

Synthesis, Characterization, and Antiproliferation Activity Test of Dibutyltin(IV)di-2-Hydroxybenzoate and Dibutyltin(IV)di-3-Hydroxybenzoate Against Cervical Cancer Line HeLa

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Abstract: Due to the various side effects of conventional cancer treatment therapy, efforts to find anticancer agents with minimum side effects are in great demand. One of them is the synthesis of organotin (IV) hydroxybenzoate derivatives. Two organotin (IV) compounds, namely dibutyltin (IV) 2-hydroxybenzoate and dibutyltin (IV) di-3-hydroxybenzoate, have been successfully synthesized. The products were obtained by reacting the dibutyltin (IV) oxide with 2-hydroxybenzoic acid and 3-hydroxybenzoic acid. The compounds synthesized were fully characterized by UV-Vis, FT-IR, and NMR spectroscopies and microelemental analyzer to see the purity of the compounds. The antiproliferative activity of compounds have been tested against the HeLa cancer cell line. The results of the antiproliferation test showed that the compound dibutyltin (IV) 2-hydroxybenzoate had better antiproliferation activity than the compound dibutyltin (IV) 3-hydroxybenzoate and showed high selectivity.

1 INTRODUCTION

The interest in the bioactivity of organotin (IV) derivative compounds is not without reasons. Apart from the chemical structure of organotin (IV) compounds are interesting to study, they show good potential in various biological tests (Annisa *et al.*, 2017; Hadi *et al.*, 2018; Hadi *et al.*, 2023a; Hadi *et al.*, 2023b; Roner *et al.*, 2011; Samsuar *et al.*, 2021; Sirajuddin *et al.*, 2021). The bioactivity of organotin (IV) derivative compounds itself is determined by the

chemical properties and number of organic groups bound to the central atom of Sn (Pellerito and Nagy, 2002). Meanwhile, the bound anion only plays a role as a secondary determinant of the bioactivity of organotin (IV) compounds (Pellerito and Nagy, 2002; Hadi *et al.*, 2021a; Hadi *et al.*, 2022).

Many bioactivity studies on organotin (IV) compounds as alternative materials have been widely carried out and are still interesting to continue considering the large potential in these compounds. Organotin(IV) compounds have been tested to have

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bioactivity such as antimicrobial (Gilles *et al.*, 2011; Hadi *et al.*, 2021b; Sirajuddin *et al.*, 2021), antifungal activity (Kovala-Demertzi *et al.*, 2002; Hadi *et al.*, 2021a), antimalarial (Hadi *et al.*, 2018; Hadi *et al.*, 2021b), antioxidant (Arraq and Hadi, 2023; Hussain *et al.*, 2023; Sari *et al.*, 2020; Tyurin *et al.*, 2015) as well as antitumor and anticancer (Al-Rikabi *et al.*, 2023; Cepeda *et al.*, 2007; Hadi *et al.*, 2023a; Hadi *et al.*, 2023b). In previous research (Hadi *et al.*, 2023), the results of in vitro tests of dibutyltin (IV) hydroxybenzoate derivatives against leukemia cancer cells were reported, obtaining an IC₅₀ value of 24.4 µg/mL. If the IC₅₀ of this compound is ≤ 50 µg/mL, then the organotin (IV) 3-hydroxybenzoate compound has the potential to be an anticancer compound (Mans *et al.*, 2000). Therefore, it is hoped that the compounds dibutyltin (IV) di-2-hydroxybenzoate and dibutyltin (IV) di-3-hydroxybenzoate, which are benzoic acid derivative compounds, have anticancer activity and have IC₅₀ values that are lower than previous studies.

Among various organotin (IV) complexes, organotin (IV) carboxylates have strong bioactivity anticancer agent (Al-Rikabi *et al.*, 2023; Cepeda *et al.*, 2007; Hadi and Rilyanti, 2010; Hadi *et al.*, 2012; Hadi *et al.*, 2023a; Hadi *et al.*, 2023b). This is also driven by the increase in cancer sufferers throughout the world, where according to the latest data from the Global Cancer Observatory (2021), in 2020 in Indonesia there were more than 396 thousand cases of cancer recorded with 234 thousand patients dying, which is 9.2 % of them are deaths due to cervical cancer. This makes researchers in this field try to find potential anticancer agents with minimum side effects for sufferers.

In this research, we reported the synthesis and characterization of dibutyltin (IV) di-2-hydroxybenzoate and dibutyltin (IV)-di-3-hydroxybenzoate to then test their antiproliferative activity against the cervical cancer cell line, HeLa.

