In Vitro Antimicrobial Activity Study of Some Organotin(IV) Chlorobenzoates against Staphylococcus aureus and Escherichia coli

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Original Article

In Vitro Antimicrobial Activity Study of Some Organotin(IV) Chlorobenzoates against *Staphylococcus aureus* and *Escherichia coli*

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ABSTRACT

In vitro antibacterial activity of some organotin(IV) chlorobenzoates including diphenyltin(IV) *o*-, *m*-, *p*-dichlorobenzoate (**2, 3, 4**) and triphenyltin(IV) *o*-, *m*-, *p*-chlorobenzoate (**6, 7, 8**) against *Staphylococcus aureus* and *Escherichia coli* was studied. The compounds were synthesized by the reaction of diphenyltin(IV) dihydroxide (**1**) and triphenyltin(IV) hydroxide (**5**) with *o*-, *m*-, *p*-chlorobenzoic acid in a maximum refluxed time of 4 h using methanol as the solvent of the reaction. The antibacterial activity tests were performed using the diffusion and dilution methods with chloramphenicol and methanol were used as a positive and a negative control, respectively. The antibacterial activity was determined by measuring the diameter of the inhibition zone in each test. The results showed that all compounds synthesized were active against *S. aureus*, where the largest inhibition zone diameter was observed to be > 16 mm for triphenyltin(IV) *o*-chlorobenzoate (**6**) with its smallest concentration of 300 ppm (5.935×10^{-4} M), however, none of the organotin(IV) chlorobenzoates synthesized has activity against *E. coli*.

Keywords: Antibacterial activity, *E. coli*, Organotin (IV) chlobenzoate, *S. aureus*

Introduction

Antimicrobial resistance (AMR) is now a global threat as a consequence of the excessive use of antimicrobials in many applications [1-3]. Extensive and inappropriate uses of antimicrobial agents have promoted microbial evolution and adaptation, leading to the existence of multi-drug resistant (MDR) strains that cause lethal infections [4]. Also, the development of resistance is attributed to the loss of power of anti-microbial drugs as a consequence of long-term and improper use [5-7].

High levels of antimicrobial resistance of *E. coli* and *S. aureus* from food-producing animals have been reported in various countries [1-7]. Antimicrobials such as ampicillin, sulfamethoxazole, and tetracycline have been widely used for many years in the treatment of animals to treat infections [8]. Resistant *S. aureus* against ampicillin is related to the ability of this microorganism to produce penicillinase [9, 10]. Ampicillin-resistant *E. coli* has been reported worldwide, suggesting the need to consider a new approach to combat this type of bacteria [11, 12]. In an attempt to develop new antibacterial agents, research on organometallic compounds for medicinal purposes continues to grow [13], inspired by successful of organometallic complexes (cisplatin) as a chemotherapy agent for the treatment of testicular and ovarian cancer [14].

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In previous studies [15, 16], it was reported that metal complexes with organic ligands exhibit significant biological activity, contributed by the ligands and the metal in the compounds. The organic ligands contribute to biological activity, increase efficiency, reduce toxic effects or side effects, reduce therapeutic doses, protect and transport the metal, avoid side reactions on the route to potential targets, and overcome the mechanism of drug resistance, while the metal acts as a carrier and or stabilizer of the drug to reach the target [15, 16].

