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The Potency Study of Organotin(IV) 3-Nitrobenzoate Compounds as Antimalarial Agents

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Abstract. This paper reports the potency study of organotin(IV) 3-nitrobenzoate as antimalarial agent. The organotin(IV) 3-nitrobenzoate compounds were synthesized by reacting the intermediate products dibutyltin(IV) oxide, diphenyltin(IV) dihydroxide and triphenyltin(IV) hydroxide, with 3-nitrobenzoic acid. The antimalarial activity study was performed against *Plasmodium falcifarum* and the result of IC₅₀ of the three compounds tested, i.e. dibutyltin(IV) di-3-nitrobenzoate, diphenyltin(IV) di-3-nitrobenzoate and triphenyltin(IV) 3-nitrobenzoate were 8.1×10^{-3} , 5.2×10^{-2} and 7.2×10^{-3} µg/mL, respectively, while the chloroquine gave IC₅₀ 2×10^{-3} µg/mL. The IC₅₀ of the compounds tested were little bit higher than the positive control, however these organotin(IV) compounds synthesized are not resistant to Plasmodium, thus the possible development as antimalarial agent is widely opened.

Keywords: antimalaria activity, IC₅₀, organotin(IV) 3-nitrobenzoate

1. Introduction

Malaria is a disease that has been known since a century ago. This disease is caused due to the bite of Plasmodium. Nowadays, it continues to be a major public health problem in Indonesia and other tropical countries. Malaria has large effect to human being thus WHO pays attention to this disease by a program called Roll Back Malaria (RBM). Few points of this program were immediate diagnoses and exact treatment to eradicate malaria [1,2]. In Indonesia, the malaria cases between the periods of 1997 – 2010 increased sharply. In the provinces of Java and Bali the malaria cases were increased by ten times, while outside these provinces were increased 4-5 times. These cases were also followed by resistance cases toward standard drugs used in the malaria treatments, the chloroquine and the sulfadoxine-pirimetamine. In some provinces, there were more than 25% resistance cases which cause the use of these standard drugs to be much more limited, therefore efforts to find new potent antimalarial drugs are urgently needed [3].

The organotin(IV) compounds are part of organometallic compounds which recently attract high attention from many chemists. [16] is because of the strong effect of organotin(IV) in many biological tests [4, 5]. The biological activities of organotin(IV) are mainly [27] determined by the number and the type of organic groups bound to Sn center [6]. The present and the nature of the anionic groups bound to organotin(IV) compound is only as a secondary factor [6]. The various researches on organotin compounds have produced some new organotin(IV) carboxylates compound which have shown some interesting biological activities such as antimicrobial [6-8], antitumor and anticancer [7-10], antifungal activity [6,11,12], a [1] corrosion inhibitor [13-15], and the latest development of these compounds has led the new finding of organotin(IV) as antimalarial agent, therefore the research on organotin(IV) as possible antimalarial agent is still very challenging, thus more attentions for future application as antimalarial drug are still needed [16, 17].

Because of promising result for organotin(IV) compounds as antimalarial agent, in this paper, we reported the potency antimalarial activity study of some organotin(IV) 3-nitrobenzoates against *P. falcifarum*.



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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 ($[(C_6H_5)_3Cl]$), 3-nitrobenzoic acid, RPMI 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

1H and ^{13}C 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 DMSO- D_6 at 298K. The number of runs used for 1H experiments were 32 with reference at DMSO signal at 2.5 ppm, while the ^{13}C were 1000-4000 scans with the reference DMSO signal at 39.5 ppm. Microelemental analyses (CHNS) were performed on Fision EA 1108 series elemental analyser. IR spectra in the range of 4000-400 cm^{-1} were recorded on a Bruker VERTEX 70 FT-IR spectrophotometer with KBr discs. The 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 concentration of 1.0×10^{-4} M.

2.3. Preparation of organotin(IV) nitrobenzoates

The organotin(IV) 3-nitrobenzoates used in this work were prepared based on the procedure previously reported [9-12,14-16] and was adapted from the work by Szorcik *et al.* [18]. An example procedure in the preparation of dibutyltin(IV) di-2-nitrobenzoate was as follows:

To 3.44 g (0.01 mol) $[(C_6H_5)_2SnCl_2]$ (4) in 50 mL methanol was added 0.8 g (0.02 mol) NaOH. The reaction mixtures were stirred for about 60 minutes. Compound $[(C_6H_5)_2Sn(OH)_2]$ (5) was precipitated out as white solid, filtered off and dried in vacuo till they are ready for analysis and further reaction. The average yield was 2.92 g (95 %).

