Published by
NIGERIAN SOCIETY OF PHYSICAL SCIENCES
Available online @ https://journal.nsps.org.ng/index.php/jnsps

J. Nig. Soc. Phys. Sci. 8 (2026) 3552

Journal of the Nigerian Society of Physical Sciences

Antiproliferative activity of synthesized dibutyltin(IV) hydroxybenzoate derivatives against A549, MCF-7, and HeLa human cancer cells

Sutopo Hadi[a,*], Ermin K. Winarno[b], Susanto Susanto[b], Khairun N. Berawi[c], Susianti Susianti[c], Noviany Noviany[a], Wasinton Simanjuntak[a], Dede Komarudin[e], Hendig Winarno[b,d]

[a]*Department of Chemistry, University of Lampung, Bandar Lampung 35145, Indonesia*
[b]*Research Center for Radiation Process Technology, Research Organization for Nuclear Energy, National Research and Innovation Agency, KST B.J. Habibie, Tangerang Selatan 15314, Indonesia*
[c]*Medical Faculty, Universitas Lampung, Bandar Lampung 35145, Indonesia*
[d]*Faculty of Pharmacy, Universitas Pancasila, Srengseng Sawah, Jakarta 12640, Indonesia*
[e]*Pharmacy Department, Institute Science and Technology Al-Kamal, Jl. Kedoya Pesing, Kebon Jeruk, Jakarta Barat 11520, Indonesia*

Abstract

The adverse effects associated with conventional cancer therapies have intensified the search for anticancer agents with fewer side effects. One approach involves the synthesis of organotin(IV) hydroxybenzoates. In this study, dibutyltin(IV) bis(2-hydroxybenzoate) [$Bu_2Sn(2\text{-}HB)_2$ (3a)], dibutyltin(IV) bis(3-hydroxybenzoate) [$Bu_2Sn(3\text{-}HB)_2$ (3b)], and dibutyltin(IV) bis(4-hydroxybenzoate) [$Bu_2Sn(4\text{-}HB)_2$ (3c)] were successfully synthesized. Compounds 3a–3c were obtained by reacting dibutyltin(IV) oxide (Bu_2SnO) (1) with 2-hydroxybenzoic acid (2-HBA, 2a), 3-hydroxybenzoic acid (3-HBA, 2b), and 4-hydroxybenzoic acid (4-HBA, 2c), respectively. Purity and structure were confirmed by ultraviolet–visible (UV–Vis), Fourier-transform infrared (FTIR), and nuclear magnetic resonance (NMR) spectroscopies and by micro-elemental analysis. Antiproliferative activity was evaluated against A549 (lung), MCF-7 (breast), and HeLa (cervical) cancer cells and compared with effects on normal Vero cells. Compound 3a was most active against A549 and HeLa cells, with half-maximal inhibitory concentration (IC_{50}) values of 3.16 μg/mL (6.23 μM) and 6.11 μg/mL (12.05 μM), respectively, whereas 3b was most active against MCF-7 cells, with an IC_{50} of 3.36 μg/mL (6.63 μM). Based on the calculated selectivity index (SI), compound 3c showed the highest selectivity toward all three cancer cell lines.

DOI: 10.46481/jnsps.2026.3552

Keywords: Antiproliferative activity, Dibutyltin(IV) hydroxybenzoates, Cancer cell lines, Half-maximal inhibitory concentration, Selectivity index

Article History:
Received: 27 May 2026
Received in revised form: 07 September 2026
Accepted for publication: 11 September 2026
Available online: 23 September 2026

Communicated by: B. J. Falaye

1. Introduction

Cancer remains a serious global public-health threat [1]. Disruption of normal mechanisms controlling cell growth and division, through inherited or acquired genetic changes, can lead to uncontrolled proliferation, tissue invasion, and metastasis [1]. The World Health Organization (WHO) estimated that cancer was responsible for nearly 10 million deaths worldwide in 2020, or approximately one in every six deaths globally [2–

*Corresponding Author Tel. No.: +628-136-905-9733.
Email address: sutopo.hadi@fmipa.unila.ac.id (Sutopo Hadi)

4]. GLOBOCAN 2022 data indicate approximately 20 million newly diagnosed cancer cases and 9.7 million cancer-related deaths; lung (12.4%), breast (11.5%), and colorectal (9.6%) cancers are among the leading cancer types globally. Indonesia has the highest number of cancer-related deaths in Southeast Asia [5].

Although chemotherapeutic agents are widely used in clinical practice, the development of new anticancer compounds remains important for improving efficacy and reducing treatment-related adverse effects. Historically, metal-based drugs, beginning with platinum complexes such as cisplatin [cis-{$Pt(NH_3)_2Cl_2$}], carboplatin, and oxaliplatin, have played an important role in oncology and remain widely used. Despite their efficacy, platinum-based agents have drawbacks including toxicity and resistance, motivating the investigation of ruthenium, iridium, gold, and tin complexes [6] and other metal complexes [7, 8].

Among non-platinum candidates, organotin(IV) complexes have attracted considerable attention because of their promising potential and wide-ranging cytotoxic effects. Several workers have reported that various organotin(IV) derivatives exhibit antiproliferative activities that are comparable to, or even better than, those of cisplatin, including improved selectivity toward cancer cells [9–13].

The antitumor properties of organotin(IV) derivatives are mainly governed by the nature and number of organic substituents attached to the tin (Sn) atom, whereas the anionic ligand typically plays a secondary role [13–16]. Recent reviews report that organotin(IV) complexes can induce apoptosis, activate mitochondrial-mediated cell-death pathways, promote cell-cycle arrest, and exert antiproliferative effects across multiple cancer cell lines, highlighting their potential as anticancer agents [9, 13, 17, 18]. In line with these findings, numerous organotin(IV) derivatives have also exhibited strong in vitro antiproliferative effects against diverse cancer-cell models [12, 19–21].

Previous studies reported that dibutyltin(IV) bis(4-hydroxybenzoate) and diphenyltin(IV) bis(4-hydroxybenzoate) inhibit the proliferation of L1210 leukemia cells, with IC_{50} values of 24.4 μg/mL and 10.3 μg/mL, respectively [20]. According to the activity classification proposed by Alitheen *et al.*, Ref. [22], pure compounds are considered strongly active in vitro at $IC_{50} \leq 5.0$ μg/mL, moderately active at IC_{50} values from 5.0 to 10.0 μg/mL, and less active at IC_{50} values from 10.0 to 25.0 μg/mL. These findings suggest that butyl-substituted organotin(IV) benzoates may possess notable anticancer potential and warrant further study.

In this study, dibutyltin(IV) hydroxybenzoate derivatives were synthesized and structurally characterized, and their antiproliferative effects were assessed against A549 (lung), MCF-7 (breast), and HeLa (cervical) human cancer cell lines. Their selectivity indices were also evaluated relative to cytotoxicity in normal Vero cells. A549 and MCF-7 cells were selected because of the high global incidence and mortality associated with lung and breast cancers and their substantial burden in Indonesia [5, 23, 24]. HeLa cells were used as a representative model of cervical cancer because cervical cancer is the third most frequently diagnosed cancer among women in Indonesia [5].

