

# IN VITRO ANTIMALARIAL ACTIVITY OF SOME ORGANOTIN(IV)2- NITROBENZOATE COMPOUNDS AGAINST PLASMODIUM FALCIPARUM

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**IN VITRO ANTIMALARIAL ACTIVITY OF SOME  
ORGANOTIN(IV)2-NITROBENZOATE COMPOUNDS AGAINST  
PLASMODIUM FALCIPARUM**

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12

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Antimalarial activity study of organotin(IV) derivatives with nitrobenzoic acid derivatives used as ligands has been performed. The targeted compounds were prepared from their organotin(IV) chlorides via dibutyltin(IV) oxide, diphenyltin(IV) dihydroxide, and triphenyltin(IV) hydroxide intermediate products, followed by reacting the intermediate products with 2-nitrobenzoic acid. The antimalarial activity was performed against *P. falciparum*. The results showed that the IC<sub>50</sub> values of dibutyltin(IV) di-2-nitrobenzoate, diphenyltin(IV) di-2-nitrobenzoate, and triphenyltin(IV) 2-nitrobenzoate were in  $8.4 \times 10^{-3}$ ,  $5.3 \times 10^{-2}$ , and  $9.1 \times 10^{-3}$  µg/ml, respectively. The IC<sub>50</sub> values were slightly higher than the value for chloroquine ( $2 \times 10^{-3}$  µg/ml) used as the positive control; however, one advantage is that all prepared organotin(IV) compounds were not resistant to *Plasmodium*, making the use of organotin(IV) as an antimalarial is possible. The results indicated that the derivative of triphenyltin(IV) was more potent when used as an antimalarial, as expected, and has potential to be developed as an antimalarial drug in the future.

**Keywords:** antimalarial activity, IC<sub>50</sub>, organotin(IV) nitrobenzoate, *P. falciparum*

**АНТИМАЛАРИСКА АКТИВНОСТ IN VITRO НА НЕКОИ СОЕДИНЕНИЈА  
НА ОРГАНОКАЛАЈ(IV) 2-НИТРОБЕНЗОАТ ВРЗ PLASMODIUM FALCIPARUM**

Спроведено е испитување на антимальариската активност на деривати на оргонокалај(IV) со нитробензоева киселина употребени како лиганд. Целните соединенија беа приготвени од нивните оргонокалај(IV) хлориди преку дибутилкалај(IV) оксид, дифенилкалај(IV) дихидроксид и трифенилкалај(IV) хидроксид како интермедијери, кои потоа реагираа со 2-нитробензоева киселина. Антимальариската активност беше изведена врз *P. falciparum*. Резултатите покажуваат дека соодветните IC<sub>50</sub> вредности на дибутилкалај(IV) ди-2-нитробензоат, дифенилкалај(IV) ди-2-нитробензоат и трифенилкалај(IV) ди-2-нитробензоат изнесуваа  $8,4 \times 10^{-3}$ ,  $5,3 \times 10^{-2}$  и  $9,1 \times 10^{-3}$  µg/ml. Вредностите IC<sub>50</sub> се нешто повисоки во однос на хлорохин ( $2 \times 10^{-3}$  µg/ml) кој беше употребен како позитивна контрола. Меѓутоа, една предност на сите приготвени соединенија на оргонокалај(IV) е што *Plasmodium* не е резистентен на нив, што овозможува нивна употреба како антимальариски средства. Резултатите укажуваат дека дериватот на трифенилкалај(IV) има поголема антимальариска активност и има потенцијал во иднина да се развие во антимальариски лек.

**Клучни зборови:** антимальариска активност; IC<sub>50</sub>; оргонокалај(IV) нитробензоат; *P. falciparum*

## 1. INTRODUCTION

Organotin(IV) compounds continue to attract chemists because of their strong effects in many biological tests [1, 2]. The number of groups that affects their biological activities is determined by the number of groups and the organic groups attached to Sn center [3], while the presence and nature of the anionic groups is a secondary factor [3]. Investigations of the coordination of carboxylates and their derivatives in organotin compounds have led to the isolation of new organotin(IV) carboxylates and carboxylate derivatives, which have shown interesting biological activities, including antitumor and anticancer [3–7], antimicrobial [5–8], antifungal [3, 8, 9], anticorrosion [10–13], and antiplasmodial [14] activities. The latest development of these compounds has led to the finding of antimalarial activities. The investigation of organotin(IV) as a possible antimalarial is still very challenging and has attracted much attention [14].