To 0.4605 g (1.5 mmol) $[(n-C_4H_9)_2Sn]$ (2) in 50 mL of methanol was added with 2 mole equivalents of 3-nitrobenzoic acid (0.501 g) and was refluxed for 4 hours at 60 – 62°C. After removal of the solvent by rotary evaporator, the produced compounds $[(C_6H_5)_2Sn(3-OOCC_6H_4(NO_2)_2)]$ were dried in vacuo until they are ready for analysis and further use for in vitro antimalarial activity. The yield was 1.67 g (92%). A similar procedure was also adapted in the preparation of dibutyltin(IV) and triphenyltin(IV) derivatives, $[(n-C_4H_9)_2Sn(3-OOCC_6H_4NO_2)_2]$ (3) and $[(C_6H_5)_3Sn(3-OOCC_6H_4NO_2)]$ (9), respectively. For triphenyltin(IV) only one mole equivalent of the 3-nitrobenzoic acid was added.

2.4. In vitro antimalarial bioactivity assays

The in vitro antimalarial assays were performed in the Institute of Tropical Disease, Universitas Airlangga, Surabaya Indonesia. The malaria parasite *P. falciparum* 3D7 clone was essentially propagated according to the previously published procedure [3]. Briefly, parasite cultures were propagated in tissue culture flasks containing RPMI-1640 medium supplemented with 25 $\mu g/mL$ gentamycin, 50 $\mu g/mL$ 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 concentration 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 a wide concentration range of each compound. 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 parasites-observed, divided by the total erythrocyte multiplied by 100%. The concentration response parasite growth data were calculated by a linear regression provided by SYSTAT Sigma Plot, using the 50% inhibitory concentration (IC_{50}). The IC_{50} value is defined as that concentration of compound producing 50% growth inhibition relative to untreated control.

3. Results and Discussion

The synthesis of the organotin(IV) 3-nitrobenzoate, i.e. dibutyltin(IV) di-3-nitrobenzoate, $[(n-C_4H_9)_2Sn(3-OOCC_6H_4NO_2)_2]$ (**3**), diphenyltin(IV) di-3-nitrobenzoate $[(C_6H_5)_2Sn(3-OOCC_6H_4NO_2)_2]$ (**6**) and triphenyltin(IV) 3-nitrobenzoate, $[(C_6H_5)_3Sn(3-OOCC_6H_4NO_2)]$ (**9**), were successfully prepared from their chlorides $[(n-C_4H_9)_2SnCl_2]$ (**1**), $[(C_6H_5)_2SnCl_2]$ (**4**) and $[(C_6H_5)_3SnCl]$ (**7**), respectively. All of these reactions were conducted via $[(n-C_4H_9)_2SnO]$ (**2**), $[(C_6H_5)_2Sn(OH)_2]$ (**5**) and $[(C_6H_5)_3SnOH]$ (**8**) respectively similar to the procedure previously reported [9-12,14-16]. Figure 1 shows an example of the reaction occurred in the synthesis of dibutyltin(IV) di-3-nitrobenzoate.

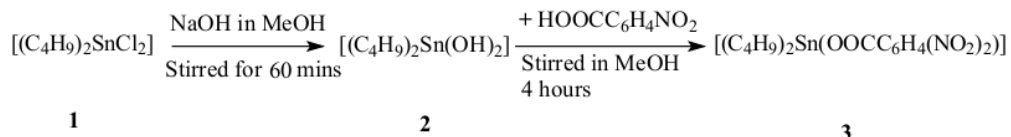


Fig. 1. The scheme of preparative route of the organotin(IV) di-3-nitrobenzoate

The data of microanalysis for all compounds synthesized are tabulated in Table 1, in general, all values obtained are very good and are close to the calculated values.

Table 1. The microanalytical data of the organotin(IV) compounds synthesized

Compound	Elemental analysis found (calculated)		
	C	H	N
$[(n-C_4H_9)_2SnCl_2]$ (1)	31.4 (31.6)	6.0 (5.9)	
$[(n-C_4H_9)_2SnO]$ (2)	38.6 (38.6)	7.1 (7.3)	
$[(n-C_4H_9)_2Sn(3-OOCC_6H_4(NO_2)_2)]$ (3)	46.8 (46.7)	4.7 (4.6)	4.8(4.96)
$[(C_6H_5)_2SnCl_2]$ (4)	41.7 (41.9)	2.8 (2.9)	
$[(C_6H_5)_2Sn(OH)_2]$ (5)	46.5 (46.9)	3.8 (3.9)	
$[(C_6H_5)_2Sn(3-OOCC_6H_4(NO_2)_2)]$ (6)	51.3 (51.6)	3.1 (2.98)	4.5 (4.63)
$[(C_6H_5)_3SnCl]$ (7)	55.8 (56.1)	4.0 (3.9)	
$[(C_6H_5)_3Sn(OH)]$ (8)	58.4 (58.9)	4.3 (4.4)	
$[(C_6H_5)_3Sn(3-OOCC_6H_4(NO_2)_2)]$ (9)	57.2 (58.1)	3.8 (3.68)	2.6 (2.71)