2. Materials and methods

2.1. Materials

All reagents used in this study were of analytical-reagent (AR) grade. The starting reactants included dibutyltin(IV) oxide [$(C_4H_9)_2SnO$/DBTO, 1], 2-hydroxybenzoic acid [(2-OH)-C_6H_4-COOH/2-HBA, 2a], 3-hydroxybenzoic acid [(3-OH)C_6H_4-COOH/3-HBA, 2b], and 4-hydroxybenzoic acid [(4-OH)C_6H_4-COOH/4-HBA, 2c]. Cell-culture reagents, including Dulbecco's modified Eagle medium (DMEM), fetal bovine serum (FBS), phosphate-buffered saline (PBS), trypsin, penicillin, $NaHCO_3$, and trypan blue, were purchased from Sigma-Aldrich (Germany). Methanol was obtained from JT Baker (United Kingdom), and distilled water (aquabidest) was purchased from Ikapharmindo (Indonesia). All chemicals were used as received without additional purification. Human cancer cell lines A549 (lung), MCF-7 (breast), and HeLa (cervical), as well as normal Vero cells, were purchased from Elabscience Biotech Inc. (USA).

2.2. Characterization techniques and instrumentation

Elemental composition was determined using an elemental analyzer (Carlo Erba–Fisons EA 1108 series, Italy). UV–Vis spectra were recorded on a Shimadzu UV-245 spectrophotometer (Japan) using methanolic sample solutions (1.0×10^{-4} M) in 1 cm quartz cuvettes. FTIR spectra were generated using a Bruker VERTEX 70 spectrophotometer (Germany) with KBr-pellet samples scanned over 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 600 MHz NMR spectrometer (Germany), operating at 600 MHz for ^1H and 150 MHz for ^{13}C. All measurements were conducted at 298 K in DMSO-d_6.

The ^1H NMR spectra were acquired with 32 scans using tetramethylsilane (TMS) as the internal reference (δ = 0.00 ppm), while the ^{13}C NMR spectra were recorded with 1000–4000 scans, using the DMSO-d_6 signal at δ = 39.5 ppm as the chemical-shift reference.

2.3. Preparation of dibutyltin(IV) hydroxybenzoate derivatives

Compounds 3a–3c were prepared according to previously reported procedures, with minor modifications [20, 21, 25–27]. In brief, the starting reactant Bu_2SnO (1) (0.747 g, 3 mmol) was dissolved in methanol (30 mL), and two molar equivalents of 2-HBA (2a) (0.828 g) were added gradually. The resulting mixture was heated under reflux at 60–61 °C for 4 h, while the H_2O produced during the reaction was continuously removed using Dean–Stark apparatus. After completion, the solvent was evaporated under reduced pressure, and the crude product, identified as dibutyltin(IV) bis(2-hydroxybenzoate) [$Bu_2Sn(2\text{-}HB)_2$] (3a), was subsequently dried under vacuum to constant dryness to obtain a solid suitable for physicochemical characterization and antiproliferative evaluation (yield: 1.462 g, 89.3%).

An analogous synthetic protocol was used to prepare dibutyltin(IV) bis(3-hydroxybenzoate) [$Bu_2Sn(3\text{-}HB)_2$, 3b] and

dibutyltin(IV) bis(4-hydroxybenzoate) [$Bu_2Sn(4\text{-}HB)_2$, 3c], using 3-HBA (2b) and 4-HBA (2c) as the respective ligands. The isolated yields of compounds 3b and 3c were 88.5% and 91.2%, respectively.

The physicochemical characteristics of the synthesized compounds are summarized as follows.

$Bu_2Sn(2\text{-}HB)_2$ (3a): white solid; UV λ_{max} (MeOH) nm: 242 and 304; IR ν_{max} (KBr) cm^{-1}: 2929–2870 (aliphatic C–H stretching in butyl), 1559 (C=O), 1252 (SnO–C), 1078 (Sn–C), 753 (Sn–O); ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): H_δ: 0.87 (t), H_γ: 1.35 (m), H_β: 1.57 (m), H_α: 1.67 (t), H(aromatic): 7.55–7.81 (m); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm): C_δ: 13.5, C_γ: 21.3, C_β: 25.55, C_α: 26.1, C_6: 130.0, C_5: 131.3, C_4: 131.9, C_3: 132.9, C_2: 133.8, C_1: 134.5, C=O: 166.125; micro-elemental analysis: found (calculated): C 51.99 (52.07), H 5.51 (5.52) [19, 25].

$Bu_2Sn(3\text{-}HB)_2$ (3b): white-light yellowish solid; UV λ_{max} (MeOH) nm: 243 and 299; IR ν_{max} (KBr) cm^{-1}: 2959–2873 (aliphatic C–H stretching in butyl), 1559 (C=O), 1259 (SnO–C), 1079 (Sn–C), 763 (Sn–O); ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): H_δ: 0.87 (t), H_γ: 1.35 (m), H_β: 1.57 (m), H_α: 1.67 (t), H(aromatic): 7.47–7.80 (m); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm): C_α: 26.1, C_β: 25.5, C_γ: 21.3, C_δ: 13.5, C_6: 128.7, C_5: 130.3, C_4: 131.9, C_3: 132.2, C_2: 133.1, C_1: 133.8, C=O: 165.024; micro-elemental analysis: found (calculated): C 52.12 (52.07), H 5.53 (5.52) [19, 21, 25–27].

$Bu_2Sn(4\text{-}HB)_2$ (3c): white solid; UV λ_{max} (MeOH) nm: 245 and 297; IR ν_{max} (KBr) cm^{-1}: 3390 (O–H, phenolic), 3030 (aromatic C–H stretching), 2957–2802 (aliphatic C–H stretching in butyl), 1610 (asym COO^-), 1555 (C=C), 1445 (asym COO^-) and 1365 (C–H bending), 1245 and 1170 (SnO–C), 1081 (Sn–C), 784 (Sn–O); ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): H_α: 1.67 (t), H_β: 1.57 (m), H_γ: 1.35 (m), H_δ: 0.84 (t), H_3 and H_5(aromatic): 7.69–7.71 (d, 2H), H_2 and H_6(aromatic): 7.79–7.89 (d, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm): C_α: 26.792, C_β: 25.546, C_γ: 21.285, C_δ: 13.524, C_1: 164.277, C_2: 131.5, C_3: 132.2, C_4: 128.5, C_5: 128.1, C_6: 128.5, C_7: 131.4; micro-elemental analysis: found (calculated): C 52.10 (52.07), H 5.52 (5.52) [19, 20, 25].