Malaria, a disease caused by *Plasmodium*, has been known for a century and continues to be a major public health problem in Indonesia and other tropical countries. Due to the wide effect caused by malaria, the World Health Organization (WHO) monitors this disease with a program called Roll Back Malaria (RBM), with focuses on immediate diagnoses and exact treatment to eradicate malaria [15, 16]. Malaria cases in Indonesia from 2008–2016 were very high [17, 18]. Based on the data released by the WHO in 2016, the rate of malaria incidence in Indonesia is 6 % [18]. Previously, malaria treatments in Indonesia have used chloroquine and sulfadoxine-pirimetamine as the main drugs [17]; however, their use is now limited due to their resistances against malaria. Therefore, efforts to find new potent antimalarial drugs is required [14, 15].

Based on the fact that organotin(IV) compounds have been found to have promising antimalarial activity, in this paper, we report the application and antimalarial activity of organotin(IV) 2-nitrobenzoates against *P. falciparum*.

## 2. EXPERIMENTAL

### 2.1. Materials

All reagents used were AR grade. Dibutyltin(IV) dichlorides ( $[(n-C_4H_9)_2Cl_2]$ ), diphenyltin(IV) dichloride ( $[(C_6H_5)_2Cl_2]$ ), triphenyltin(IV) chloride ( $[(C_6H_5)_3Cl]$ ), 2-nitrobenzoic acid, and Roswell Park Memorial Institute (RPMI) medium were obtained from Sigma. Water (HPLC grade),

sodium hydroxide (NaOH), and methanol ( $CH_3OH$ ) were JT Baker products and were used without further purification.

### 2.2. Characterization and instrumentation

Microelemental analyses (CHNS) were performed on a Fisher EA 1108 series elemental analyzer. Infrared (IR) spectra in the range of 4000–400  $cm^{-1}$  were recorded on a Bruker VERTEX 70 Fourier-Transform infrared (FT-IR) spectrophotometer with KBr discs. The ultraviolet (UV) spectra were recorded in the UV region and were measured using a UV-Shimadzu UV-245 Spectrophotometer. Measurements were performed in 1 ml quartz cells. Solutions were prepared using methanol as the solvent with a concentration of  $1.0 \times 10^{-4}$  M.

$^1H$  and  $^{13}C$  nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 600 MHz NMR (600 MHz for  $^1H$  and 150 MHz for  $^{13}C$ ). All experiments were run in dimethyl sulfoxide ( $DMSO$ )– $D_6$  at 298 K. The number of runs used for  $^1H$  experiments were 32 with reference at  $DMSO$  signal at 2.5 ppm, while the  $^{13}C$  spectra involved 1000–4000 scans with the reference  $DMSO$  signal at 39.5 ppm.

### 2.3. Preparation of organotin(IV) nitrobenzoates

The organotin(IV) 2-nitrobenzoates used in this work were prepared based on the procedure previously reported [6–10, 12, 13] and adapted from the work by Szorcik *et al.* [19]. An example procedure in the preparation of diphenyltin(IV) di-2-nitrobenzoate is as follows:

Approximately 0.8 g (0.02 mol) NaOH was added to 3.44 g (0.01 mol)  $[(C_6H_5)_2SnCl_2]$  (4) in 50 ml methanol. The reaction mixture was stirred for about 60 minutes. The compound  $[(C_6H_5)_2Sn(OH)_2]$  (5) was precipitated out as a white solid, filtered, and dried in vacuo until analysis and further reaction. The average yield was 2.92 g (95 %).

Approximately 2 mole equivalents of 2-nitrobenzoic acid (0.501 g) was added to 0.4605 g (1.5 mmol) of compound 2 in 50 ml of methanol, and the solution was refluxed for 4 hours at 60–62°C. After removal of the solvent by rotary evaporation, the produced compounds  $[(C_6H_5)_2Sn(2-OOCC_6H_4(NO_2)_2)]$  were dried in vacuo until analysis and further use for in vitro antimalarial activity studies. The yield was 1.67 g (greater than ~92 %).

A similar procedure was also adapted in the preparation of dibutyltin(IV) and triphenyltin(IV) derivatives,  $[(n-C_4H_9)_2Sn(2-OOCC_6H_4NO_2)_2]$  (3) and  $[(C_6H_5)_3Sn(2-OOCC_6H_4NO_2)]$  (9), respective-

ly. For triphenyltin(IV), only one mole equivalent of the nitrobenzoic acid was added.

