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The potential of derivatives of organotin(IV) benzoate compounds in medicinal chemistry

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Abstract. This paper deals with short review about the application of organotin(IV) compounds. The discovery of bacterial resistance to antibiotics drew the attention of chemists to discover new types of chemical compounds that have the antibacterial activity to overcome the resistance. Increased antibiotic resistance is a consequence of the evolution and adaptation of microbes, caused by excessive anthropogenic antibiotic consumption. Increased cases of bacterial resistance will be a bigger problem if not treated with the discovery of new antibiotics. The discovery of medicinal chemicals may contribute to the advancement of treatment, especially antibiotic resistant. Organotin(IV) compounds are part of organometallic compounds that have been studied their pharmacological effects on several types of bacteria. The derivatives of organotin(IV) benzoate compounds proven to have biological activity against some types of bacteria. The type and structure of the ligand in the compound derivative of organotin(IV) benzoate gives the influence of different biological activity against bacteria.

1. Introduction

In the last decade many promising developments in medicinal chemistry, with the discovery of organometallic compounds as anticancer [1-5], applications as antibiotics and antibacterial [6-9], antiviral agents [7], antiparasitic agents [10], antimalarial [10, 11], antifungi [7, 13] as well have been as anticorrosion [14, 15]. The number of antibacterial agents found and introduced to the market continues to decline and fails to answer the challenges posed by increased pathogenic resistance to general antibacterial drugs [16]. Drug resistance has also become a medical and clinical problem globally. Therefore, it is very important to develop drugs that specifically and selectively target processes in which resistance mechanisms emerge [17].

Handling the problem of antibiotic resistance is the most urgent public health problem that challenges modern medicine [16]. Increasing frequency of antibiotic resistance is a consequence of evolution and microbial adaptation, which is caused by excessive consumption of anthropogenic antibiotics [17]. For example, the case of *S. aureus* resistance to penicillin occurred in more than 86% of cases. This case of resistance causes failure of therapy using amoxicillin in *S. aureus* infection [18].

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Attention to organometallic chemistry is a field of research involving the use of organometallic compounds for medicinal purposes, which have continued to develop over the past years, but this research is still very less compared to research on catalysis or even biosensing [5].

Medicinal chemistry is the science which is a branch of chemistry and biology that is used to understand chemical compounds or drugs that have beneficial effects in the living system, and involves the study of the relationship of chemical structures of compounds with biological activity and the mechanism of how compounds work in biological systems in an effort to get effects maximal treatment and minimize adverse side effects [19].

2. Organometallic compounds

Organometallic compounds are complex compounds formed between organic groups and metal atoms. Organometallic complexes can be divided into two complexes containing carbon-carbon σ bonds and metal complexes with π bonds of unsaturated hydrocarbons, namely compounds with double bonds between carbon atoms [3, 5, 7].

The use of metal complexes as chemotherapy agents in the treatment of diseases, which are a major public health problem, emerged as a very interesting alternative. The discovery of cisplatin for the treatment of testicular and ovarian cancer attracted the attention of researchers on other metal-based antineoplastic agents. Metal-based compounds are very interesting because of their physical and chemical properties. Properties such as ligand exchange rate, redox properties, oxidation state, coordination status, solubility, biodegradability, and biodistribution can be modified to enhance therapeutic effects while significantly reducing side effects [20].

Metal-based complex compounds designed by combining ligands produce important biological activity. The complex compounds produced can increase efficiency and reduce toxic effects or side effects while reducing therapeutic doses and/or overcoming the mechanism of drug resistance. Besides, that metal can act as a drug carrier and/or stabilizer to be able to reach the target. At the same time, well-known organic ligands with biological activity can transport and protect metals, then avoid side reactions on the route to potential targets. The combined metal-ligand effect can produce a significant increase in the activity of the coordination compounds produced [21, 22].

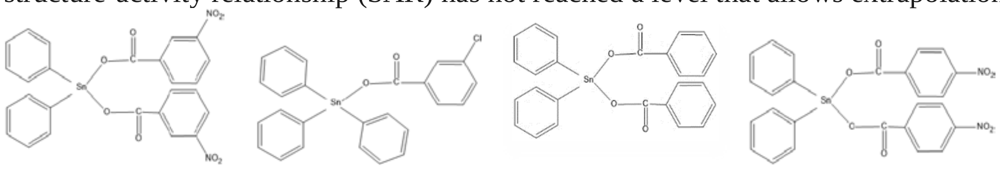
Organometallic complexes provide versatile platforms for drug design. Metal-carbon bonds can exert major electronic and steric effects, which in turn can be used to control their biological activity. In particular, such complexes offer the possibility of novel mechanisms of action compared to purely organic drugs and have the potential for combating drug resistance as well as treating currently intractable conditions [23].

Organometallic compounds can experience ligand exchange, this leads to applications in various fields of medicinal chemistry, especially for the preparation of new chemotherapy agents. Some organometallic compounds are thought to exert their antiproliferative activity through ligand exchange mechanisms [24].

