

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

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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) [Bu₂Sn(2-HB)₂ (3a)], dibutyltin(IV) bis(3-hydroxybenzoate) [Bu₂Sn(3-HB)₂ (3b)], and dibutyltin(IV) bis(4-hydroxybenzoate) [Bu₂Sn(4-HB)₂ (3c)] were successfully synthesized. Compounds 3a–3c were obtained by reacting dibutyltin(IV) oxide (Bu₂SnO) (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 (IC₅₀) 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 IC₅₀ 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.

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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–

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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 [$\text{cis-}\{\text{Pt}(\text{NH}_3)_2\text{Cl}_2\}$], 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 $\mu\text{g/mL}$ and 10.3 $\mu\text{g/mL}$, respectively [20]. According to the activity classification proposed by Alitheen *et al.*, Ref. [22], pure compounds are considered strongly active in vitro at $\text{IC}_{50} \leq 5.0 \mu\text{g/mL}$, moderately active at IC_{50} values from 5.0 to 10.0 $\mu\text{g/mL}$, and less active at IC_{50} values from 10.0 to 25.0 $\mu\text{g/mL}$. 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 fre-

quently 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 [$[(\text{C}_4\text{H}_9)_2\text{SnO/DBTO}]$, 1], 2-hydroxybenzoic acid [$[(2\text{-OH})\text{-C}_6\text{H}_4\text{-COOH/2-HBA}]$, 2a], 3-hydroxybenzoic acid [$[(3\text{-OH})\text{-C}_6\text{H}_4\text{-COOH/3-HBA}]$, 2b], and 4-hydroxybenzoic acid [$[(4\text{-OH})\text{-C}_6\text{H}_4\text{-COOH/4-HBA}]$, 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 $4000\text{--}400 \text{ cm}^{-1}$. ^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 ($\delta = 0.00$ ppm), while the ^{13}C NMR spectra were recorded with 1000–4000 scans, using the DMSO-d_6 signal at $\delta = 39.5$ 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 $60\text{--}61^\circ\text{C}$ 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) [$\text{Bu}_2\text{Sn}(2\text{-HB})_2$] (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) [$\text{Bu}_2\text{Sn}(3\text{-HB})_2$, 3b] and

dibutyltin(IV) bis(4-hydroxybenzoate) [$\text{Bu}_2\text{Sn}(\text{4-HB})_2$, 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.

$\text{Bu}_2\text{Sn}(\text{2-HB})_2$ (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); ^1H 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].

$\text{Bu}_2\text{Sn}(\text{3-HB})_2$ (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); ^1H 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].

$\text{Bu}_2\text{Sn}(\text{4-HB})_2$ (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); ^1H 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 $\mu\text{g/mL}$ for A549 and MCF-7

cells; 0.5, 1, 4, 8, 16, and 32 $\mu\text{g/mL}$ for HeLa cells; and 1, 4, 8, 32, and 128 $\mu\text{g/mL}$ 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 $\times$ magnification.

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

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

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, ^1H 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