#### 2.4. In vitro antimalarial bioactivity assays

The *in vitro* antimalarial assays were performed at the Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia. The malaria parasite *P. falciparum* 3D7 clone was essentially propagated according to a previously published procedure [11]. Briefly, parasite cultures were propagated in tissue culture flasks containing RPMI-1640 medium supplemented with 25 µg/ml gentamycin, 50 µg/ml hypoxanthine, 25 mM Hepes buffer, 25 mM sodium bicarbonate, 10 % AB+ human serum, 5 % haematocrit, and human erythrocytes with the pH maintained at 7.4. Each compound tested was first dissolved in DMSO and diluted to different concentrations by adding complete malaria medium. Chloroquine was used as a positive control. To determine the antiplasmodial activity of each isolated compound, parasites were placed in a 24-well culture plate in the presence of each compound, where the concentration was 10 µg/ml, 1 µg/ml, 0.1 µg/ml, 0.01 µg/ml, or 0.001 µg/ml. The parasite growth was monitored by making a blood smear that was fixed with methanol and stained with Giemsa. Total parasitaemia was calculated as the number of observed parasites divided by the total erythrocyte, multiplied by 100

%. The concentration response parasite growth data was calculated by linear regression provided by SYSTAT Sigma Plot using the 50 % inhibitory concentration (IC<sub>50</sub>). The IC<sub>50</sub> value is defined as 50 % concentration of a compound producing 50 % growth inhibition relative to the untreated control.

### 3. RESULTS AND DISCUSSION

Following the preparation of the organotin(IV) carboxylate compounds, preparation and characterization of three organotin(IV) 2-nitrobenzoates of dibutyltin(IV) di-2-nitrobenzoate [*n*-C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>Sn(2-OOCC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>)<sub>2</sub>] (3), diphenyltin(IV) di-2-nitrobenzoate [(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>Sn(2-OOCC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>)<sub>2</sub>] (6), and triphenyltin(IV) 2-nitrobenzoate [(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>Sn(2-OOCC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>)] (9) were successfully performed from their chlorides [*n*-C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>SnCl<sub>2</sub>] (1), [(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>SnCl<sub>2</sub>] (4), and [(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>SnCl] (7), respectively, where all reactions in all cases were performed via [(*n*-C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>SnO] (2), [(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>Sn(OH)<sub>2</sub>] (5) and [(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>SnOH] (8) in the same way as the procedure previously reported [6–9, 12, 13]. An example of the reaction step that occurred in the preparation of dibutyltin(IV) dinitrobenzoate is shown in Figure 1. The microanalysis data for all compounds synthesized is provided in Table 1. In general, all values obtained were very good and close to the calculated values.

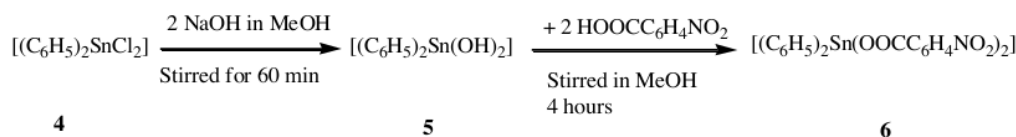


Fig. 1. Scheme for the preparation of organotin(IV) di-2-nitrobenzoate

Table 1

#### The microanalytical data of the organotin(IV) compounds synthesized

Compound	Elemental analysis found (calculated)		
	C	H	N
[( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> SnCl <sub>2</sub> ](1)	31.4 (31.6)	6.0 (5.9)	
[( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> SnO](2)	38.6 (38.6)	7.1 (7.3)	
[( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> Sn(2-OOCC <sub>6</sub> H <sub>4</sub> (NO <sub>2</sub> ) <sub>2</sub> )] (3)	46.8 (46.7)	4.7 (4.6)	4.8(4.96)
[(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> SnCl <sub>2</sub> ](4)	41.7 (41.9)	2.8 (2.9)	
[(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> Sn(OH) <sub>2</sub> ](5)	46.5 (46.9)	3.8 (3.9)	
[(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> Sn(2-OOCC <sub>6</sub> H <sub>4</sub> (NO <sub>2</sub> ) <sub>2</sub> )](6)	51.3 (51.6)	3.1 (2.98)	4.5 (4.63)
[(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> SnCl] (7)	55.8 (56.1)	4.0 (3.9)	
[(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> Sn(OH)] (8)	58.4 (58.9)	4.3 (4.4)	
[(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> Sn(2-OOCC <sub>6</sub> H <sub>4</sub> (NO <sub>2</sub> )] (9)	57.2 (58.1)	3.8 (3.68)	2.6 (2.71)