2 MATERIALS AND METHOD

2.1 Materials

All reagents used were of Analytical Reagent grade. Dibutyltin(IV) oxide (**1**), 2-hydroxybenzoic acid, 3-hydroxybenzoic acid, Dulbecco's Modified Eagle's Medium (DMEM), NaHCO₃, fetal bovine serum (FBS) were obtained from Sigm-Aldrich (MA, USA). Methanol and dimethylsulfoxide (DMSO) were obtained from Merck Millipore (MA, USA). All of these reagents were used as received and without

any further purification. Cervical cancer line HeLa was obtained from Elabscience®, USA.

2.2 Synthesis of Dibutyltin (IV) hydroxybenzoate

The synthesis procedure for the compounds **2** and **3** was adopted from the procedure carried out (Hadi & Rilyanti, 2010; Hadi *et al.*, 2012), which was an adaptation of the procedure used by Szorcsik *et al.* (2002).

In the synthesis of dibutyltin(IV) di-2-hydroxybenzoate (**2**) the starting materials used as follows: 1.3579 grams of dibutyltin(IV) oxide (**1**) was reacted with 0.9036 grams of 2-hydroxybenzoic acid in 10 mL of methanol p.a. as a solvent The reaction mixture was refluxed for 4 hours in a hotplate stirrer at a temperature of 60-61°C. After the reaction was complete, the methanol was evaporated and dried in a vacuum desiccator until dry crystals with constant weight are obtained. The compound was then characterized using an UV-Vis, FT-IR, ¹H-NMR and ¹³C-NMR spectroscopic analyses, the composition of the element (hydrogen and carbon) was determined using a microelemental analyzer, and then tested its antiproliferative activity against cervical cancer cell line HeLa. The same procedure was used in the preparation of compound **3**.

The compounds synthesized obtained were as follows:

Compound **2**: white solid; UV λ_{max}. (MeOH) nm (log ε): 242 and 304.8; IR ν_{max}. (KBr) cm⁻¹: 2928.98-2870.07 (C-H (-CH₃) in Bu), 1558.7 (C=O), 1419.6 (CO₂ asym), 1251.74 (Sn-O-C), 1077.62 (Sn-C in Bu), 753.35 (Sn-O); ¹H NMR (in DMSO-*d*₆, 600 MHz) δ (ppm): H_α: 1.6 (t), H_β: 1.4 (m); H_γ: 1.29 (t); H_δ: 0.93 (t), H in benzoate = 7.35–7.85 (m); ¹³C NMR (in DMSO-*d*₆, 150 MHz): δ (ppm): C_α: 26.8, C_β: 25.5, C_γ: 21.4, C_δ: 13.5, C1: 164.3; C2: 131.5, C3: 132.2, C4: 138.4, C5: 125.1, C6: 128.6, C7: 129.7; microelemental analysis: found (calculated): C 52.29 (52.07), H 5.48 (5.52).

Compound **3**: white-light yellowish solid; UV λ_{max}. (MeOH) nm (log ε): 243 and 299; IR ν_{max}. (KBr) cm⁻¹: 2958.78-2872.92 (C-H (-CH₃) in Bu), 1558.7 (C=O), 1419.6 (CO₂ asym), 1258.73 (Sn-O-C), 1079.10 (Sn-C in Bu), 763.34 (Sn-O); ¹H NMR (in DMSO-*d*₆, 600 MHz) δ (ppm): H_α: 1.6 (t), H_β: 1.4 (m); H_γ: 1.29 (t); H_δ: 0.93 (t), H in benzoate = 7.35–7.85 (m); ¹³C NMR (in DMSO-*d*₆, 150 MHz): δ (ppm): C_α: 26.8, C_β: 25.5, C_γ: 21.4, C_δ: 13.5, C1: 164.3; C2: 131.5, C3: 132.2, C4: 138.4, C5: 125.1, C6: 128.6, C7: 129.7; microelemental analysis: found (calculated): C 52.29 (52.07), H 5.48 (5.52).

2.3 Antiproliferation Activity Test

The procedure for testing antiproliferative activity as an anticancer in this study is part of a series of cancer cell bioassays adopted from procedures carried out by Winarno *et al.*, (2009) and Hadi & Rilyanti (2010).

The media was prepared as follows: 10.4 grams of Dulbecco's Modified Eagle's Medium (DMEM) that is containing L-glutamine was dissolved in 1 L of aquabiadest and then was added with 2.3 grams of NaHCO₃ that was dissolved in 1 L of aquabidest in an Erlenmeyer flask, then the solution mixture was stirred until homogeneous, and the pH of the solution was then measured with a pH indicator until a normal pH was obtained (pH 7-7.5). For cell culture purposes, 15 mL of 10% fetal bovine serum (FBS) was added to 85 mL of the prepared media. All works were carried out in laminar air flow under sterile conditions.