2.4. *Bioassay of compounds 3a–3c on human cancer and normal cells*

The antiproliferative activities of compounds 3a–3c were evaluated against human cancer cell lines (A549 lung, MCF-7 breast, and HeLa cervical) and normal Vero cells following previously reported protocols [23, 28], with slight modifications. MCF-7 breast cancer cells were cultured in DMEM supplemented with 10% FBS and 2% penicillin–streptomycin. The cells were maintained at 37 °C in a humidified incubator containing 5% CO_2 for 72 h until adequate confluence was achieved. To maintain optimal cell viability and growth, the culture medium was replaced every 2 d. Cells at an initial density of 2×10^6 cells/mL were seeded into 24-well plates at a volume of 1 mL per well.

The cells were then treated with the tested compounds at concentrations of 0.5, 1, 4, and 8 μg/mL for A549 and MCF-7 cells; 0.5, 1, 4, 8, 16, and 32 μg/mL for HeLa cells; and 1, 4, 8, 32, and 128 μg/mL for Vero cells. All samples were dissolved in DMSO and appropriately diluted with culture medium. The negative control consisted of cells treated with culture medium containing the corresponding amount of DMSO, whereas doxorubicin was used as the positive control. All experiments were conducted using DMEM containing L-glutamine.

For each sample concentration, the sample solution was prepared once and then distributed among three separate wells to provide triplicate measurements. The three wells were incubated independently for 72 h under the same culture conditions. Following incubation, all medium was carefully removed from each well, and the adherent cells were washed with 200 μL of PBS. Cells were detached by adding 100 μL of trypsin–EDTA and incubating them in a 5% CO_2 incubator for 10 min. Subsequently, 20 μL of trypan blue solution was added, and viable cells were counted using an improved Neubauer haemocytometer (0.1 mm depth) under an Olympus microscope at 400× magnification.

The inhibitory activity was calculated using Eq. (1):

$$\text{Inhibitory activity} = \left[1 - \frac{\frac{\text{viable cells in}}{\text{tested sample}}}{\frac{\text{viable cells in}}{\text{control}}}\right] \times 100\%. \quad (1)$$

The half-maximal inhibitory concentration (IC_{50}) was determined by linear regression analysis. The x-axis represented the logarithm of sample concentration; only non-zero concentrations were used in the logarithmic regression. The y-axis represented the corresponding probit-transformed percentages of growth inhibition, following procedures reported previously [23, 28].

3. Results and discussion

3.1. *Synthesis of dibutyltin(IV) hydroxybenzoate derivatives*

Compounds 3a–3c were successfully synthesized by reacting DBTO (1) with 2-HBA (2a), 3-HBA (2b), and 4-HBA (2c), respectively, giving high isolated yields for all derivatives. The structures of the compounds were confirmed by comprehensive spectroscopic analyses, including UV–Vis, FTIR, ^{1}H NMR, and ^{13}C NMR, which provided well-defined and interpretable spectra. In addition, micro-elemental analysis data were consistent with calculated values and previous data reported by Hadi *et al.* [20, 21, 25–27], thereby confirming the successful synthesis of the desired compounds. The synthesis pathways leading to compounds 3a–3c are illustrated in Figure 1.

The UV–Vis spectra of compounds 3a–3c showed distinct absorption maxima (λ_{max}) attributable to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions. These spectral features are consistent with those previously reported for dibutyltin(IV) hydroxybenzoate derivatives by Hadi *et al.* [20, 21, 25–27].

The reaction of DBTO (1) with 4-HBA (2c) to yield compound 3c (Figure 1) resulted in a distinct bathochromic shift associated with the carbonyl chromophore and the additional benzene ring. An $n \rightarrow \pi^*$ transition was also observed at 297 nm and was associated with the lone-pair electrons of the hydroxyl group, as shown in Figure 2c [20, 25]. Similar spectral shifts

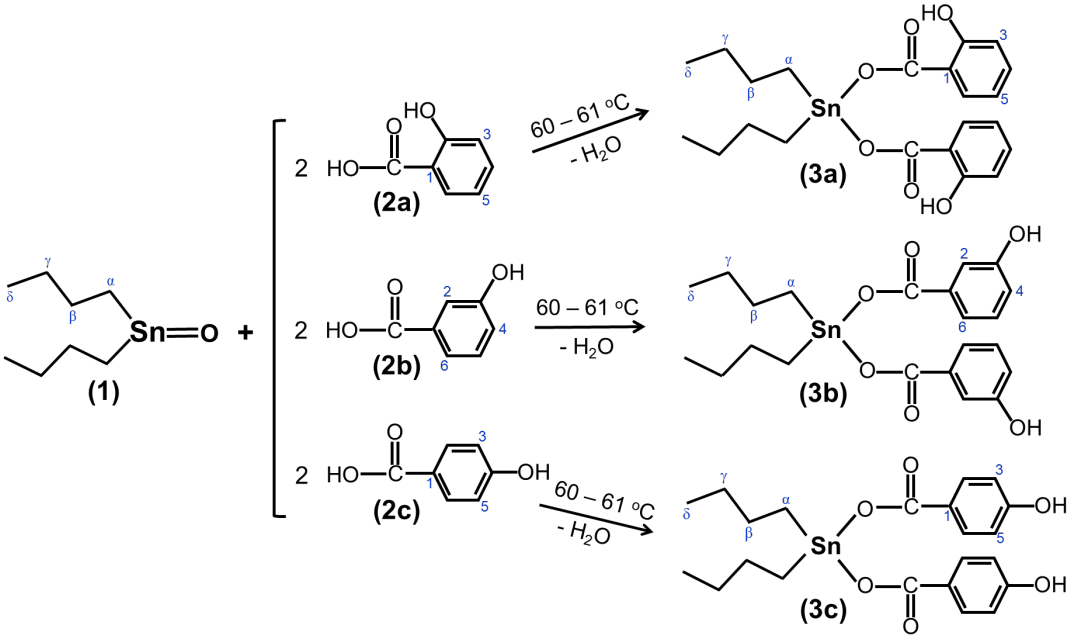


Figure 1: Synthesis pathways of dibutyltin(IV) hydroxybenzoate derivatives 3a–3c.

were observed for compounds 3a and 3b, although slight differences in λ_{max} (304 and 299 nm, respectively) were noted, as shown in Figure 2a and b [21, 25–27].

Figure 3 presents representative FTIR spectra for $Bu_2Sn(HB)_2$ (3a–3c). The spectra show diagnostic absorption bands supporting successful product formation. For compound 3c (Figure 3c), the broad band at approximately 3390 cm^{-1} was assigned to the O–H stretching vibration of the phenolic group. The bands at approximately 3030 and 2957–2802 cm^{-1} were attributed to C–H stretching vibrations of the aromatic and aliphatic groups, respectively.

