Iqbal *et al.,* 2017).



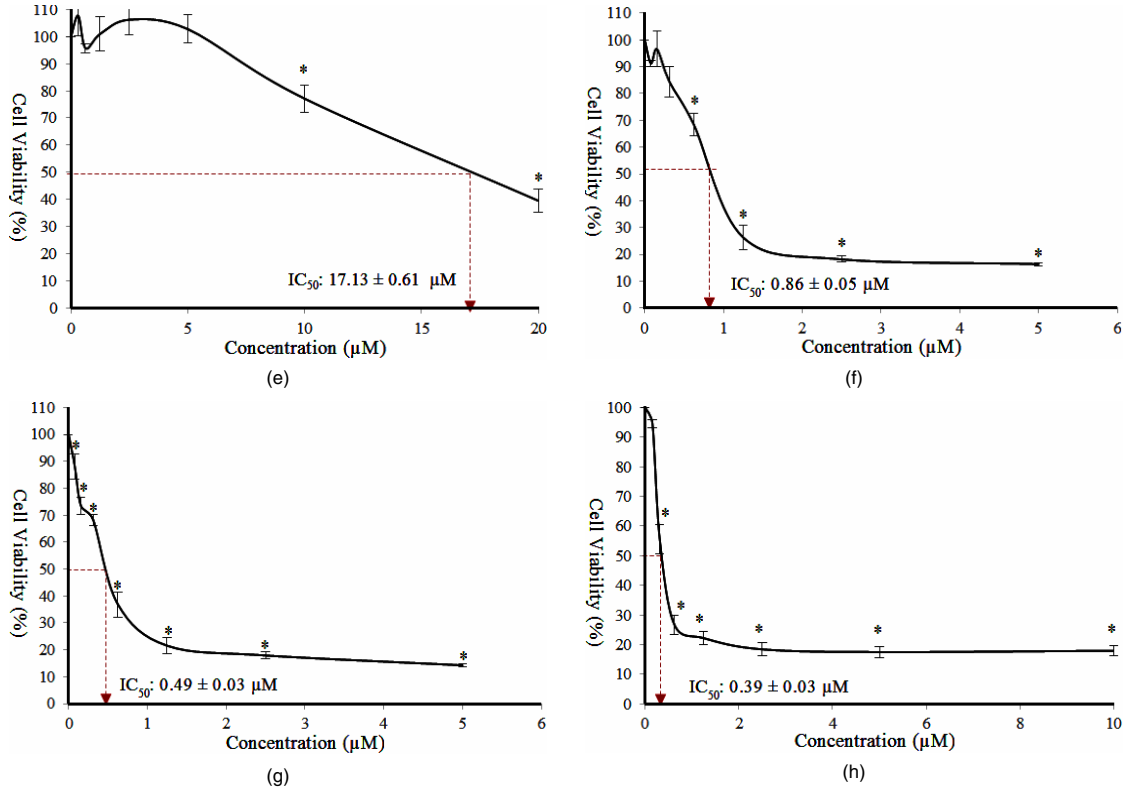


Fig. 2. IC_{50} values for Jurkat E6.1 cells following treatment with (a) menadione, (b) Compound 1, (c) Compound 2, and (d) Compound 3, as well as the IC_{50} values for WIL2-NS cells after treatment with (e) menadione, (f) Compound 1, (g) Compound 2, and (h) Compound 3. Values represent the mean with standard error (± S.E.M.), based on three independent experiments

Table 1: IC_{50} values of Compounds 1, 2, and 3 against Jurkat E6.1 cells

Compound	IC_{50} ± S.E.M. (μM)
1	0.23 ± 0.01
2	0.58 ± 0.05
3	0.28 ± 0.02
Menadione	16.56 ± 0.17

*Significant difference, a p-value of less than 0.05

Table 2: IC_{50} values of Compounds 1, 2, and 3 against WIL2-NS cells

Compound	IC_{50} ± S.E.M. (μM)
1	a0.86 ± 0.05
2	0.49 ± 0.03
3	0.39 ± 0.03
Menadione	17.13 ± 0.61

The selectivity index (SI) of the compounds for cancer cells in comparison to normal cells was evaluated to identify potential cytotoxic agents, with an SI greater than 2 indicating a promising candidate (Badisa *et al.,* 2009). As shown in Table 3, Compound 1 demonstrated the highest selectivity toward Jurkat E6.1 cells with an SI of 3.74, followed by Compound 3 (1.39), while Compound 2 showed the lowest selectivity (0.84). These results indicate that Compound 1 may have tumor-specific properties, highlighting its potential as a promising candidate for further development. Overall, the data underscore the relevance of selective cytotoxicity in the search for effective anticancer agents.