The tin(II) compound with a Schiff bases derived from 2-hydroxy-1- naphth-aldehyde has a significant influence on the inhibition of *S. aureus* and *E. coli* [17]. Organotin(IV) derivatives based on 2-((2-methoxyphenyl)carbamoyl)benzoic acid compounds are known to have good activity as antibacterial compounds [18]. Antibacterial testing against bacterium *Bacillus sp* by the diffusion method with the best results obtained using diphenyltin(IV) di-4-nitrobenzoate with a concentration of 200 ppm, whereas in the dilution test, diphenyltin(IV) di-4-nitrobenzoate) was effective at concentration of 0.4 mg/2mL [19]. Diphenyltin(IV) and triphenyltin(IV) 3-chlobenzoate have been reported to exhibit activity against *Pseudomonas aeruginosa* and *Bacillus subtilis* [17]. The antibacterial activity using the diffusion method on diphenyltin(IV) dibenzoate and triphenyltin(IV) benzoate compounds on *B. substilis* and *P. aeruginosa* gave maximum growth inhibition at a concentration of 200 ppm [20]. In recent years, studies on organometallic chemistry revealed that derivatives of organotin(IV) posses activity as anticancer [16, 18, 21, 22,], antifungal [23, 24], antimalarial [25-27], corrosion inhibitor [28, 29] and antimicrobial [17-20].

Based on the interesting results reported in the literature on the activity of organotin(IV) derivatives, this work aims to investigate the potential of diphenyltin(IV) *o-*, *m-*, *p-* dichlorobenzoate and triphenyltinIV) o-, m-, p-chlorobenzoate as antimicrobials against *S. aureus* and *E. Coli*.

Materials and Methods

Materials

The materials used in this work were diphenyltin(IV) dihydroxide [$(C_6H_5)_2Sn(OH)_2$], triphenyltin (IV) hydroxide [$(C_6H_5)_3SnOH$], *o-*, *m-*, *p*-chlorobenzoic acids [*o,- m-, p-* ($C_6H_4(Cl)COOH$)], chloramphenicol, nutrient Agar (NA) media, and sodium chloride (NaCl) were obtained from Sigma-Aldrich, methanol (CH_3OH) was obtained from J.T Baker. All of these chemicals were used as received, double distilled water purchased from Ikapharmindo, Indonesia, Gram-negative bacteria *E. coli* and Gram-positive bacteria *S. aureus* were obtained from the Lampung Provincial Health Laboratory.

Preparation of Solution test

Test solutions consisting of: Diphenyltin(IV) dihydroxide (**1**), triphenyltin(IV) hydroxide (**2**), diphenyltin(IV) di-*o*-dichlorobenzoate (**3**), diphenyltin(IV) di-*m*-dichlorobenzoate (**4**), diphenyltin(IV) *p*-dichlorobenzoate (5) , triphenyltin(IV) *o*-chlorobenzoate (**6**), triphenyltin(IV) *m*-chlorobenzoate (**7**) and triphenyltin(IV) *p*-chlorobenzoate (**8**). The compounds 3-8 were prepared based on the procedure previously described [19-29]. The antibacterial activity test was carried using the procedure available in the literatures [19, 20, 29-32].

0.614 g (0.002 moles) diphenyltin(IV) dihydroxide [$(C_6H_5)_2Sn(OH)_2$] was reacted with 0.626 g (0.004 moles) *o-*, *m-*, *p*-chlorobenzoic acids in 30 mL of methanol solvent. The reaction mixtures were refluxed for 4 h at 60 °C. Upon completion of the reaction, the solvent was evaporated and the products obtained were dried in a desiccator until the compounds were completely dried. The same procedure was used in the preparation of triphenyltin(IV) derivatives, in this reaction, 0.7336 gram (0.002 moles) triphenyltin(IV) hydroxide was reacted with 0.313 g -chlorobenzoic acid in 30 mL of methanol. The results obtained diphenyltin(IV) di-*o-*, *m-*, *p*-chlorobenzoate were white solid compound, 1.0781 g (92.30%); for triphenyltin(IV) *o-*, *m-*, *p*-chlorobenzoate 0.9236 g (91.36%)

The nutrient agar (NA) media were made by 2.8 g of NA was dissolved in 100 mL double distilled water, then heated and sterilized in an autoclave at 121 °C and 1 atm for 15 min. The warm NA media were placed into a test tube-tilted, let stand until solidified, and then stored in the refrigerator. 1 ose of each bacterium was diluted with 2 mL of saline water (NaCl 0.85%) and then used as a bacterial suspension. A 1 ml bacterial suspension was inoculated into a sloping NA test media previously prepared and flattened on the surface of the media using a spreader.