The bands at 1610 and 1445 cm^{-1} were assigned to the asymmetric [$\nu_{as}(COO^-)$] and symmetric [$\nu_s(COO^-)$] stretching vibrations of the coordinated carboxylate group, respectively. The separation between these bands ($\Delta\nu$) was 165 cm^{-1} [$\Delta\nu$ = 1610 – 1445 cm^{-1}]. This value supports the proposed coordination of the carboxylate group to the Sn(IV) center. The band at 1555 cm^{-1} was attributed to aromatic C=C stretching, whereas the band at 1245 cm^{-1} was assigned to Sn–O–C stretching. Additional characteristic bands at 1080 and 783 cm^{-1} were attributed to Sn–C and Sn–O stretching vibrations, respectively. Overall, these spectral features are consistent with the formation of dibutyltin(IV) bis(4-hydroxybenzoate) [$Bu_2Sn(4\text{-}HB)_2$], in agreement with previous reports [20, 25–27].

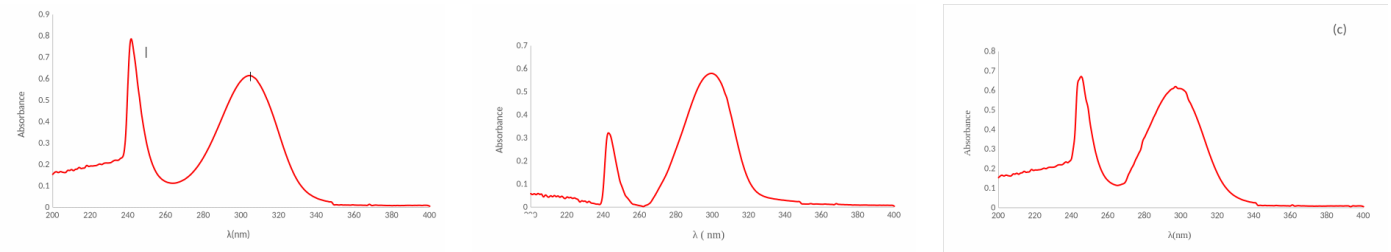
The ^1H (Figure 4) and ^{13}C NMR (Figure 5) spectra of dibutyltin(IV) hydroxybenzoate derivatives 3a–3c further support the proposed structures. For compound 3c, the ^1H NMR spectrum showed resonances attributable to the butyl chains at 0.84–1.67 ppm, while the aromatic protons of the 4-hydroxybenzoate ligand appeared as doublets at 7.70 ppm (2H) and 7.84 ppm (2H) (Figure 4c). These signals are consistent with those previously reported for $Bu_2Sn(4\text{-}HB)_2$ (3c) [20, 25]. Similar spectral features were observed for compounds 3a and 3b.

In the ^{13}C NMR spectra, the carbon atoms of the butyl substituents resonated at 13.524 (C_δ)–26.792 (C_α) ppm, whereas the aromatic carbons of the benzoate group appeared at 128.06–131.53 ppm. The carbonyl carbons of compounds 3a–3c were observed at 166.1, 165.024, and 164.277 ppm, respectively, consistent with expected chemical shifts for coordinated benzoate ligands. Similar spectral features were observed for compounds 3a and 3b, confirming structural consistency across the series [21, 25–27].

3.2. *Antiproliferative activity against human cancer and normal cells*

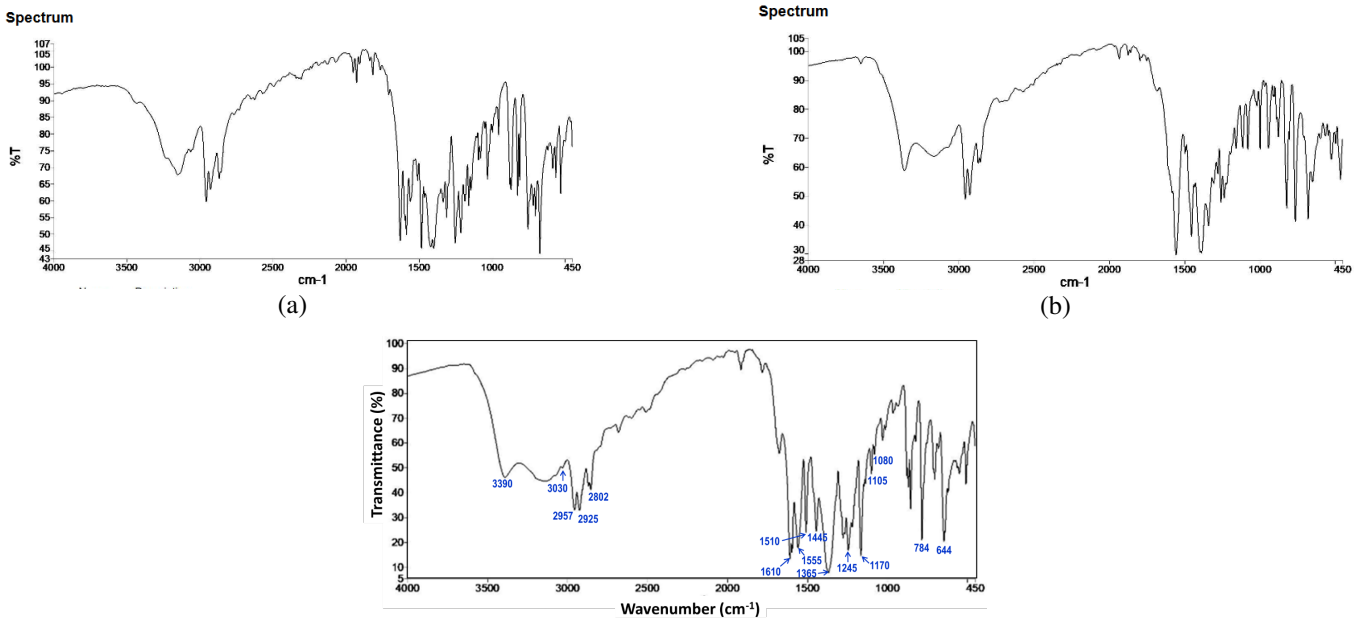
The antiproliferative activities of compounds 3a–3c against A549 (lung), MCF-7 (breast), and HeLa (cervical) cancer cell lines and normal Vero cells are summarized in Table 1; a comparison of their IC_{50} values is shown in Figure 6. The antiproliferative activities varied considerably across the tested cancer cell lines. Compounds 3a and 3b were strongly active against A549 and MCF-7 cells, with IC_{50} values $\leq$ 5.0 μg/mL. Compound 3c was strongly active against A549 cells but moderately active against MCF-7 cells (IC_{50} = 5.37 ± 0.47 μg/mL). Compound 3a showed the strongest activity toward HeLa cells and was moderately active (IC_{50} = 6.11 ± 0.68 μg/mL), whereas compounds 3b and 3c were classified as less active (IC_{50} = 10.0–25.0 μg/mL) [22].

The three compounds exhibited distinct antiproliferative profiles across the evaluated cancer cell lines. Compound 3a had the lowest IC_{50} values against A549 and HeLa cells, at 3.16 μg/mL (6.23 μM) and 6.11 μg/mL (12.05 μM), respectively, whereas compound 3b showed the greatest potency toward MCF-7 cells, with an IC_{50} of 3.36 μg/mL (6.63 μM).