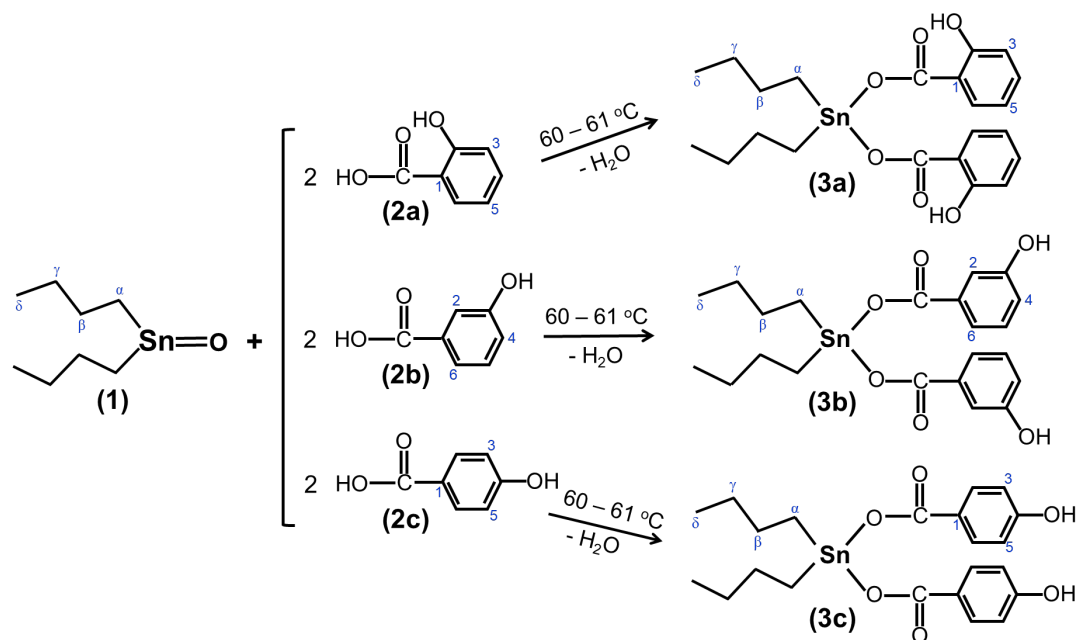


Figure 1: Synthesis pathways of dibutyltin(IV) hydroxybenzoate derivatives 3a–3c.

were observed for compounds 3a and 3b, although slight differences in $\lambda_{\max}$ (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 $2957\text{--}2802\text{ cm}^{-1}$ 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 [$\nu_{\text{as}}(\text{COO}^-)$] and symmetric [$\nu_{\text{s}}(\text{COO}^-)$] stretching vibrations of the coordinated carboxylate group, respectively. The separation between these bands ($\Delta\nu$) was 165 cm^{-1} [$\Delta\nu = 1610 - 1445\text{ cm}^{-1}$]. 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 $0.84\text{--}1.67\text{ ppm}$, 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 $128.06\text{--}131.53\text{ ppm}$. 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 $\leq 5.0\text{ }\mu\text{g/mL}$. Compound 3c was strongly active against A549 cells but moderately active against MCF-7 cells ($\text{IC}_{50} = 5.37 \pm 0.47\text{ }\mu\text{g/mL}$). Compound 3a showed the strongest activity toward HeLa cells and was moderately active ($\text{IC}_{50} = 6.11 \pm 0.68\text{ }\mu\text{g/mL}$), whereas compounds 3b and 3c were classified as less active ($\text{IC}_{50} = 10.0\text{--}25.0\text{ }\mu\text{g/mL}$) [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 $3.16\text{ }\mu\text{g/mL}$ ($6.23\text{ }\mu\text{M}$) and $6.11\text{ }\mu\text{g/mL}$ ($12.05\text{ }\mu\text{M}$), respectively, whereas compound 3b showed the greatest potency toward MCF-7 cells, with an IC_{50} of $3.36\text{ }\mu\text{g/mL}$ ($6.63\text{ }\mu\text{M}$).

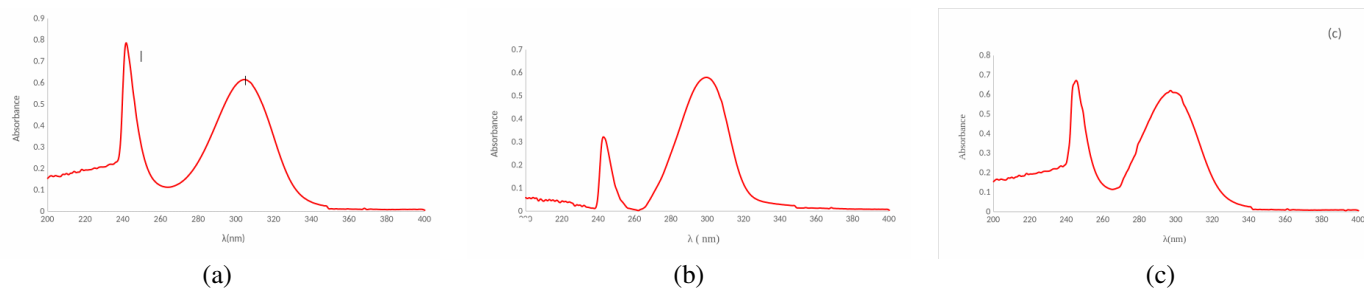


Figure 2: UV-Vis spectra of (a) dibutyltin(IV) bis(2-hydroxybenzoate) (3a), (b) dibutyltin(IV) bis(3-hydroxybenzoate) (3b), and (c) dibutyltin(IV) bis(4-hydroxybenzoate) (3c).