Table 2. The characteristic and important IR bands of the organotin(IV) compounds (cm^{-1}) synthesized

Compound	3	6	9	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 ₂ asym	1419.1	1531.7	1557.5	1600-1400
CO ₂ sym	1558.1	1659.3	1630.4	1700-1550
C-H	2954 –			2960 –
aliphatic	2860	-	-	2850
Phenyl	-	1467.0; 750.7	1428.4; 729.1	1450, 730

Table 2 lists some important FT-IR data of the compound synthesized. The starting materials (**1**, **4**, **7**) gave characteristic strong stretching band of Sn-Cl bond at 390 – 310 cm^{-1} . For example, in **1** the Sn-Cl bond appeared at 334.2 cm^{-1} . The other characteristic bands of **1** is the present of stretching band from butyl ligands at 1069 cm^{-1} . The bending vibration of C-H aliphatic stretch of the butyl appeared at 2956 – 2865 cm^{-1} . Once compound **1** is reacted with NaOH to produce compound **2**, the

band of Sn–Cl disappeared and a new strong band of Sn–O bond at of 417.4 cm⁻¹ in compound **2** appeared in the spectrum. The other stretching band due to the presence of butyls and their bending vibrations as expected although the frequencies have little bit shifted are still present. The formation of dibutyltin (IV) di-3-nitrobenzoate compounds, [(n-C₄H₉)₂Sn(3-OOCC₆H₄(NO₂))₂], **3** is confirmed by the strong asymmetric stretching bands of the carboxylate groups which occurred at ca. 1400 cm⁻¹ and the symmetric stretch at ca. 1600 cm⁻¹ as well as the present of Sn–O stretching of the acid at 435 cm⁻¹, and the appearance of these bands is confirming the success of the substitution reaction [9-12,14-16].

The UV-Vis spectroscopy analyses of all the compounds have also been utilized to obtain λ_{\max} and the data obtained presented in Table 3. The λ_{\max} for each compound in any steps of the reaction have been observed to have shifted. The compound **1** has λ_{\max} of 210.7 nm, while compound **2** has λ_{\max} of 202.9 nm. This information gave an indication that there was a shift to a shorter λ_{\max} value when the conversion of compound **1** to **2** took place. The wave-length shift to a shorter λ_{\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 which is methanol, the shift in the λ_{\max} that occurred must be due to the auxochrome effect. In case of compound **1** and **2**, there is an oxide group which has electron drawing effect bigger in compound **2** than that of chloride group in **1**. As a result, the electron transition in **2** is hard to occur, thus, λ_{\max} measured was getting shorter in compound **2** than in compound **1** [19-22]. Similar results are also observed for other changes as shown in Table 3. For instance, in compound **3**, the electron drawing effect of 3-C₆H₄(NO₂)COOH is less than chloride in **1**, so the electron transition in this molecule will be easier (the energy required is less), thus producing longer λ_{\max} , 291.3 nm.

Table 3. The λ_{\max} of the UV-Vis spectra of the organotin(IV) 3-nitrobenzoate compounds

Compound	λ_{\max} (nm)		
	π - π^*	n- π	Benzene ring secondary band
23 [(n-C ₄ H ₉) ₂ SnCl ₂](1)	210.7	-	-
2 [(n-C ₄ H ₉) ₂ SnO](2)	202.9	-	-
2 [(n-C ₄ H ₉) ₂ Sn(3-OOCC ₆ H ₄ (NO ₂)) ₂](3)	203.5	291.8	-
2 [(C ₆ H ₅) ₂ Sn(3-OOCC ₆ H ₄ (NO ₂)) ₂](6)	201.3	299.9	407.6
2 [(C ₆ H ₅) ₃ Sn(3-OOCC ₆ H ₄ (NO ₂))](9)	204.5	304.0	410.2