Antibacterial Activity test with diffusion method

Each sterile petri dish containing 15 mL of NA media was added with 1 mL of a bacterial suspension before solidifying, homogenized for 5 min, and allowed to solidify. After the media has solidified, four wells are made using the blue tip. The diffusion method test uses the procedure available in the literature [19, 20, 30-32]. In petri dish 1, the first well was filled with positive control K (+) chloramphenicol, the second well was filled with negative control K (-) (containing methanol p.a.), the third well was filled with a solution of compound **1**, diphenyltin(IV) dihydroxide and the fourth well with diphenyltin(IV) di-*o*-chlorobenzoate 100 ppm. Petri dish 2, four wells were filled with diphenyltin(IV) di-*o*-chlorobenzoate test solution with concentrations of 200, 300, 400, and 800 ppm. Each experiment was performed three times. Then they were incubated for 1-2 days at 37 °C, then the inhibition zone was observed and measured using calipers. Data on the inhibition zone were calculated as average from the three repetitions. Similar procedures were carried out for compounds **2**, and **4**-**8**.

Antibacterial Activity test with dilution method

Based on the results of the diffusion test, the most effective inhibitory concentration from compounds **1-8** was obtained and each compound was dissolved in methanol. The dilution test was performed using the procedure as in the literature [19, 20, 31] by preparing volume variations for the compounds having inhibitory properties to bacteria. 15 mL of liquid NA media were prepared and kept at 55 °C, followed by placing the compounds tested into the liquid NA media. Homogenized with vortex, then the mixture was poured into a petri dish, let stand until solidified. The suspension of *E. coli* and *S. aureus* inoculated in the NA media were incubated at 37 °C for 2-3 days. The growth of bacteria was observed daily. The most effective compound tested was the compound having the smallest concentration but having the highest inhibitory effect on bacterial growth [19, 20, 30-32].

Results and Discussion

The results of the antibacterial activity test on compounds **1-8** by diffusion and dilution methods against *S. aureus* and *E. coli* are shown in **Table 1.**

Table 1. The average inhibition zone of compounds tested

No	Compound	The average diameter of the inhibition zone (mm)									
		S. aureus					*E. coli*				
		Concentration (ppm) of solution test					Concentration (ppm) of solution test				
		100	200	300	400	800	100	200	300	400	800
1	**1**	17.1	16.9	17.9	21.8	22.5	0	0	0	0	0
2	**2**	17.8	16.9	17.1	17.4	17.9	0	0	0	0	0
3	**3**	0	0	0	0	0	0	0	0	0	0
4	**4**	9.6	10.33	11.9	12.47	15.87	0	0	0	0	0
5	**5**	0	0	0	0	10.2	0	0	0	0	0
6	**6**	8.13	11.4	18.13	19.43	20.5	0	0	0	0	0
7	**7**	6.5	9.77	16.03	19.37	20.6	0	0	0	0	0
8	**8**	9.2	13.67	14.6	20.67	21.2	0	0	0	0	0
9	K(+)	31	32.7	34.3	36.2	36.8	21.8	26.3	32.1	34.4	36.2
10	K(-)	0	0	0	0	0	0	0	0	0	0

The starting materials tested both diphenyltin(IV) dihydroxy and triphenyltin(IV) hydroxy gave inhibition against *S. aureus* but not against the *E. coli*. Out of the diphenyltin(IV) di-chlorobenzoates (compounds **3-5**), diphenyltin(IV) di-o-chlorobenzoate (**3**) produced no inhibition, while compound **4** and **5** showed activity against *S aureus*. However, compounds (**3-5**) did not give inhibition against *E. coli*. The same observations were also found for the derivative of triphenyltin(IV) chlorobenzoate as shown in **Table 1**. The results reported here for these compounds were surprisingly weaker than similar compounds reported by others [17] for bacterial activity against *E. coli* although the compounds reported also showed very weak activity [17].