Spectroscopy techniques have been used to characterize all synthesized compounds. The important FT-IR data and their assignments are presented in Table 2. The characteristic band of the starting materials (1, 4, 7) is the strong stretching band of the Sn–Cl bond at 390–310  $\text{cm}^{-1}$ . In **1**, for example, the Sn–Cl bond appeared at a frequency of 334.2  $\text{cm}^{-1}$ . The other characteristic bands of this compound appear as the stretching band from butyl ligands at 1069  $\text{cm}^{-1}$  and the bending vibration of the C–H aliphatic stretch of the butyl at a frequency of 2956–2865  $\text{cm}^{-1}$ . When compound **1** was converted to compound **2**, the main stretching band of Sn–Cl disappeared and a new strong band at a frequency of 417.4  $\text{cm}^{-1}$  appeared as one of the main stretching bands. This band is characteristic of the Sn–O bond in compound **2**. The stretching band and the bending vibrations due to the presence of butyls were still observed, as expected, although the frequencies were a little shifted. The formation of dibutyltin(IV) di-2-nitrobenzoate compounds  $[(n\text{-C}_4\text{H}_9)_2\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2))_2]$  (**3**) was confirmed by the strong asymmetric stretching bands of the carboxylate groups, which occurred at ca. 1400  $\text{cm}^{-1}$ , and the symmetric stretch at ca. 1600  $\text{cm}^{-1}$ , as well as the present of Sn–O stretching of the acid at 435  $\text{cm}^{-1}$ . The appearance of these bands confirmed the success of the substitution reaction [6–9, 12, 13].

UV spectroscopy analyses of all compounds were utilized to obtain  $\lambda_{\text{max}}$ . The data obtained is shown in Table 3. It is clear that there was a shifting change in the  $\lambda_{\text{max}}$  for each compound in any step of the reaction. For example, compound **1** had a  $\lambda_{\text{max}}$  of 210.7 nm, while compound **2** had a  $\lambda_{\text{max}}$  of 202.9 nm. This information indicates that there was a shift to a shorter  $\lambda_{\text{max}}$  value when the conversion of compound **1** to **2** took place. The wavelength shift to a shorter  $\lambda_{\text{max}}$  could occur due to either the solvent used in the measurement or the effect of an auxochrome of the ligand. However, in this study, as the solvent used for all measurements was the same (methanol), the change in the  $\lambda_{\text{max}}$  that occurred must have been due to the auxochrome effect. In the case of compound **1** and **2**, there was an oxide group, which has a bigger electron drawing effect in compound **2** compared to the chloride group in compound **1**. As a result, the electron transition in **2** is too difficult to occur. Thus, the measured  $\lambda_{\text{max}}$  was shorter in compound **2** compared to compound **1** [20–22]. Similar results were observed for other changes, as can be seen in Table 3. For example, in compound **3**, the electron drawing effect of 2- $\text{C}_6\text{H}_4(\text{NO}_2)\text{COOH}$  was less than that of the chloride in compound **1**; therefore, the electron transition in this molecule will be easier (the energy required is less), thus producing a longer  $\lambda_{\text{max}}$  (291.3 nm).

Table 2

The characteristic and important IR bands of the organotin(IV) compounds ( $\text{cm}^{-1}$ ) synthesized

Compound	<b>3</b>	<b>6</b>	<b>9</b>	References
Sn–O	434.4	594.0	735.42	800–400
Sn–O–C	1029.1	1238.2	1243.4	1050–900
Sn–Bu	674.4	–	–	740–660
CO <sub>2</sub> asym	1419.1	1531.7	1557.5	1600–1400
CO <sub>2</sub> sym	1558.1	1659.3	1630.4	1700–1550
C–H aliphatic	2954 – 2860	–	–	2960 – 2850
Phenyl	–	1467.0; 750.7	1428.4; 729.1	1450, 730

Table 3

The  $\lambda_{\text{max}}$  of the UV-Vis spectra of the organotin(IV)2-nitrobenzoate compounds

Compound	$\lambda_{\text{max}}$ (nm)		
	$\pi\text{-}\pi^*$	n- $\pi$	Benzene ring secondary band
$[(n\text{-C}_4\text{H}_9)_2\text{SnCl}_2]$ ( <b>1</b> )	210.7	–	–
$[(n\text{-C}_4\text{H}_9)_2\text{SnO}]$ ( <b>2</b> )	202.9	–	–
$[(n\text{-C}_4\text{H}_9)_2\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2))_2]$ ( <b>3</b> )	–	291.3	–
$[(\text{C}_6\text{H}_5)_2\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2))_2]$ ( <b>6</b> )	201	299.2	407
$[(\text{C}_6\text{H}_5)_2\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2))]$ ( <b>9</b> )	204	303.8	410

The analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts of the prepared compounds is shown in Table 4 and based on the numbering of the proposed structure as in Figure 2. Certain signals in the recorded spectra were carefully characterized. The chemical shift ( $\delta$ ) of the butyl protons attached to the tin metal appeared at 0.92 ppm for  $\text{H}_\delta$  and 1.36 – 1.61 ppm for  $\text{H}_\alpha$  and  $\text{H}_\beta$ . The carbons of the butyl ligands were observed at positions comparable to other similar compounds reported previously [7, 12, 13, 19, 21–23]. The chemical shift of the phenyl protons attached to the tin metal appeared at 7.35 – 7.58 ppm, while the carbon of the carboxyl group of all compounds appeared in the region of 176 ppm, as expected [13, 20, 22–24]. The carbon atoms of the phenyl ligand appeared in  $\delta$  of 131 – 126 ppm, while the carbons in the nitrobenzoate derivatives appeared in  $\delta$  range of 140 – 130 ppm, close to the reported values of similar compounds [13, 20, 22–24].

In our previous study on the antifungal and anticancer activity of the compounds reported here [6–9, 12, 13], it has been shown that optimal activity of the **5** antifungals and anticancers is associated with the number of carbon atoms of the ligand present in the organotin(IV) [6–9, 12, 13, 25], where the derivative of triphenyltin(IV) carboxylate, which contains 18 carbon atoms, has the highest activity [6–9, 12, 13, 25]. The same phenomena, interestingly, was also observed in this study.

Table 4

 $^1\text{H}$  and  $^{13}\text{C}$  spectra of the compounds synthesized

Compounds	H in butyl or phenyl (ppm)	H in benzoate (ppm)	C in butyl, phenyl and benzoate (ppm)
$[(n\text{-C}_4\text{H}_9)_2\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2)_2)]$ ( <b>3</b> )	$\text{H}_\alpha$ & $\text{H}_\beta$ : 1.36–1.61 (m); $\text{H}_\gamma$ : 1.29 (m); $\text{H}_\delta$ : 0.92 (t)	7.33 – 7.85 (m)	$\text{C}_\alpha$ : 21.1; $\text{C}_\beta$ : 26.5; $\text{C}_\gamma$ : 25.8; $\text{C}_\delta$ : 14.1; $\text{C}_1$ : 174.8; $\text{C}_2$ : 139.2; $\text{C}_3$ & $\text{C}_7$ : 129.6; $\text{C}_4$ & $\text{C}_6$ : 128.5; $\text{C}_5$ : 125.2
$[(\text{C}_6\text{H}_5)_2\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2)_2)]$ ( <b>6</b> )	$\text{H}_2$ & $\text{H}_6$ : 7.58 (d, 4H); $\text{H}_3$ & $\text{H}_5$ : 7.47 (t, 4H); $\text{H}_4$ : 7.35 (t, 2H)	7.80 – 7.92 (m)	$\text{C}_1$ – $\text{C}_6$ (phen): 131.6–126.8; $\text{C}_7$ : 175.6; $\text{C}_8$ : 139.4; $\text{C}_9$ & $\text{C}_{13}$ : 130.1; $\text{C}_{10}$ & $\text{C}_{12}$ : 129.2; $\text{C}_{11}$ : 128.4
$[(\text{C}_6\text{H}_5)_3\text{Sn}(2\text{-OOC}_6\text{H}_4(\text{NO}_2)_2)]$ ( <b>9</b> )	$\text{H}_2$ & $\text{H}_6$ : 7.56 (d, 6H); $\text{H}_3$ & $\text{H}_5$ : 7.44 (t, 6H); $\text{H}_4$ : 7.01 (t, 3H)	7.80 – 7.9 (d)	$\text{C}_1$ – $\text{C}_6$ (phen): 131.0–126.2; $\text{C}_7$ : 175.2; $\text{C}_8$ : 139.1; $\text{C}_9$ & $\text{C}_{13}$ : 130.2; $\text{C}_{10}$ & $\text{C}_{12}$ : 128.5; $\text{C}_{11}$ : 128.1

As shown in Table 5, the derivatives of triphenyltin(IV) compounds showed the highest antimalarial activities in the series, and the diphenyltin(IV) compounds were stronger inhibitors than those of dibutyltin(IV) compounds, similar to pre-