(a) (b) (c)

Figure 2: UV–Vis spectra of (a) dibutyltin(IV) bis(2-hydroxybenzoate) (3a), (b) dibutyltin(IV) bis(3-hydroxybenzoate) (3b), and (c) dibutyltin(IV) bis(4-hydroxybenzoate) (3c).



(a) (b) (c)

Figure 3: FTIR spectra of dibutyltin(IV) hydroxybenzoate derivatives: (a) 3a, (b) 3b, and (c) 3c.

Table 1: Antiproliferative activity (IC_{50}) of synthesized compounds 3a–3c against selected human cancer and normal Vero cells

No.	Synthesized compound	IC_{50} (μg/mL)			
		A549	MCF-7	HeLa	Vero
1	Doxorubicin	1.75 ± 0.31	1.08 ± 0.08	0.91 ± 0.02	Not tested[a]
2	$Bu_2Sn(2\text{-}HB)_2$ (3a)	3.16 ± 0.47	3.75 ± 0.26	6.11 ± 0.68	24.09 ± 1.09
3	$Bu_2Sn(3\text{-}HB)_2$ (3b)	4.45 ± 0.45	3.36 ± 0.23	16.68 ± 0.89	97.10 ± 2.11
4	$Bu_2Sn(4\text{-}HB)_2$ (3c)	4.75 ± 0.46	5.37 ± 0.47	12.14 ± 0.75	> 128.00

Each value was the mean ± standard deviation of triplicate assays.

[a]Interpreted from source text note ("not tested, as it is not toxic").

Compound 3c showed the weakest antiproliferative effect against A549 and MCF-7 cells, whereas compound 3b was the least active against HeLa cells. Compared with the tested compounds, the positive control, doxorubicin, showed substantially stronger cytotoxic activity against A549 (IC_{50} = 1.75 ± 0.31 μg/mL), MCF-7 (IC_{50} = 1.08 ± 0.08 μg/mL), and HeLa (IC_{50} = 0.91 ± 0.02 μg/mL) cells.

The IC_{50} values obtained in this study are comparable with those reported previously for organotin(IV)-based anticancer agents [13, 17, 19, 28–33]. For example, dinuclear complexes such as $[Bu_2Sn(iminodiacetate)(H_2O)]_2$·phenanthroline and $[Bu_2Sn(iminodiacetate)(H_2O)]_2$·bipyridine exhibited complete growth inhibition (100%) against P388 (murine leukemia), HL-60 (promyelocytic leukemia), and A549 (lung) cancer cells at concentrations of 10.0, 10.0, and 0.1 μM, respectively [30].

In addition, Bu_2tin(IV) and Ph_3tin(IV) methoxyethyldithiocarbamate complexes were reported to exert strong cytotoxic effects against HL-60 cells, with IC_{50} values of 0.40 and

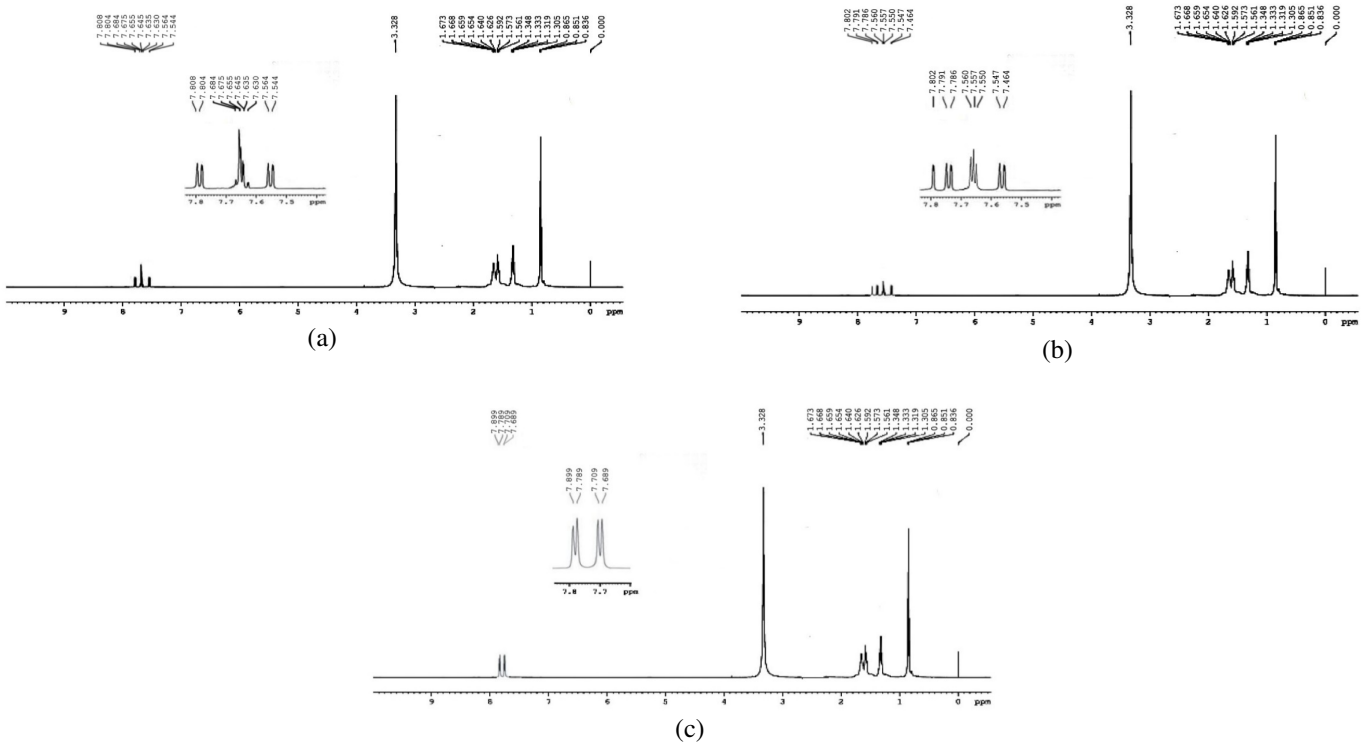


Figure 4: ^{1}H NMR spectra of compounds 3a–3c: (a) 3a, (b) 3b, and (c) 3c.