3. Organotin compounds and their derivatives

Organotin compounds are organometallic characterized by tin (Sn) atoms which are covalently bonded to one or more organic substituents (C-Sn) for example, methyl, ethyl, butyl, propyl, phenyl, and octyl. The general organotin formula is RSnX, where R is an organic or aryl alkyl group and X is an inorganic or organic ligand such as, for example, chloride, fluoride, oxide, hydroxide, carboxylic or thiolate. Organotin compounds tend to have the character of one or more covalent bonds between lead and carbon. Based on the number of carbon-tin bonds, organotin can be classified into four different classes, namely mono organotin ($RSnX_3$), diorganotin (R_2SnX_2), triorganotin (R_3SnX) and tetraorganotin (R_4Sn) and can be formulated as R_nSnX_{4-n} (n = 1- 4) . The R group in organotin compounds is usually in the form of methyl, butyl octyl or phenyl, whereas X is generally in the form of chloride, fluoride, oxide, hydroxide or carboxylate [25].

At present some of the organotin(IV) benzoate derivatives that have been shown to have antibacterial activity, some of which are summarized in Figure 1. The design concept of organotin(IV) benzoate derivatives for medical chemistry, however, is still in its early stages mainly due to understanding the structure-activity relationship (SAR) has not reached a level that allows extrapolation of general rules.



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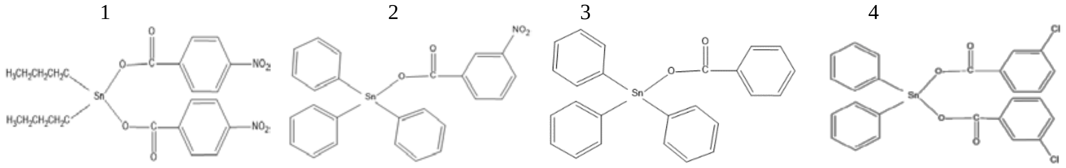

5 6 7 8

Figure 1. Some examples of antibacterial activity the organotin(IV) benzoate derivatives

The results of antibacterial activity by diffusion method against Pseudomonas aeruginosa and Bacillus substilis showed that the triphenyltin(IV) 3-chlorobenzoate **(2)** and diphenyltin(IV) di 3-chlorobenzote **(8)** has active at concentration of 3.9560 x 10^{-4}M (200 ppm), while the chloramphenicol gave inhibition of 6.1894 x 10^{-4} M (200 ppm), although the halozone was bigger. This result indicated that compound 4 is potential to be used as antibacterial substance, although the search of other derivatives of organotin(IV) with other ligands is still needed to get much higher and much better activity [8]. The results of antibacterial activity by diffusion method against Pseudomonas aeruginosa and Bacillus subtilis showed that both compounds were active at concentration of 200 ppm, which are about 3.8900 x 10^{-4} M for diphenyltin(IV) dibenzoate **(3)** and 4.4700 x10^{-4} M for triphenyltin(IV) benzoate **(7)** , while the chloramphenicol, as control positive, at the same concentration 200 ppm (6.1894 x 10^{-4} M), gave inhibition with halozone was bigger. This result indicated that both compounds have potentially to be used as antibacterial substances [8, 9].

Antibacterial activity testing on the diffusion method found triphenyltin(IV) 3-nitrobenzoate **(6)** and diphenyltin(IV) di 3-nitrobenzoate **(1)** had the best antibacterial activity against Bacillus subtilis with 200 ppm concentration and the dilution test showed triphenyltin(IV) 3-nitrobenzoate had activity better antibacterial with levels of 0.4 mg /2 mL [16]. Diphenyltin(IV) in 4-nitrobenzoate and dibutyltin(IV) in 4-nitrobenzoate **(5)** has antibacterial activity against Bacillus sp by diffusion method. The best results were shown on diphenyltin(IV) di 4-nitrobenzoate **(4)** with a concentration of 200 ppm, whereas in the dilution test, the effective levels of diphenyltin(IV) di(4-nitrobenzoate) were 0.4 mg / 2 mL [9].

4. Conclusions

Derivatives of organotin(IV) benzoate compounds have antibacterial activity and can undergo ligand exchange. The exchange of ligand gave difference antibacterial activity. Derivatives of organotin(IV) benzoate compounds the potentially in medicinal chemistry.