The activity test was carried out on each sample dissolved in DMSO. 5 concentration variations were used, i.e. 0; 0.5; 1; 4; 8 µg/mL which was then compared with Vero cells with 5 concentration variations at 0; 16; 32; 64; 128 µg/mL. Media containing HeLa cell suspension (2 x 10⁶ cells/mL) was placed into a multi-well plate tissue's culture with 24 wells, 1 mL in each well. As a control, 10 µL of DMSO was used to which 990 µL of HeLa cell suspension was added and a sample of the compound tested was added in each concentration. Then, 30 µL of penicillin as an antibiotic was added. The experiment was carried out in triplicate, then the cell suspension filled with the test substance was closed tightly and wrapped in HVS. Then, incubated for 72 hours at 37°C in a 5% CO₂ incubator.

Cell counting was carried out using an improved Neubauer hemocytometer. To differentiate between live cells and dead cells, before counting, 20 µL of 1% trypan blue solution was added and homogenized. A mixture of samples that had been stained with trypan blue in the amount of 100 µL of solution was flowed into the Neubauer Improved Haemocytometer. The cell suspension was inserted into the chamber where the suspension must be sufficiently dilute so that cells or other particles do not overlap in the counting chamber and must be evenly distributed. After that, the number of living cells was counted under a microscope with 4000x magnification. Live cells appear as clear spheres with a blue spot of cell nucleus in the center of the sphere, while dead cells appear as dark blue-black spots with an irregular shape. The percentage of inhibition of the test substance on the growth of HeLa cancer cells was calculated as follows:

$$\% \text{ inhibition} = 1 - A/B \times 100\% \quad (1)$$

A: the number of living cells in the medium containing the test substance

B: number of living cells in media that does not contain the test substance (control).

The inhibition percentage data was plotted into a probit table to obtain a probit value. Then a graph was made between log concentration (x) and probit (y) to obtain the linear regression equation $y = a + bx$. By entering the value $y = 5$ (probit of 50%), the x value (log concentration) was obtained, the IC₅₀ value by converting the log concentration value to anti-log form. IC₅₀ is the concentration of the test substance that can inhibit cell division by 50% after an incubation period of 72 hours. The activity of a sample is said to be active as an anti-cancer if the IC₅₀ value is ≤ 50 µg/mL (Mans *et al.*, 2000).

3 RESULTS AND DISCUSSION

3.1 Synthesis and Characterization of Dibutyltin (IV) hydroxybenzoate

Compounds **2** and **3** were obtained as white solids with the yields of 84.45% and 80.88% respectively. Characterization using UV, FT-IR, ¹H NMR, and ¹³C NMR, provide good spectra, and the values of micro elemental analysis data are in agreement with those of the theoretical values, confirming successful synthesis of the compounds. The reaction scheme for the preparation of **2** and **3** is shown in Figure 1.

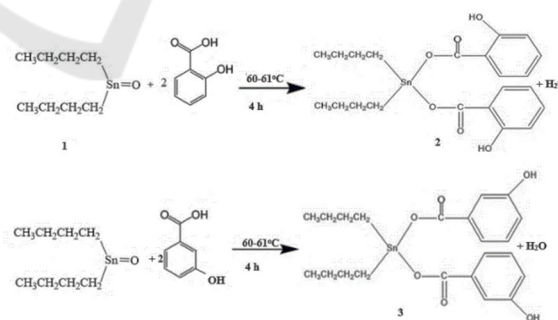


Figure 1: The Scheme of the preparation of the compounds studied

The UV spectroscopy analysis of compounds **2** and **3** produced characteristic absorption values with λ_{max} of the compounds prepared, associated with transitions of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$. At the same time, the starting material **1** gives only one characteristic peak

at 203 nm resulted from a $\pi \rightarrow \pi^*$ transition due to delocalization of butyl electrons. In Figure 1a, the reaction of **1** with 2-hydroxybenzoic acid to produce compound **2**, a bathochromic shift, occurs due to the influence of the chromophore group from the carbonyl group and addition of the benzene ring. In compound **2**, there is also a $n \rightarrow \pi^*$ transition at 304 nm due to lone pair electrons at the hydroxide group. Similar shift changes were also observed in the formation of compounds **3** (Hadi and Rilyanti, 2010; Hadi *et al.* 2012; Hadi *et al.*, 2022; 2023a; Hadi *et al.*, 2023b).

The ^1H and ^{13}C NMR spectra of compounds **2** and **3** were carefully evaluated. The data for compound **2** were compared with those previously available for similar compounds (Hadi and Rilyanti, 2010; Hadi *et al.* 2012; Hadi *et al.*, 2022; 2023a; Hadi *et al.*, 2023b). In ^1H NMR, the chemical shifts of the butyl protons bound to the Sn atom appeared as expected in the range of 0.836 – 1.673 ppm, while the chemical shifts of the benzoate protons were in the range of 7.544 – 7.808 ppm.