Table 4. ¹H and ¹³C spectra of the compounds synthesized

Compounds	H in butyl or phenyl (ppm)	H in benzoate (ppm)	C in butyl, phenyl and benzoate (ppm)
[(n-C ₄ H ₉) ₂ Sn(3-OOCC ₆ H ₄ (NO ₂)) ₂](3)	H α & H β : 1.37-1.62 (m); H γ : 1.30 (m); H δ : 0.93 (t)	7.34-7.86 (m)	C α : 21.2; C β : 26.6; C γ : 25.9; C δ : 14.2; C1: 174.9; C2: 139.3; C3 & C7: 129.7; C4 & C6: 128.5; C5: 125.2
[(C ₆ H ₅) ₂ Sn(3-OOCC ₆ H ₄ (NO ₂)) ₂](6)	H2 & H6 7.59 (d, 4H); H3 & H5 7.48 (t, 4H); H4: 7.36 (t, 2H)	7.82 - 7.93 (m)	C1-6 (phen): 131.7-126.9; C7: 175.7; C8: 139.5; C9 & C13: 130.2; C10 & C12: 129.3; C11: 128.5

2 [(C ₆ H ₅) ₃ Sn(3-OOCC ₆ H ₄ (NO ₂))] (9)	H2 & H6 7.58	C1-6 (phen): 131.1-126.2;
	(d, 6H); H3 & 7.81 - 7.92	C7: 175.3; C8: 139.2; C9 &
	H5 7.46 (t, 6H); (d)	C13: 130.3; C10 & C12:
	H4: 7.03 (t, 3H)	128.6; C11: 128.2

The results of ¹H and ¹³C NMR for all compounds synthesized are tabulated in Table 4. A number of signals in the spectra recorded have been characterized carefully. The chemical shift (δ) of butyl protons attached to the tin metal appeared in the range of 0.93 ppm for Hδ up to 1.37-1.62 ppm for Hα and Hβ, and the carbons of butyl ligands are observed at position comparable and in agreement with other similar compounds reported previously [9-12,14-16, 19, 21-23]. The chemical shift of phenyl protons attached to tin metal appeared in the range of 7.36 – 7.58 ppm, while the carbon of carboxyl group of all compounds as expected appeared in the region of 176 ppm [13,19,21-23]. The carbon atoms of the phenyl ligand as also expected appeared in δ of 131 – 126 ppm, while the carbons in the nitrobenzoate derivatives appeared in δ range of 140 – 130 ppm close to the reported values of similar compounds [9-12,14-16, 19, 21-23].

In our previous study on the antifungal and anticancer activity of the compounds reported here [9-12,14-16], it has been shown that optimal activity of the antifungal and anticancer has been associated with the number of carbon atoms of the ligand present in the organotin(IV) used [9-12,14-16], where in general, the derivative of triphenyltin(IV) carboxylate which contain 18 carbon atoms has the highest activity [6-9,12,13,24]. The same phenomena interestingly was also observed in this study.

As shown in Table 5, the derivatives of triphenyltin(IV) compounds showed the highest antimalarial activity in the series, and the diphenyltin(IV) compounds are stronger in inhibiting than those of dibutyltin(IV) compounds, similar to those previously reported [9-12,14-16]. Thus the number of carbon atoms present as well as the type of the ligands has significant effect on the antimalarial activity of the organotin(IV) compounds tested [24].

Table 5. The IC₅₀ of the compound tested

Compounds	IC ₅₀ (μg/mL)
Chloroquine	2.0 x 10 ⁻³
18 [(n-C ₄ H ₉) ₂ Sn(3-OOCC ₆ H ₄ (NO ₂)) ₂] (3)	8.1 x 10 ⁻²
2 [(C ₆ H ₅) ₂ Sn(3-OOCC ₆ H ₄ (NO ₂)) ₂] (6)	5.2 x 10 ⁻²
2 [(C ₆ H ₅) ₃ Sn(3-OOCC ₆ H ₄ (NO ₂))] (9)	7.2 x 10 ⁻³

The organotin(IV) 3-nitrobenzoate compounds synthesized have been found exhibited much higher antimalarial activity compared to those of the ligands, 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 than in their uncomplexed forms [25]. Crowe stated the actual biological activity of diorganotin compounds of the type RR'SnXY (R and R' = alkyl or aryl; X and Y = anions) was determined solely by the RR'Sn²⁺ moiety [26].

4. Conclusion

The organotin(IV) 3-nitrobenzoate compounds were successfully prepared and it is quite clear from the discussion above that they have shown some promising result to be used as antimalarial drug. The fact that triphenyltin(IV) 3-nitrobenzoate derivatives have shown the highest antimalarial activity

was in line with other data relating to the number of carbon atom present in the compound. To find the best explanation for this phenomenon, more studies will be carried out to .

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