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References

[1] Gleeson B, Claffey J, Ertler D, Hogan M, Müller-Bunz H, Paradisi F, Wallis D and Tacke M 2008 Novel organotin antibacterial and anticancer drugs, *Polyhedron,* **27,** 3619
[2] Rehman W, Badshah A, Khan S and Tuyet LTA 2009 Synthesis, characterization, antimicrobial and antitumor screening of some diorganotin(IV) complexes of 2-[(9H-Purin-6-ylimino)]-phenol, *Eur. J. Med. Chem.,* **44**, 3981
[3] Hadi S, Rilyanti M 2010 Synthesis and *in vitro* anticancer activity of some organotin(IV) benzoate compounds, *Orient. J. Chem.,* **26**, 775
[4] Hadi S, Rilyanti M and Suharso 2012 *In Vitro* Activity and Comparative Studies Of Some Organotin(IV) Benzoate Derivatives Against Leukemia Cancer Cell: L-1210, *Indo. J. Chem.,* **12**, 172
[5] Gassera G, Metzler N, Ott I 2011 Organometallic Anticancer Compounds *J. Med. Chem* 54 pp 3-25
[6] Patra M, Gasser G and Metzler-Nolte N 2012 Small Organometallic Compounds as Antibacterial Agents *Dalton Transactions*, **41** pp 350-6358
[7] Chohan ZH 2009 Synthesis of organometallic-based biologically active compounds: In vitro antibacterial, antifungal and cytotoxic properties of some sulfonamide incorporated ferrocences *Journal of Enzyme Inhibition and Medicinal Chemistry* **24**(1) pp 169–175
[8] Annissa, Suhartati T, Yandri and Hadi S 2017 Antibacterial Activity of Diphenyltin(IV) and Triphenyltin(IV) 3-Chlorobenzoate Againts Pseudomonas aeruginosa and Bacillus subtilis. *Orient. J. Chem.* **33** (3): 1133-1139
[9] Hadi S, Hermawati E, Noviany, Suhartati T and Yandri 2018 Antibacterial Activity Test Of DiphenyltinIV) Dibenzoate and Triphenyltin(IV) Benzoate Compounds Against *Bacillus substilis* and *Pseudomonas aeruginosa*. *Asian Jr. of Microbiol. Biotech. Env. Sc.* **20** (1): 113-119
[10] Chellan P, Land KM, Shokar A, Au A, An SH, Taylor D, Smith PJ, Chibale K and Smith GS 2013 Di- and Trinuclear Ruthenium-, Rhodium-, and Iridium-Functionalized Pyridyl Aromatic Ethers: A New Class of Antiparasitic Agents, *Organometallics* 32, 4793
[11] Hansch C and Verma RP 2009 Larvicidal activities of some organotin compounds on mosquito larvae: A QSAR study, *Eur. J. Med. Chem.,* **44**, 260.
[12] Hadi S, Noviany and Rilyanti M 2018 In vitro antimalarial activity of some organotin(IV)2-nitrobenzoate compounds against *Plasmodium falciparum*. *Maced. J. Chem. Chem Eng.* **37,** 191
[13] Hadi S, Irawan B and Efri 2008 The Antifungal Activity Test of Some Organotin(IV) Carboxylates, *J. Appl. Sci. Res.,* **4**, 1521
[14] H. Kurniasiah, M. Nurissalam, B. Iswantoro, H. Afiyani, 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).
[15] 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).
[16] Laxminarayan R, Duse A, Wattal C, Zaidi AK and Wertheim HF 2013 Antibiotic resistance-the need for global solutions *The Lancet infectious diseases* 13 pp 1057–1098
[17] Rodríguez-Rojas A, Rodríguez-Beltrán J, Couce A and Blázquez J 2013 Antibiotics and antibiotic resistance: a bitter fight against evolution *International Journal of Medical Microbiology* 303 pp 293–297
[18] Shituu AO, Okon K, Adesida S, Oyedara O, Witte W, Strommrnenger B, Layer F and Nubel U Antibiotic Resistance and Molecular Epidemiology of *Staphylococcus aureus* in Nigeria *BMC Microbiology* 11 (92) pp 1-8
[19] Siwodihardjo S and Sukardjo B 2017 Kimia Medisinal, Airlangga University Press, Surabaya
[20] Garza-Ortiz A, Camacho-Camacho C, Sainz-Espunes T, Rojas-Oviewedo I, Gutierrez-Lucas LR, Carrillo AG and Ramirez MAV 2013 Novel Organotin(IV) Schiff Base Complexes with

Histidine Derivatives: Synthesis, Characterization, and Biological Activity *Bioinorg, Chem. Appl.* Pp 1 –12
[21] Roy S, Hagen KD and Maheswari PU 2008 Phenanthroline derivatives with improved selectivity as DNA-targeting anticancer or antimicrobial drugs *Chem. Med Chem,* **3** (9) pp 1427–1434
[22] Pellerito L and Nagy L 2002 Organotin (IV)$^{n+}$ Complexes Formed with Biologically Active Ligands: Equilibrium and Structural Studies and Some Biological Aspect. *Coor. Chem. Rev.* **224** pp 111–150
[23] Pizarro AM, Habtermariam A and Sadler PJ 2010 *Activation Mechanism for Organometallic Anticancer Complexes. In Medicinal Organometallic Chemistry*. Edited by Jaouen G, Metzler-Nolte N: Springer-Verlag
[24] Hartinger C and Dyson PJ 2009 Bioorganometallic chemistry **-** from teaching paradigms to medicinal applications. *Chem. Soc. Rev.* **38** pp 391-401
[25] Hoch M 2001 Organotin compounds in the environment: An overview. *Appl Geochem,* **16** (7-8): 719-743