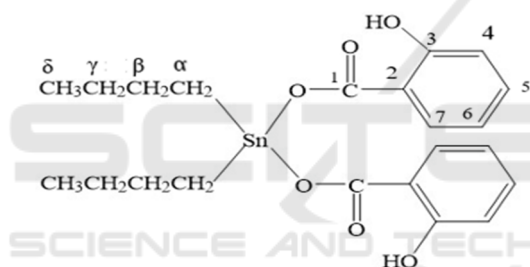


Figure 2. The numbering system of carbon atoms in compound **2**

The ^{13}C NMR of the butyl bonded to the Sn atom showed absorption at 130.012 – 166.125 ppm and for benzoate carbon at 166.125. The expected chemical shift of carbonyl carbon appears at 166-167 ppm (Hadi and Rilyanti, 2010; Hadi *et al.* 2012; Hadi *et al.*, 2022; 2023a; Hadi *et al.*, 2023b). A similar pattern was observed for compound **3**. The example of numbering the carbon atom for compound **2** is shown in Figure 2 and the ^1H and ^{13}C NMR spectra of the compound are presented in Figure 3a and 3b.

3.2 Antiproliferative Activity

The results of the antiproliferative activity test of compounds **2** and **3** against cervical cancer line HeLa are shown in Table 1. Based on these data, it was found that both compounds **2** and **3** have very low IC_{50} values. The relatively small IC_{50} value ($\text{IC}_{50} < 20 \mu\text{g/mL}$) shows that the activity of the compounds

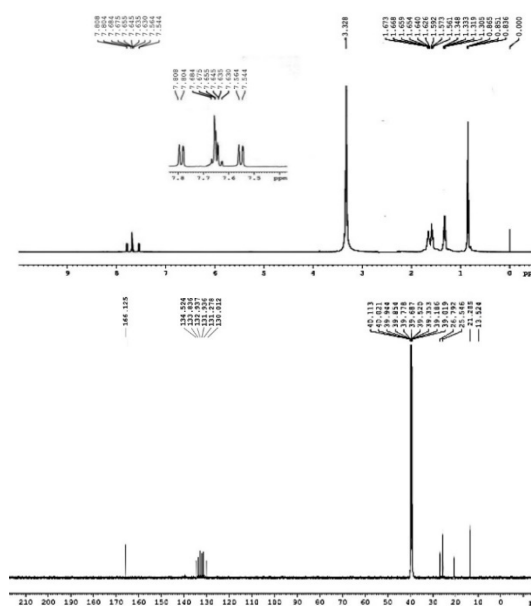


Figure 3: (a) The ^1H NMR and (b) ^{13}C NMR spectra of compound **2**

synthesized is categorized to be active as an anticancer based on the National Cancer Institute (NCI) Guideline so that further clinical testing can be carried out for its use as a safe anticancer agent. Furthermore based on the IC_{50} value for Vero cells, the selectivity index (SI) can be calculated by dividing the IC_{50} of Vero cells by the IC_{50} of HeLa cells. The SI numbers of compounds **2** and **3** for HeLa cells were 3.94 and 5.82, respectively. A sample is said to have high selectivity if it has a $\text{SI} > 3$ (López-Lázaro, 2015), therefore, compounds **2** and **3** have high selectivity.

Table 1: Results of antiproliferative activity test of compounds against HeLa cancer cells

Compound	IC_{50} Value against HeLa ($\mu\text{g/mL}$)	IC_{50} Value against Vero ($\mu\text{g/mL}$)
2	6.11	24.09
3	16.68	97.10

The reported results are almost similar to the results obtained by several other researchers such as Gielen (2003) and Pellerito *et al.* (2006). More promising fact is that based on the IC_{50} values data in the literatures (Gielen, 2003; Pellerito *et al.*, 2006), the results obtained in the research that has been carried out show that the compound that has been synthesized actually shows higher anticancer activity than the currently available cisplatin, *cis-*

[Pt(NH₃)₂Cl₂]. It is widely used to treat various types of cancer. The results obtained are certainly very promising that organotin (IV) carboxylate derivative compounds are potential candidates for metal-based anticancer drugs in the future.

4 CONCLUSIONS

The results showed that the two dibutyltin (IV) hydroxybenzoates synthesized have quite high anticancer activity when viewed from their antiproliferative activity. The antiproliferative activity of the tested compound indicated that the IC₅₀ value of compound **2** is higher than compound **3** with an IC₅₀ value of 6.11 µg/mL against cervical cancer cell HeLa, although the SI of compound **3** against Vero cell line is higher than 2. Therefore, these two compounds are promising to be candidate as anticancer metal based-drug.

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