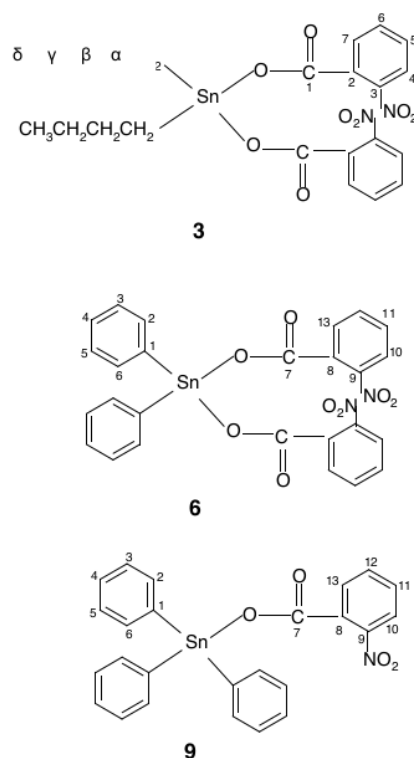


Fig. 2. The proposed structures of the synthesized compounds and the suggested numbering of carbons in each compound

vious reports [12, 13]. Thus, the number of carbon atoms present, as well as the type of the ligands, has a significant effect on the antimalarial activity of the organotin(IV) compounds tested [25].

Table 5

The  $IC_{50}$  values of the compounds tested

Compounds	$IC_{50}$ ( $\mu\text{g/ml}$ )
Chloroquine	$2.0 \times 10^{-3}$
$[(n\text{-C}_4\text{H}_9)_2\text{Sn}(2\text{-OOCCH}_2\text{H}_4(\text{NO}_2)_2)](3)$	$8.4 \times 10^{-2}$
$[(\text{C}_6\text{H}_5)_2\text{Sn}(2\text{-OOCCH}_2\text{H}_4(\text{NO}_2)_2)](6)$	$5.3 \times 10^{-2}$
$[(\text{C}_6\text{H}_5)_3\text{Sn}(2\text{-OOCCH}_2\text{H}_4(\text{NO}_2)_2)](9)$	$9.1 \times 10^{-3}$

It was also observed that the synthesized organotin(IV) 2-nitrobenzoate compounds exhibited much higher antimalarial activities compared to those of the ligand starting materials, and intermediate products. In this respect, our results are consistent with a well-known fact that many biologically active compounds become more active upon complexation [26]. According to Crowe, the actual biological activity of diorganotin compounds of the type  $\text{RR}'_2\text{SnXY}$  (R and R' = alkyl or aryl, X and Y = anions) is determined solely by the  $\text{RR}'_2\text{Sn}^{2+}$  moiety [27].

#### 4. CONCLUSION

Organotin(IV) nitrobenzoate compounds were successfully prepared and had promising results regarding their use as antimalarial drugs. The fact that triphenyltin(IV) nitrobenzoate derivatives have the highest antimalarial activity was in line with other data relating the number of carbon atoms present in the compound. Further studies using artemisinin-based combination therapy (ACT) as the positive control, as well as comprehensive antimalarial experiments, are being carried out to find the best explanation for this phenomenon.