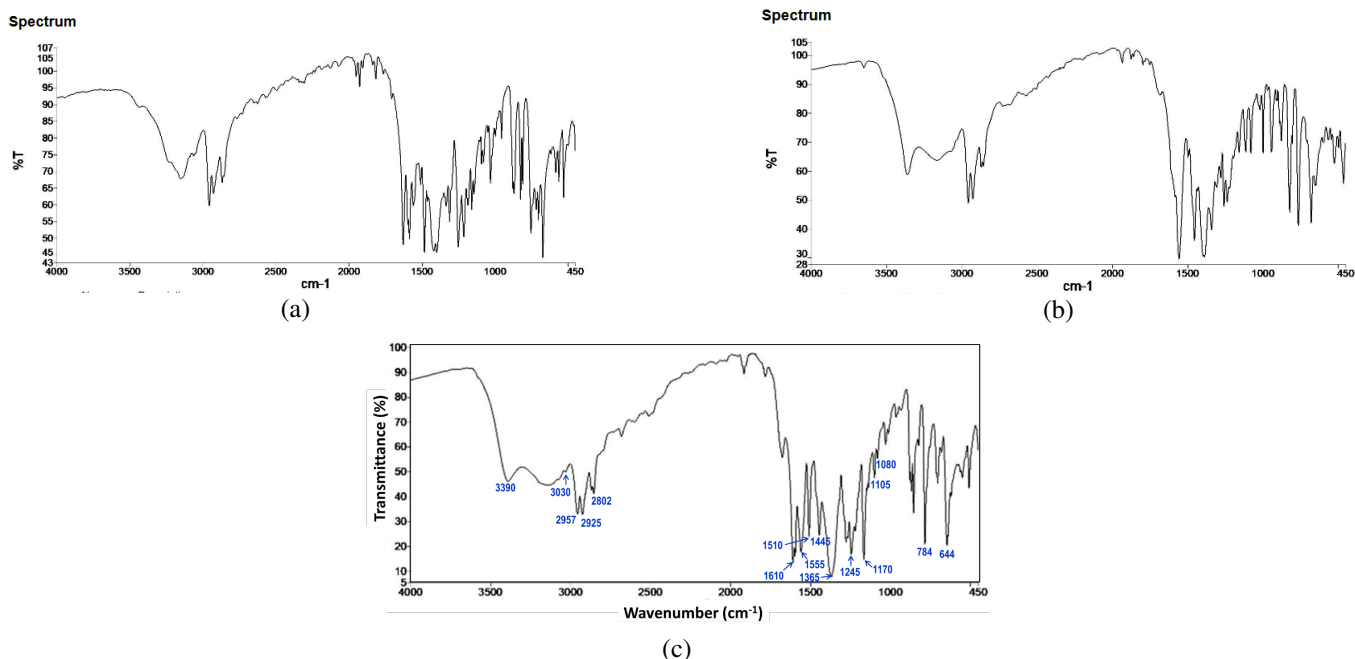


Figure 3: FTIR spectra of dibutyltin(IV) hydroxybenzoate derivatives: (a) 3a, (b) 3b, and (c) 3c.

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

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

^aEach value was the mean $\pm$ standard deviation of triplicate assays.