Table 3: Values of selective index for Compounds 1, 2, and 3

Compound	IC_{50} Values (μM)		Selectivity Index
	Jurkat E6.1 Cells	WIL2-NS Cells	
Menadione	16.56	17.13	1.03
Compound 1	0.23	0.86	3.74
Compound 2	0.58	0.49	0.84
Compound 3	0.28	0.39	1.39

A morphological evaluation was conducted on Jurkat E6.1 cells treated with the respective IC_{50} concentrations of Compounds 1-3

(0.23 µM, 0.58 µM, and 0.28 µM, as determined from the MTT assay). Fig. 3 illustrates the morphological alterations observed in Jurkat E6.1 cells after 24 h of exposure to Compounds 1, 2, and 3, along with menadione, which served as the positive control.

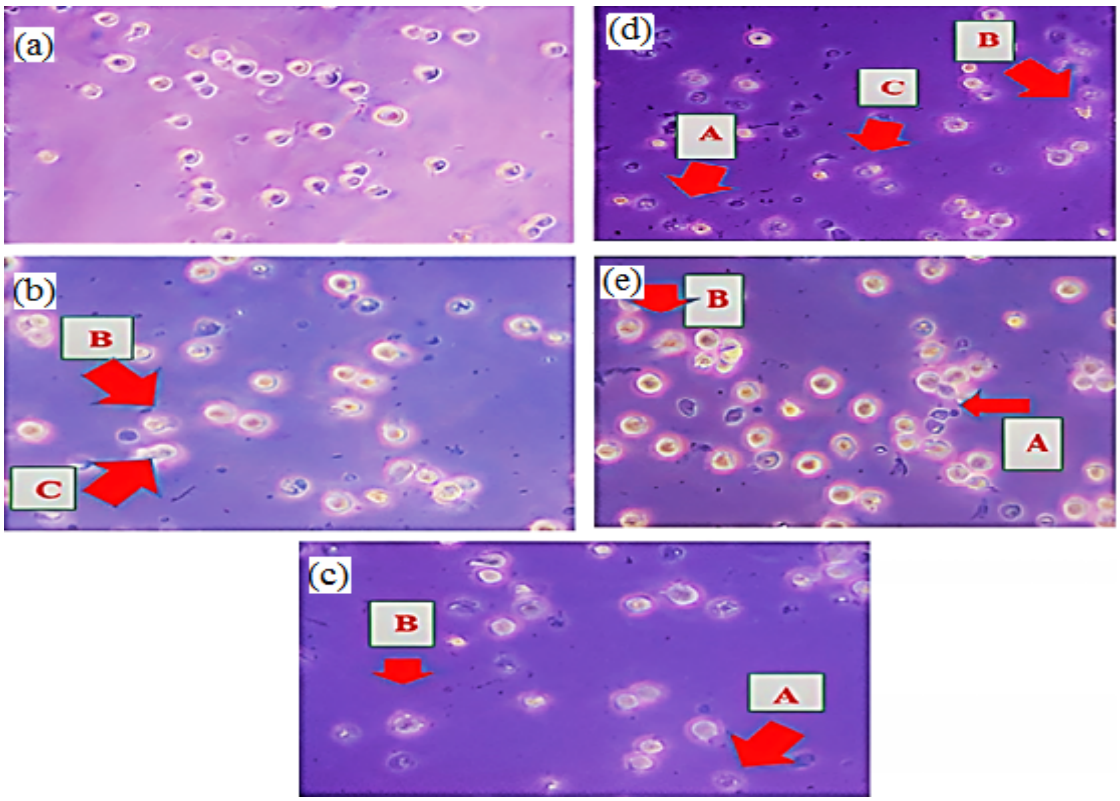


Fig. 3. Morphological alterations in Jurkat E6.1 cells were assessed after 24 h using an inverted microscope (x40). Observations include: (a) untreated cells, (b) menadione-treated, (c) Compound 1, (d) Compound 2, and (e) Compound 3. Key apoptotic features such as apoptotic bodies (A), membrane blebbing (B), and cell shrinkage (C) were noted

After 24 h of treatment, all tested compounds-including menadione-induced morphological signs of apoptosis in Jurkat E6.1 cells, unlike untreated controls. This process is marked by chromatin condensation, DNA breakdown, cellular shrinkage, and membrane blebbing, eventually forming apoptotic bodies (Mills *et al.*, 1998; Zhang *et al.,* 2018). The observations in this study confirm that the compounds activated programmed cell death pathways, with consistent patterns observed across all treatments. These findings align with previous reports on organotin-induced apoptosis in leukemia models (Hamid *et al.,* 2020).