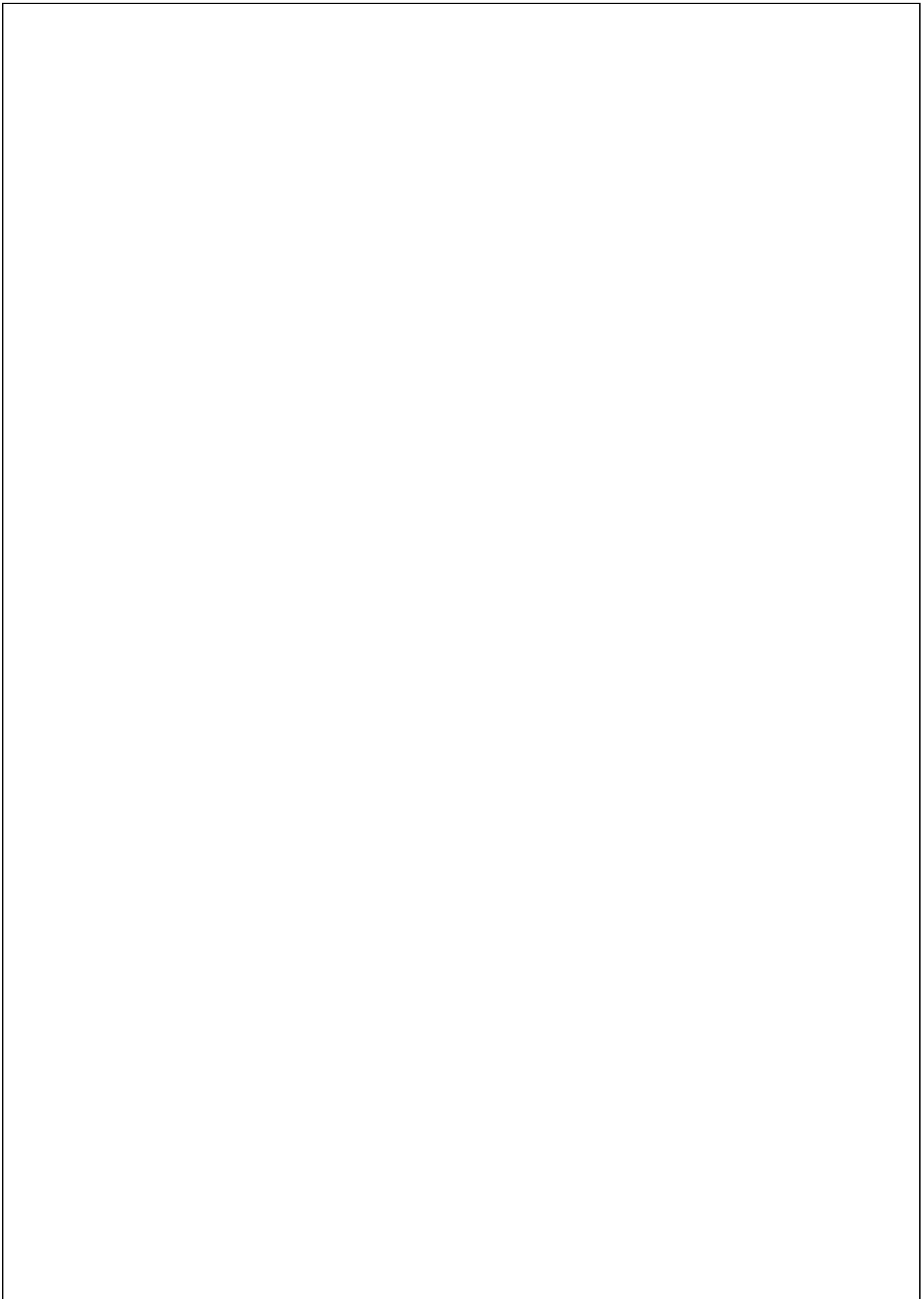
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#### REFERENCES

- [1] E. R. T. Tiekink, Structural chemistry of organotin carboxylates: A review of the crystallographic literature, *App. Organomet. Chem.* **5**, 1–30 (1991).
- [2] K. Shahid, S. Ali, S. Shahzadi, Z. Akhtar, Organotin(IV) complexes on aniline derivatives, Part II: Synthesis and spectroscopic characterization of organotin(IV) derivatives of 2-[4-bromoaniline]carboxyl]benzoic acid, *Turk. J. Chem.*, **27**, 209–215 (2003).
- [3] L. Pellerito, L. Nagy, Organotin(IV)<sup>2+</sup> complexes formed with biologically active ligands: equilibrium and structural studies, and some biological aspects. *Coord. Chem. Rev.*, **224**, 111–150 (2002).
- [4] B. Gleeson, J. Claffey, D. Ertler, M. Hogan, H. Müller-Bunz, F. Paradisi, D. Wallis, and M. Tacke, Novel organotin antibacterial and anticancer drugs, *Polyhedron*, **27**, 3619–3624 (2008).
- [5] W. Rehman, A. Badshah, S. Khan, L. T. A. Tuyet, Synthesis, characterization, antimicrobial and antitumor screening of some diorganotin(IV) complexes of 2-[(9H-Purin-6-ylimino)]-phenol, *Eur. J. Med. Chem.*, **44**, 3981–3985 (2009).
- [6] S. Hadi, M. Rilyanti, Synthesis and *in vitro* anticancer activity of some organotin(IV)benzoate compounds, *Orient. J. Chem.*, **26**, 775–779 (2010).
- [7] S. Hadi, M. Rilyanti, Suharso, *In Vitro* activity and comparative studies of some organotin(IV) benzoate derivatives against leukemia cancer cell: L-1210, *Indo. J. Chem.*, **12**, 172–177 (2012).
- [8] S. Hadi, B. Irawan, Efri, The antifungal activity test of some organotin(IV) carboxylates, *J. Appl. Sci. Res.*, **4**, 1521–1525 (2008).
- [9] S. Hadi, M. Rilyanti, Nurhasanah, Comparative study on the antifungal activity of some di- and tributyltin(IV) carboxylate compounds, *Modern Appl. Sci.*, **3** (2), 12–17 (2009).
- [10] R. Singh, P. Chaudary, N. K. Khausik, A Review: Organotin compounds in corrosion inhibition, *Rev. Inorg. Chem.*, **30**, 275–294 (2010).
- [11] R. B. Rastogi, M. M. Singh, K. Singh, M. Yadav, Organotin dithiobiurets as corrosion inhibitors for mildsteel-dimethyl sulfoxide containing HCl, *Afr. J. Pure Appl. Chem.*, **5**(2), 19–33 (2011).
- [12] H. Kurniasiah, M. Nurissalam, B. Iswantoro, H. Afriyani, H. I. Qudus, S. Hadi., The Synthesis, characterization and comparative anticorrosion study of some organotin(IV) 4-chlorobenzoates, *Orient. J. Chem.*, **31**, 2377–2383 (2015).
- [13] S. Hadi, H. Afriyani, W. D. Anggraini, H. I. Qudus, T. Suhartati, The synthesis and potency study of some dibutyltin(IV) dinitrobenzoate compounds as corrosion inhibitor for mild steel HRP in DMSO-HCl solution, *Asian J. Chem.*, **27**, 1509–1512 (2015).
- [14] C. Hansch, R. P. Verma, Larvicidal activities of some organotin compounds on mosquito larvae: A QSAR study, *Eur. J. Med. Chem.*, **44**, 260–273 (2009).