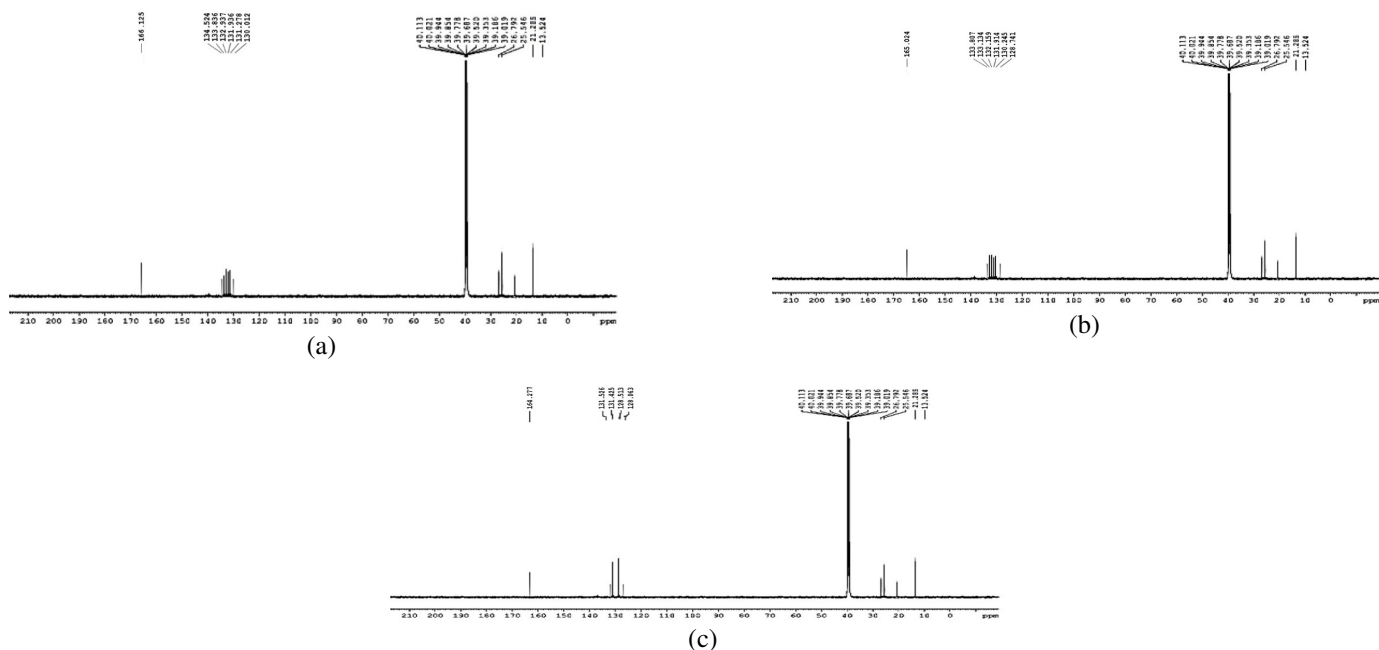
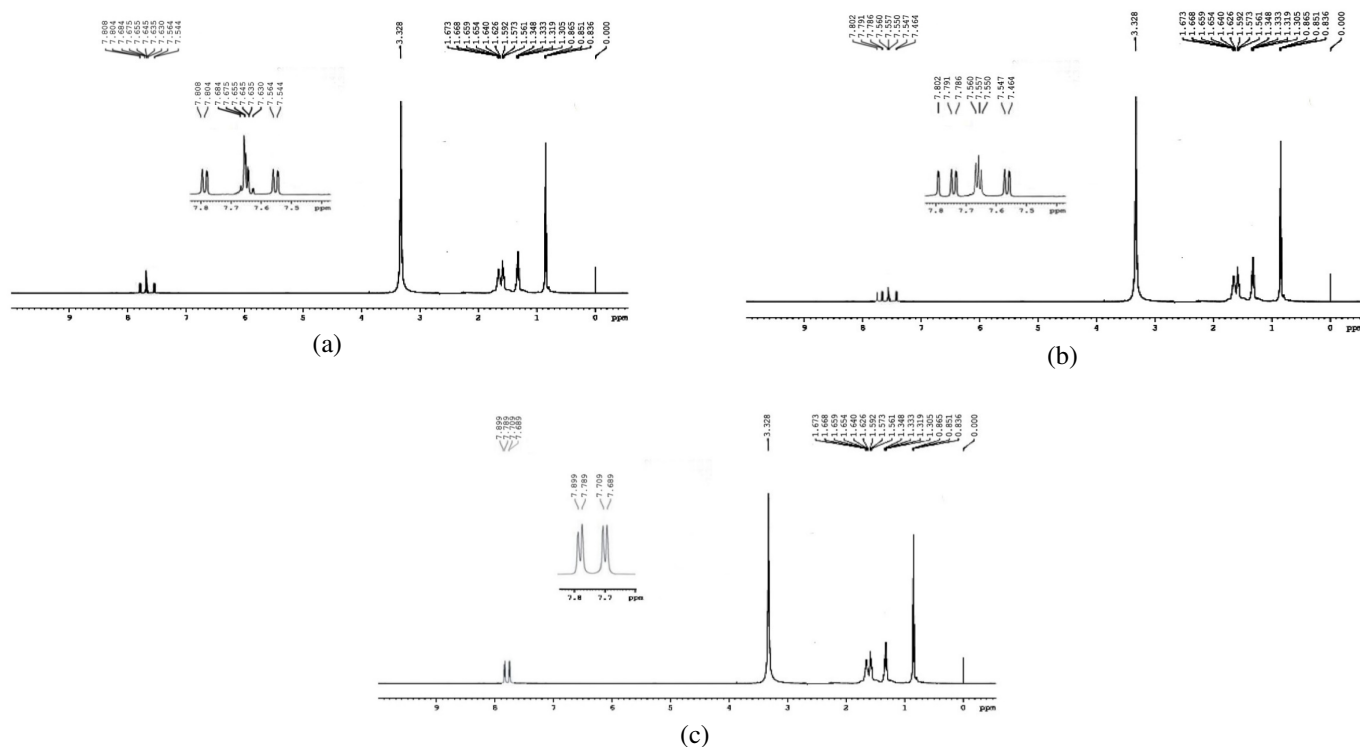
^aInterpreted from source text note ("not tested, as it is not toxic").