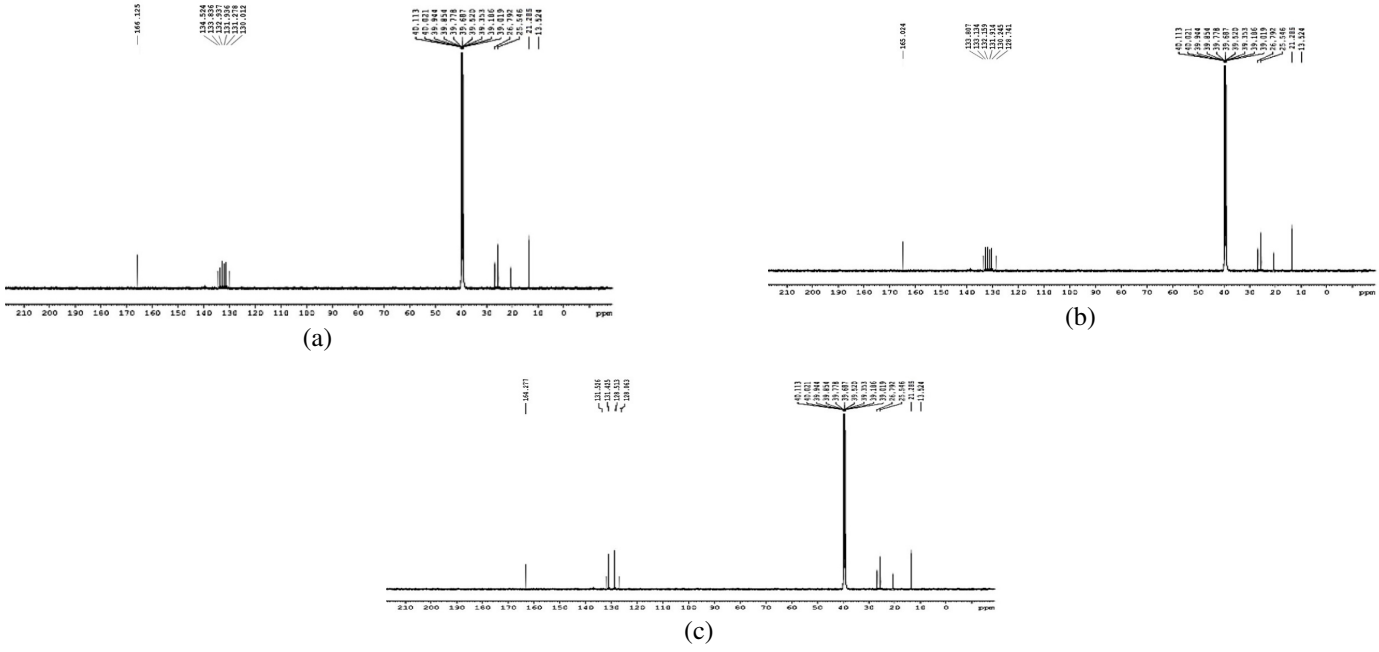


Figure 5: ^{13}C NMR spectra of compounds 3a–3c: (a) 3a, (b) 3b, and (c) 3c.

0.35 μM, respectively [31]. Diorganotin(IV) valsartan complexes [$Bu_2Sn(valsartan)_2$ and $Ph_2Sn(valsartan)_2$] exhibited antiproliferative activity against A549 cells, with IC_{50} values of 0.04 and 67.9 μg/mL, respectively [32]. These comparisons support further biological evaluation of the compounds reported here.

To further assess anticancer potential, selectivity index (SI) values were calculated from the IC_{50} values of each compound against cancer cell lines and normal Vero cells. According to Khunoana *et al.*, Ref. [33], the SI indicates the degree of cytotoxic selectivity of the tested sample against cancer cells versus normal cells (Vero) and was calculated by dividing the IC_{50} of

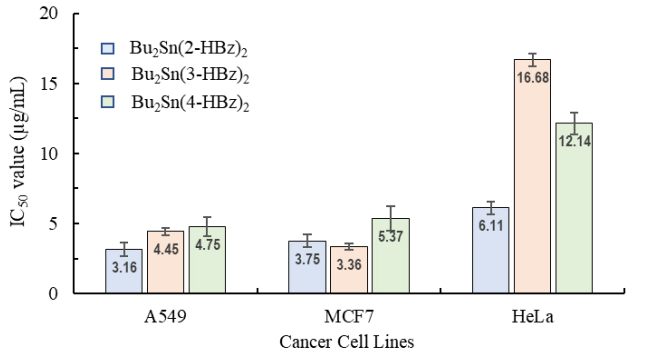


Figure 6: IC_{50} values of synthesized compounds 3a–3c against A549, MCF-7, and HeLa cells.

Table 2: Selectivity index (SI) of synthesized compounds 3a–3c toward cancer cells relative to Vero cells.

No.	Synthesized compound	A549	MCF-7	HeLa
1	$Bu_2Sn(2\text{-}HB)_2$ (3a)	7.6	6.4	3.9
2	$Bu_2Sn(3\text{-}HB)_2$ (3b)	21.8	28.9	5.8
3	$Bu_2Sn(4\text{-}HB)_2$ (3c)	> 26.9	> 23.8	> 10.5

the tested sample in normal cells by the IC_{50} of cancer cells. An ideal anticancer agent should exhibit high toxicity toward cancer cells while maintaining minimal toxicity toward normal cells [34]. Therefore, the SI provides an indication of therapeutic selectivity [35, 36]. Mohammed *et al.* [32] proposed SI ≥ 10 as indicative of a promising candidate, whereas Weerapreeyakul *et al.* [37] suggested SI ≥ 3 as sufficient to classify a compound as a potential anticancer agent.

In the present study, SI values were obtained by dividing the IC_{50} value of each synthesized compound (3a–3c) toward Vero cells by its IC_{50} value against each cancer cell line. The calculated SI values are summarized in Table 2.

As shown in Table 2, all tested compounds exhibited SI values above 3 across the tested cancer cell lines, indicating acceptable selectivity under the criterion cited above. Compound 3c consistently exhibited SI values above 10 for all cancer cell lines, whereas compound 3b showed SI values above 10 for A549 and MCF-7 cells. These findings suggest that compounds 3c and 3b have enhanced selectivity toward malignant cells and are the most promising candidates for further preclinical and clinical investigation. Compound 3a had comparatively lower SI values across all tested cancer cell lines, although its SI values remained above 3. Across the series, lower SI values were observed for HeLa cells than for the other cancer cell lines, suggesting lower selectivity toward this cell type while remaining above the stated SI threshold.

This observation highlights the importance of evaluating anticancer activity using SI values because assessments based solely on cytotoxicity toward malignant cell lines or animal models provide limited predictive value for clinical performance [38]. Ideally, an effective anticancer agent should selectively eliminate cancer cells while minimizing toxicity to normal cells [36]. The present findings are consistent with those reported by Uddin *et al.* [19]. Overall, the results suggest that organotin(IV) benzoate derivatives have potential as candidates for metal-based anticancer drugs. Further advanced preclinical studies and clinical evaluation are warranted to establish their therapeutic efficacy and safety profiles [39].

Based on the IC_{50} value (< 4 μg/mL) and SI value (> 10), compound 3b meets these criteria against MCF-7 cancer cells and is therefore the most promising candidate for further testing.

4. Conclusion

The results demonstrate that the three synthesized dibutyltin(IV) hydroxybenzoate derivatives (3a–3c) exhibited considerable anticancer potential based on their antiproliferative activities. Compound 3a showed the strongest activity against A549 and HeLa cells but relatively low selectivity, with SI values below 10. Compound 3b showed the strongest antiproliferative activity against MCF-7 cells (IC_{50} = 3.36 ± 0.23 μg/mL) and the highest SI value (28.9) for this cell line. Compound 3c, although less active based on its IC_{50} values, showed high selectivity, with SI values of > 26.9 and > 23.8 against A549 and MCF-7 cells, respectively.