- [15] WHO, *Roll Back Malaria Program*. Available at. <http://www.who.int/malaria/en/>. 2011. [Verified April 20, 2011]
- [16] A. A. James, Mosquito molecular genetics: the hands that feed bite back, *Science*, **257**, 37–38 (1992).
- [17] I. R. F. Elyazar, S. I. Hay, J. K. Baird. Malaria distribution, prevalence, drug resistance and control in Indonesia, *Adv Parasitol.*, **74**, 41–175 (2011).
- [18] WHO. *Malaria Profile of Indonesia*. [http://www.who.int/malaria/publications/country-profiles/profile\\_idn\\_en.pdf](http://www.who.int/malaria/publications/country-profiles/profile_idn_en.pdf). 2016 (Verified on October 5, 2018)
- [19] A. Szorcik, L. Nagy, K. Gadja-Schranz, L. Pellerito, E. Nagy, E. T. Edelmann, Structural studies on organotin(IV) complexes formed with ligands containing {S, N, O} donor atoms, *J. Radioanal. Nucl. Chem.* **252**, 523–530 (2002).
- [20] M. N. R. Yadav, M. Gielen, H. Dalil, D. de Vos, G. Eng. Synthesis, characteristic spectral studies and *in vitro* antimicrobial and antitumour activities of organotin(IV) complexes of Schiff bases derived from aminoacids, *Appl. Organometal. Chem.*, **11**, 727–736 (1997).
- [21] Sudjadi, *The Structure Determination of Organic Compounds*. Ghalia Publishers, 1985. (In Indonesian).
- [22] M. Rilyanti, S. Hadi, Synthesis, characterization and thermal stability of complex *cis*-[Co(bipy)<sub>2</sub>(CN)<sub>2</sub>] and its interaction with NO<sub>2</sub> gas, *Russ. J. Inorg. Chem.*, **56**, 418–421 (2011).
- [23] S. Hadi, T. G. Appleton, G. A. Ayoko, Reactions of *fac*-[PtMe<sub>2</sub>(OMe)(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> with halide ions: effect of halide trans effect on methoxide hydrolysis, *Inorg. Chim. Acta.*, **352**, 201–207 (2003).
- [24] S. Hadi, T. G. Appleton, Reactions of cisplatin hydrolytes, *cis*-[Pt(<sup>15</sup>NH<sub>3</sub>)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup>, with N-acetyl-L-cysteine, *Russ. J. Inorg. Chem.*, **55**, 223–228 (2010).
- [25] Z. H. Chohan, A. Rauf, Some biologically active mixed ligand complexes of Co(II), Cu(II) and Ni(II) with ONO, NNO and SNO donor nicotinoylhydrazine-derived ligands, *Synth. React. Inorg. Met.-Org. Chem.*, **26**, 591–604 (1996).
- [26] Gershon, Antifungal activity of bischelates of 5-, 7-, and 5,7-halogenated 8-quinols with copper(II). Determination of the long and short axes of the pores in the fungal spore wall, *J. Med. Chem.*, **17**, 824–827 (1974).
- [27] A. J. Crowe, The antitumour activity of tin compounds; in Gielen M., (Ed.) *Metal-Based Drugs*, **1**, 103–149 (1989).





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---
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- 
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