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 ($\text{IC}_{50} = 1.75 \pm 0.31 \mu\text{g/mL}$), MCF-7 ($\text{IC}_{50} = 1.08 \pm 0.08 \mu\text{g/mL}$), and HeLa ($\text{IC}_{50} = 0.91 \pm 0.02 \mu\text{g/mL}$) 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 $[\text{Bu}_2\text{Sn}(\text{iminodiacetate})(\text{H}_2\text{O})]_2\text{-phenanthroline}$ and $[\text{Bu}_2\text{Sn}(\text{iminodiacetate})(\text{H}_2\text{O})]_2\text{-bipyridine}$ 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, $\text{Bu}_2\text{tin(IV)}$ and $\text{Ph}_3\text{tin(IV)}$ methoxyethyldithiocarbamate complexes were reported to exert strong cytotoxic effects against HL-60 cells, with IC_{50} values of 0.40 and



0.35 μ M, respectively [31]. Diorganotin(IV) valsartan complexes [Bu₂Sn(valsartan)₂ and Ph₂Sn(valsartan)₂] exhibited antiproliferative activity against A549 cells, with IC₅₀ values of 0.04 and 67.9 μ g/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

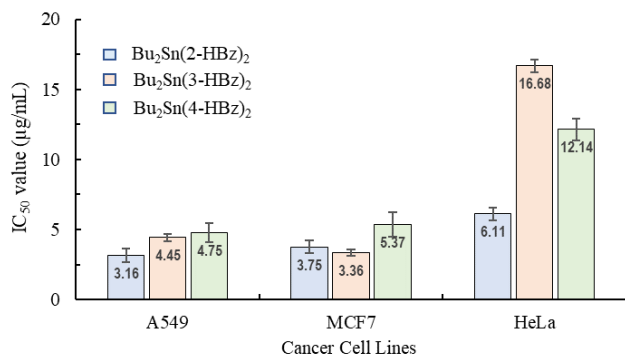


Figure 6: IC₅₀ values of synthesized compounds 3a–3c against A549, MCF-7, and HeLa cells.

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 ₂ Sn(2-HB) ₂ (3a)	7.6	6.4	3.9
2	Bu ₂ Sn(3-HB) ₂ (3b)	21.8	28.9	5.8
3	Bu ₂ Sn(4-HB) ₂ (3c)	> 26.9	> 23.8	> 10.5

the tested sample in normal cells by the IC₅₀ 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 IC₅₀ value of each synthesized compound (3a–3c) toward Vero cells by its IC₅₀ 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 nor-

mal 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 IC₅₀ 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 (IC₅₀ = 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 IC₅₀ values, showed high selectivity, with SI values of > 26.9 and > 23.8 against A549 and MCF-7 cells, respectively.

Overall, considering both IC₅₀ 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.

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