CONCLUSION

This study confirms that organotin(IV) complexes of *N*-methyl-*N*-benzyldithiocarbamate possess cytotoxic potential against Jurkat E6.1 cells. Among the three, Compound 1 displayed the strongest effect and notable selectivity. Apoptotic features were prominent, and the compound's selective action supports its further evaluation in cancer therapy.

ACKNOWLEDGMENT

We express our heartfelt gratitude to the Ministry of Higher Education (MOHE), Malaysia, for sponsoring this research via the Fundamental Research Grant Scheme (FRGS) with grant number FGRS/1/2021/STG04/UKM/02/5. We also express our gratitude to the Faculty of Health Sciences, Universiti Kebangsaan Malaysia, for providingthe laboratory facilities that aided in the completion of this research.

Conflict of interest

All researchers involved in this study have declared that they have no competing interests that could affect the results or interpretation of the findings.

REFERENCES

1. Sung, H.; Ferlay, J.; Siegel, R. L.; Laversanne, M.; Soerjomataram, I.; Jemal, A. & Bray, F., *CA Cancer J. Clin.*, **2021**, *71*, 209-249.
2. Lim, J. Y. S.; Bhatia, S.; Robison, L. L.; Yang, J. J., *Cancer*, **2014**, *120*(7), 955-962.
3. Du, M.; Chen, W.; Liu, K.; Wang, L.; Hu, Y.; Mao, Y.; Sun, X.; Luo, Y.; Shi, J.; Shao, K.; Huang, H.; Ye, D., J. Oncol., 2022, 2022, 1612702.
4. Tebbi, C. K., *Cancers (Basel).,* **2021**, *13*(9), 2256.
5. Ansari, S.; Navin, A. H.; Babazadeh Sangar, A.; Vaez Gharamaleki, J.; Danishvar, S., *Electronics (Switz.),* **2023**, *12*(5), 1116.
6. Dong, Y.; Shi, O.; Zeng, Q.; Lu, X.; Wang, W.; Li, Y.; Wang, Q., *Exp. Hematol. Oncol.*, **2020**, *9*, 14.
7. Ahmed, N.; Yigit, A.; Isik, Z.; Alpkocak, A., *Diagnostics.*, **2019**, *9*(3), 104.
8. Kakaje, A.; Alhalabi, M. M.; Ghareeb, A.; Karam, B.; Mansour, B.; Zahra, B.; Hamdan, O., *Sci. Rep.*, **2020**, *10*(1), 6756.
9. Yasuj, S. R.; Obeidi, N.; Khamisipour, G.; Gharehdaghi, Z.; Zangeneh, Z., *Iran. J. Pathol.*, **2020**, *15*(4), 282-291.
10. Aureli, A.; Marziani, B.; Venditti, A.; Sconocchia, T.; Sconocchia, G., *Cancers (Basel).,* **2023**, *15*(13), 3346.
11. Wilkinson, A. N.; Sumar, N., *Can. Fam. Physician.,* **2022**, *68*(1), 30-34.
12. Al-Aamri, H. M.; Ku, H.; Irving, H. R.; Tucci, J.; Meehan-Andrews, T.; Bradley, C., *BMC Cancer.*, **2019**, *19*(1), 179.
13. Roman Diaz, J. L.; Vazquez Martinez, M.; Khimani, F., *Cancers (Basel).,* **2024**, *16*(3), 677.
14. Pui, C. H.; Robison, L. L.; Look, A. T. *The Lancet.*, **2008**, *371*(9617), 1030-1043.
15. Fielding, A. K.; Richards, S. M.; Chopra, R.; Lazarus, H. M.; Litzow, M. R.; Buck, G.; Durrant, I. J.; Luger, S. M.; Marks, D. I.; Franklin, I. M.; McMillan, A. K.; Tallman, M. S.; Rowe, J. M.; Goldstone, A. H., *Blood.*, **2007**, *109*(3), 944-950.
16. Abd Aziz, N. A.; Awang, N.; Chan, K. M.; Kamaludin, N. F.; Mohamad Anuar, N. N., *Molecules.*, **2023a**, *28*(15), 5841.
17. Attanzio, A.; D'Agostino, S.; Busà, R.; Frazzitta, A.; Rubino, S.; Girasolo, M. A.; Sabatino, P.; Tesoriere, L., *Molecules.*, **2020**, *25*(4), 859.