Overall, considering both IC_{50} and SI values, compound 3b emerged as the most promising candidate for further investigation, particularly against A549 and MCF-7 cells, whereas compound 3c also warrants further evaluation for its potential against MCF-7 cells. Future studies should focus on comprehensive mechanistic pathways, in vitro toxicity profiling, pharmacological properties, and subsequent in vivo investigations.

Data availability

All relevant data are included in the manuscript and are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare no conflict of interest.

Funding

The authors gratefully acknowledge financial support from the Higher Education, Technology and Innovation Program of Universitas Lampung through the Domestic Innovation Research and Collaboration scheme (Contract No. 2884/UN26/HK.01.03/2025). Additional funding was received from the Applied Research Grant of the Directorate of Research & Community Services, Directorate General for Research & Development (Contract No. 076/C3/DT.05.00/PL/2025), and from the Institute for Research & Community Service of Universitas Lampung under the Applied Research program (Contract No. 707/UN26.21/PN.2025).

Acknowledgment

The authors also express their sincere appreciation to Dr. Huy Hoang of the Institute of Molecular Biosciences–The University of Queensland for assistance with NMR measurements.

References

[1] M. McCall, M. McDonald, S. Thorne, A. Ward & C. Heneghan, "Yoga for health-related quality of life in adult cancer: A randomized controlled feasibility study", Evidence-Based Complementary and Alternative Medicine **2015** (2015) 816820. https://doi.org/10.1155/2015/816820.

[2] H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal & F. Bray, "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries", CA: A Cancer Journal for Clinicians **71** (2021) 209. https://doi.org/10.3322/caac.21660.

[3] H. Sung, A.M. Filho, M. Laversanne, J. Ferlay, R. L. Siegel, I. Soerjomataram, A. Jemal & F. Bray, "Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries", CA: A Cancer Journal for Clinicians **76** (2026) e70090. https://doi.org/10.3322/caac.70090.

[4] World Health Organization, *Global Health Estimates 2021: Disease burden by cause, age, sex, by country and by region, 2000–2021*, World Health Organization, Geneva, Switzerland, 2024. Available online: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates.

[5] International Agency for Research on Cancer–World Health Organization, *Indonesia fact sheet: Global Cancer Observatory*, 2024. Available online: https://gco.iarc.who.int/media/globocan/factsheets/populations/360-indonesia-fact-sheet.pdf.

[6] Y. Bai, G. Aodeng, L. Ga, W. Hai & J. Ai, "Research progress of metal anticancer drugs", Pharmaceutics **15** (2023) 2750. https://doi.org/10.3390/pharmaceutics15122750.

[7] U. B. Amadi, M. Ogwuegbu, C. K. Enenebeaku & G. Onyedika, "Design, synthesis and studies on thermodynamic and biological activities of lanthanide III complexes of hydrazinecarbothioamide ligands", Journal of the Nigerian Society of Physical Sciences **7** (2025) 2540. https://doi.org/10.46481/jnsps.2025.2540.

[8] I. E. Otuokere, J. G. Ohwimu, K. C. Amadi, C. O. Alisa, F. C. Nwadire, O. U. Igwe, A. A. Okoyeagu & C. M. Ngwu, "Synthesis, characterization and molecular docking studies of Mn(II) complex of sulfathiazole", Journal of the Nigerian Society of Physical Sciences **1** (2019) 95. https://doi.org/10.46481/jnsps.2019.20.

[9] S. N. S. Annuar, N. F. Kamaludin, N. Awang & K. M. Chan, "Cellular basis of organotin(IV) derivatives as anticancer metallodrugs: A review", Frontiers in Chemistry **9** (2021) 657599. https://doi.org/10.3389/fchem.2021.657599.

[10] S. K. Hadjikakou & N. Hadjiliadis, "Antiproliferative and anti-tumor activity of organotin compounds", Coordination Chemistry Reviews **253** (2009) 235. https://doi.org/10.1016/j.ccr.2007.12.026.

[11] A. Attanzio, S. D'Agostino, R. Busà, A. Frazzitta, S. Rubino, M. A. Girasolo, P. Sabatino & L. Tesoriere, "Cytotoxic activity of organotin(IV) derivatives with triazolopyrimidine containing exocyclic oxygen atoms", Molecules **25** (2020) 859. https://doi.org/10.3390/molecules25040859.

[12] M. Sirajuddin, S. Ali & M. N. Tahir, "Organotin(IV) derivatives based on 2-((2-methoxyphenyl)carbamoyl)benzoic acid: Synthesis, spectroscopic characterization, assessment of antibacterial, DNA interaction, anticancer and antileishmanial potentials", Journal of Molecular Structure **1229** (2021) 129600. https://doi.org/10.1016/j.molstruc.2020.129600.

[13] J. Devi & J. Yadav, "Recent advancements in organotin(IV) complexes as potential anticancer agents", Anti-Cancer Agents in Medicinal Chemistry **18** (2018) 335. https://doi.org/10.2174/1871520617666171106125114.

[14] L. Pellerito & L. Nagy, "Organotin(IV)$^{n+}$ complexes formed with biologically active ligands: Equilibrium and structural studies, and some biological aspects", Coordination Chemistry Reviews **224** (2002) 111. https://doi.org/10.1016/S0010-8545(01)00399-X.

[15] S. Hadi, M. D. Fenska, N. Noviany, H. Satria, W. Simanjuntak & M. M. Naseer, "Synthesis and antimalarial activity of some triphenyltin(IV) aminobenzoate compounds against *Plasmodium falciparum*", Main Group Metal Chemistry **44** (2021) 256. https://doi.org/10.1515/mgmc-2021-0028.

[16] S. Hadi, T. Suhartati, N. Noviany, K. D. Pandiangan, Y. Yandri & W. Simanjuntak, "Disinfecting activity of some diphenyltin(IV) benzoate derivative compounds", Pure and Applied Chemistry **94** (2022) 799. https://doi.org/10.1515/pac-2021-1106.

[17] N. A. Abd Aziz, N. Awang, K. M. Chan, N. F. Kamaludin & N. N. Mohamad Anuar, "Organotin(IV) dithiocarbamate compounds as anticancer agents: A review of syntheses and cytotoxicity studies", Molecules **28** (2023) 5841. https://doi.org/10.3390/molecules28155841.

[18] Y. Tan, Z. Zhang, J. Liu, Y. Tan & W. Jiang, "Syntheses, crystal structures, and anticancer activities of organotin carboxylates based on Alrestatin", Journal of Molecular Structure **1322** (2025) 140697. https://doi.org/10.1016/j.molstruc.2024.140697.