Based on **Table 1**, the weak antibacterial activity against *S. aureus i.e.* inhibition zone diameter <10 mm was observed for compound **4** (100) ppm, compound **6** (100) ppm, compound **7** (100 and 200 ppm), and compound **8** (100) ppm. Medium antibacterial activity i.e. inhibition zone diameter of 10-16 mm against *S. aureus* were observed for compound **4** (200, 300, 400, and 800 ppm), compound **5** (800 ppm), compound **6** (200 ppm), compound **8** (200 and 300 ppm). Strong antibacterial activity i.e. inhibition zone diameter > 16 mm against *S. aureus* were observed for compound **6** (300, 400, and 800 ppm), compound **7** (300, 400, and 800 ppm), and compound **8** (400 and 800 ppm). Unfortunately, no compound was found to exhibit activity against *E coli*.

The effectiveness of compounds against bacteria was also calculated based on the ratio of the diameter of the inhibition zone (in cm) to the concentration of the compound (in ppm). Based on **Table 2**, of six organotin(IV) chlorobenzoate derivative compounds prepared, compound **4** (100 ppm) is the most effective to inhibit the growth of *S. aureus* with a ratio of 0.0096 and it was the highest inhibition ratio among all of the compounds tested comparable to other compounds reported [17, 19, 20].

Table 2. The effectiveness of compounds tested against S. aureus

Concetration (ppm)	3	4	5	6	7	8
100	-	0.0096	-	0.0013	0.0065	0.0092
200	-	0.0052	-	0.0057	0.0049	0.0068
300	-	0.0040	-	0.0060	0.0053	0.0049
400	-	0.0031	-	0.0049	0.0048	0.0052
800	-	0.0020	0.0013	0.0027	0.0026	0.0027

The dilution method is used to determine the minimum inhibitory concentration (MIC). The MIC for compound **4** (100 ppm), **5** (600 ppm), **6-8** (60 ppm) against *S. aureus* is shown in **Table 3**.

The differences in antibacterial activity of a compound against *S. aureus* and *E coli* are due to the differences in the structure and composition of the cells of the two bacteria [17, 19, 20]. It is also observed that the small difference in the structure of the compound produces different antibacterial activities [17, 19, 20].

Table 3. Minimum inhibitory concentrations (MIC) using dilution method

No	Compounds	Concentration (ppm)								Bacteria
1	**4**	60	70	80	90	100	110	120	130	*S.aureus*
		+++++	+++	++	+	-	-	-	-	
2	**5**	300	350	400	450	500	550	600	650	
		+++++	++++	++++	+++	++	+	-	-	
		30	35	40	45	55	60	70	80	
1	**6**	+++++	+++++	++++	++	+	-	-	-	
2	**7**	+++++	+++++	++++	++	+	-	-	-	
3	**8**	+++++	+++++	++++	++	+	-	-	-	

Note:
+++++ = very high bacterial growth
++++ = high bacterial growth
+++ = medium bacterial growth
++ = little bacterial growth
+ = very little bacterial growth
- = no bacterial growth

Conclusion

In this study, the activity of diphenyltin(IV) dichlorobenzoates (compounds **3-5**) and triphenyltin(IV) chlorobenzoates (compounds **6-8**) compounds were tested against *S. aureus* and *E. coli*. The experimental results demonstrated that triphenyltin(IV) chlorobenzoates (compounds **6-8**) exhibit appreciable activity against *S. aureus*, but none of the compounds were observed to exhibit activity against *E. coli*.

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Conflict of interest: None

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Ethics statement: This article does not contain any studies with human participants or animals performed by any of the authors.

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