18. Rabiee, N.; Safarkhani, M.; Amini, M. M., *Rev. Inorg. Chem.*, **2019**, *39*(1), 13-45.
19. Syed Annuar, S. N.; Kamaludin, N. F.; Awang, N.; Chan, K. M., *Food Chem. Toxicol.,* **2022**, *168*, 113336.
20. Syed Annuar, S. N.; Kamaludin, N. F.; Awang, N.; Chan, K. M., *Front. Chem.*, **2021**, *9*, 657599.
21. Jakši, Ž., *Biochem. Biol. Eff. Organotins.*, **2012**, 149-163.
22. Stathopoulou, M. E. K.; Zoupanou, N.; Banti, C. N.; Douvalis, A. P.; Papachristodoulou, C.; Marousis, K. D.; Spyroulias, G. A.; Mavromoustakos, T.; Hadjikakou, S. K., *Steroids.*, **2021**, *167*, 108798.
23. 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., *Int. J. Mol. Sci.*, **2019**, *20*(4), 854.
24. Sofuoglu, M.; Kosten, T. R., *CNS Drugs.*, **2005**, *19*(1), 13-25.
25. Fu, D. J.; Li, J. H.; Yang, J. J.; Li, P.; Zhang, Y. B.; Liu, S.; Li, Z. R.; Zhang, S. Y., *Bioorg. Chem.*, **2019**, *86*, 375-385.
26. Mohamad, R.; Awang, N.; Kamaludin, N. F., *Res. J. Pharm. Biol. Chem. Sci.*, **2016**, *7*(2), 1920–1925.
27. Abd Aziz, N. A.; Awang, N.; Chan, K. M.; Kamaludin, N. F.; Mohamad Anuar, N. N.; Jamaludin, N. A. N.; Tan, Y. S.; Tiekink, E. R. T., Z. Kristallogr. *-N.Cryst. Struct.*, **2023b**, *238*, 15-18.
28. Haezam, F. N.; Awang, N.; Kamaludin, N. F.; Mohamad, R., *Saudi J. Biol. Sci.*, **2021**, *28*(5), 3160–3168.
29. Bich-Loan, N. T.; Kien, K. T.; Thanh, N. L.; Kim-Thanh, N. T.; Huy, N. Q.; The-Hai, P.; Muller, M.; Nachtergael, A.; Duez, P.; Thang, N. D., *Life.*, **2021**, *11*(3), 257.
30. Koch, B.; Basu Baul, T. S.; Chatterjee, A., *Invest. New Drugs.*, **2009**, *27*(4), 319-326.
31. Verma, P.; Kunwar, A.; Arai, K.; Iwaoka, M.; *Indira Priyadarsini, K., Toxicol. Res. (Camb).,* **2016**, *5*(2), 434-445.
32. Kamaludin, N. F.; Awang, N.; Baba, I.; Hamid, A.; Meng, C. K., *Pak. J. Biol. Sci.*, **2013**, *16*(1), 12-21.
33. Javed, F.; Sirajuddin, M.; Ali, S.; Khalid, N.; Tahir, M. N.; Shah, N. A.; Rasheed, Z.; Khan, M. R., *Polyhedron.*, **2016**, *104*, 80-90.
34. Hussain, S.; Ali, S.; Shahzadi, S.; Tahir, M. N.; Shahid, M., *J. Coord. Chem.*, **2015**, *68*(14), 2369-2387.
35. Alavijeh, M. S.; Chishty, M.; Qaiser, M. Z.; Palmer, A. M., *NeuroRx.*, **2005**, *2*(4), 554-571.

36. Riley, R. J.; Parker, A. J.; Trigg, S.; Manners, C. N., *Pharm. Res.*, **2001**, *18*(5), 652-655.
37. Iqbal, M.; Ali, S.; Haider, A.; Khalid, N., *Rev. Inorg. Chem.*, **2017**, *37*(2), 51–70.
38. Mills, J. C.; Stone, N. L.; Erhardt, J.; Pittman, R. N., *J. Cell. Biol.*, **1998**, *140*(3), 627-636.
39. Zhang, Y.; Chen, X.; Gueydan, C.; Han, J., *Cell Res.*, **2018**, *28*, 9–21.
40. Hamid, A.; Azmi, M. A.; Rajab, N. F.; Awang, N.; Jufri, N. F., *Sains Malays.,* **2020**, *49*(6), 1421–1430.
41. Badisa, R. B.; Darling-Reed, S. F.; Joseph, P.; Cooperwood, J. S.; Latinwo, L. M.; Goodman, C. B., *Anticancer Res.*, **2009**, *29*(8), 2993-2996.
42. Mohd Shafiee, M. A.; Muhamad Asri, M. A.; Syed Alwi, S. S., *Malays. J. Med. Health Sci.,* **2021**, *17*(2), 261-269.