[19] N. Uddin, F. Rashid, A. Haider, S. A. Tirmizi, A. Raheel, M. Imran, S. Zaib, P. L. Diaconescu, J. Iqbal & S. Ali, "Triorganotin(IV) carboxylates as potential anticancer agents: Their synthesis, physiochemical characterization, and cytotoxic activity against HeLa and MCF-7 cancer cells", Applied Organometallic Chemistry **35** (2021) e6165. https://doi.org/10.1002/aoc.6165.

[20] S. Hadi, E. K. Winarno, H. Winarno, K. N. Berawi, T. Suhartati, N. Noviany, W. Simanjuntak & Y. Yandri, "Synthesis and in vitro activity investigation of some dibutyl-, diphenyl- and triphenyltin(IV) carboxylates against leukemia cancer cell, L-1210", Pure and Applied Chemistry **95** (2023) 823. https://doi.org/10.1515/pac-2023-0107.

[21] S. Hadi, E. K. Winarno, H. Winarno, K. N. Berawi, T. Suhartati, Y. Yandri & W. Simanjuntak, "Synthesis, characterization and in vitro activity study of some organotin(IV) carboxylates against leukemia cancer cell, L-1210", Physical Sciences Reviews **9** (2024) 2187. https://doi.org/10.1515/psr-2022-0303.

[22] N. B. Alitheen, A. R. Mashitoh, S. K. Yeap, M. Shuhaimi, A. A. Manaf & L. Nordin, "Cytotoxic effect of damnacanthal, nordamnacanthal, zerumbone and betulinic acid isolated from Malaysian plant sources", International Food Research Journal **17** (2010) 711. Available online: https://eprints.unisza.edu.my/2885/.

[23] H. Winarno, S. Susanto & E. K. Winarno, "Gamma irradiation effect on physicochemical properties of *Guazuma ulmifolia* leaves and their antiproliferative activities against human cancer cell lines", Journal of Radiation Research and Applied Sciences **16** (2023) 100576. https://doi.org/10.1016/j.jrras.2023.100576.

[24] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R. L. Siegel, I. Soerjomataram & A. Jemal, "Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries", CA: A Cancer Journal for Clinicians **74** (2024) 229. https://doi.org/10.3322/caac.21834.

[25] S. Hadi, H. Mustafidah, Y. Yandri, W. Simanjuntak & T. Suhartati, "Synthesis, characterization, and bioactivity test of dibutyltin(IV) dihydroxyibenzoate as disinfectant agent", Pure and Applied Chemistry **96** (2024) 413. https://doi.org/10.1515/pac-2023-1102.

[26] S. Hadi, M. Rilyanti & Suharso, "In vitro activity and comparative studies of some organotin(IV) benzoate derivatives against leukemia cancer cell, L-1210", Indonesian Journal of Chemistry **12** (2012) 172. https://doi.org/10.22146/ijc.21359.

[27] S. Hadi, S. Lestari, T. Suhartati, H. I. Qudus, M. Rilyanti, D. Herasari & Y. Yandri, "Synthesis and comparative study on the antibacterial activity organotin(IV) 3-hydroxybenzoate compounds", Pure and Applied Chemistry **93** (2021) 623. https://doi.org/10.1515/pac-2020-1103.

[28] S. Hadi, E. K. Winarno, H. Winarno, S. Susanto, D. A. S. Thian, M. D. Fansang, K. N. Berawi & T. Suhartati, "Synthesis, characterization and antiproliferative activity test of some diphenyltin(IV) hydroxybenzoates against A549, MCF-7 and HeLa human cancer cell lines", Journal of Inorganic and Organometallic Polymers and Materials **34** (2024) 2980. https://doi.org/10.1007/s10904-024-03042-2.

[29] M. K. Amir, S. Khan, Zia-Ur-Rehman, A. Shah & I. S. Butler, "Anticancer activity of organotin(IV) carboxylates", Inorganica Chimica Acta **423** (2014) 14. https://doi.org/10.1016/j.ica.2014.07.053.

[30] Z. A. Siddiqi, M. Shahid, S. Kumar, M. Khalid & S. Noor, "Synthesis, crystal structure and in vitro antitumor activity of carboxylate bridged dinuclear organotin(IV) complexes", Journal of Organometallic Chemistry **694** (2009) 3768. https://doi.org/10.1016/j.jorganchem.2009.07.030.

[31] N. Awang, N. F. Kamaludin, I. Baba, K. M. Chan, N. F. Rajab & A.

Hamid, "Synthesis, characterization and antitumor activity of new organotin(IV) methoxyethyldithiocarbamate complexes", Oriental Journal of Chemistry **32** (2016) 101. https://doi.org/10.13005/ojc/320110.

[32] A. Mohammed, R. Makia, M. Ali, R. Raheem & E. Yousif, "Cytotoxic effects of valsartan organotin(IV) complexes on human lung cancer cells", Biointerface Research in Applied Chemistry **11** (2021) 8156. https://doi.org/10.33263/BRIAC111.81568164.

[33] E. T. Khunoana, J. N. Eloff, T. E. Ramadwa, S. M. Nkadimeng, M. A. Selepe & L. J. McGaw, "In vitro antiproliferative activity of ptaeroxylon obliquum leaf extracts, fractions and isolated compounds on several cancer cell lines", Applied Sciences **12** (2022) 11004. https://doi.org/10.3390/app122111004.

[34] G. Indrayanto, G. S. Putra & F. Suhud, "Validation of in-vitro bioassay methods: Application in herbal drug research", Profiles of Drug Substances, Excipients, and Related Methodology **46** (2021) 273. https://doi.org/10.1016/bs.podrm.2020.07.005.

[35] O. A. Peña-Morán, M. L. Villarreal, L. Álvarez-Berber, A. Meneses-Acosta & V. Rodríguez-López, "Cytotoxicity, post-treatment recovery, and selectivity analysis of naturally occurring podophyllotoxins from *Bursera fagaroides* var. *fagaroides* on breast cancer cell lines", Molecules **21** (2016) 1013. https://doi.org/10.3390/molecules21081013.

[36] M. López-Lázaro, "How many times should we screen a chemical library to discover an anticancer drug?", Drug Discovery Today **20** (2015) 167. https://doi.org/10.1016/j.drudis.2014.12.006.

[37] N. Weerapreeyakul, A. Nonpunya, S. Barusrux, T. Thitimetharoch & B. Sripanidkulchai, "Evaluation of the anticancer potential of six herbs against a hepatoma cell line", Chinese Medicine **7** (2012) 15. https://doi.org/10.1186/1749-8546-7-15.

[38] M. López-Lázaro, "Two preclinical tests to evaluate anticancer activity and to help validate drug candidates for clinical trials", Oncoscience **2** (2015) 91. https://doi.org/10.18632/oncoscience.132.

[39] M. López-Lázaro, "A simple and reliable approach for assessing anticancer activity in vitro", Current Medicinal Chemistry **22** (2015) 1324. https://doi.org/10.2174/0929867322666150209150639.