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ONE-POT SYNTHESIS, ANTIOXIDANT ACTIVITY AND TOXICITY EVALUATION OF SOME HYDROXYXANTHONES

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Abstract. Some new hydroxyxanthone compounds were prepared through one pot cyclodehydration reaction of hydroxybenzoic acid derivatives (salicylic acid or resorcylic acid) with phloroglucinol or pyrogallol in the presence of Eaton's reagent (P_2O_5/$MeSO_3H$). The synthesized compounds were screened for their antioxidant activities by 2,2-diphenyl-1-picrylhydrazyl (DPPH) methods to determine their inhibitory concentration (IC_{50}). Cytotoxicity of the prepared compounds was also evaluated by MMT assay on Vero cell line. It was observed that the position and the number of hydroxyl groups could significantly affect the potent antioxidant activity of the prepared compounds. Cytotoxicity evaluation of new compounds indicated that the synthesized series of hydroxyl xanthone were categorized as very strong antioxidants and showed potential development as a commercial antioxidant compound.

Keywords: antioxidant, hydroxyxanthones, 2,2-diphenyl-1-picrylhydrazyl assay, Eaton's reagent.

1. Introduction

Development of an effective and safe antioxidant compound for cosmetic, food preservation and pharmaceutical are still challenging in the last few decades. Free radicals, known as reactive oxygen species (ROS), are produced during the biochemical process in the human tissues, besides it comes from the environmental factor such as air pollutants. The existence of a highly reactive molecule ROS in body potentially can cause cellular metabolic injury, accelerating aging, cardiovascular disease, inflammation, cancer, and decrease the body's ability for reducing oxidative stress [2-4]. Antioxidants, which are commonly phenolic compounds, contribute to scavenging of free radicals due to their ability to donate electrons and decrease the ROS effect in human body. Considerable interest has been paid to the plant sources of antioxidants because synthetic antioxidant such as butylated hydroxyanisole (BHA), which is used in food preservation, is a subject to strict regulation due to the potential health hazards imposed [5] and carcinogenesis effect [6].

Xanthones antioxidants have been reported to have stronger effect than vitamin C and E and it has been revealed that xanthones play an important preventive role against diseases caused by ROS or free radicals [7]. The strong free radical scavenging activity occurred in xanthones is closely related to the dihydroxy groups present in the shikimate-derived ring [8]. In the researches that were carried out, among thirteen isolated xanthones, five xanthones demonstrated to be potent antioxidants. These five xanthones possess one or more prenyl side chains attached to the phenolic rings [9]. Isolated xanthones compounds from plants are considered unfavorable because the yield is very small. Isolated xanthone from *Garcinia* generates yield from 0.02 to 0.1 % [7]. Some isomers of α-mangosteen are very small, about <0.007 % [10]. Thus, the synthesis pathway is considered to be more advantageous to obtain xanthone compounds.

Xanthones as heterocyclic compounds are synthesized in three major routes [11]. The first one is based on the cyclization of 2-hydroxybenzophenones [12-14]. The second one involves the cyclodehydration of *o*-phenoxy benzoic acids [15-17]. Recently, synthesis has also been conducted *via* *N*-heterocyclic carbene catalyzed nucleophilic aroylation [18]. Various types of catalysts are also used for cyclization reactions to form xanthone core, such as NaH/CsF/THF [19], $NaOC_2H_5$/Cu/Cu_2O [20], $ZnCl_2$/$POCl_3$ [21], $AlCl_3$/anhydrous ether [22, 23], Pd

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(PPh3)4/K_2CO_3/acetone [24]. But the utilization of NaH/CsF/THF as catalyst is revealed to give a low percentage of the synthesized compounds (30–40 %) [19]. Meanwhile, the presence of $AlCl_3$/anhydrous ether catalyst requires further eight reduction steps followed by cyclization using pyridine/$(CH_3)_4NOH$ which need 36 h for the reaction completion [22].

In this study, we report the synthesis of hydroxyxanthones *via* cyclodehidration of 2,4-dihydroxybenzoic acid with the Eaton's reagents as the calatyst. The synthesis using Eaton's reagent has only been reported few times. In 2002, Moreau *et al*. have been reported the synthesis of 2-arylhydrazonomethyl)-substituted xanthones as antimycotics using Eaton's reagents [25]. The second study was the synthesis of 1-hydroxyl-3-aminoalkoxy xanthone as anticancer agent [26]. The last was reported in 2017 by Syahri *et al*. [27], aiming to synthesize a series of hydroxyxanthone as antimalarial medication. The inclusion of only hydroxyl groups on xanthone core as an antioxidant and its activity and toxicity evaluation has not been reported so far.

The use of new compounds as antioxidants in the food and pharmaceutical industry requires proof of their antioxidant effect *in vivo*, as well as their bioavailability and toxicological properties. In this study, the toxicological properties was determined using MMT assay in normal cell line, that is Vero cell line, which has not been used very much in toxicological studies [28]. Response given by the Vero cell line to MMT assay is similar to those of other cell lines, like renal cells; therefore the line could be considered as an alternative model for such toxicological studies [29].

Thus, the objective of this report is to synthesize series of hydroxyxanthones in one pot reaction, to determine the antioxidant properties using 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay for further toxicity evaluation to find out the safety and friendliness of the hydroxyxanthone compounds as commercial antioxidants.

2. Experimental

2.1. Materials and Methods

All chemicals, reagents, and solvents used in this study were high purity purchased from Merck and Sigma-Aldrich. Melting point was determined on an Electrothermal 9100 melting point apparatus and was not corrected. Infrared spectra were obtained on a Shimadzu FTIR-8201 PC spectrometer. ^{1}H NMR was recorded at 500 MHz with a JEOL JNM-ECA spectrometer using TMS as an internal reference. Mass spectra were measured on a Shimadzu QP-5000 GC-MS spectrometer.

Some hydroxyxanthones (**3a-c**) were synthesized according to a reported procedure [28] by reacting acid derivatives **1a-1b** with phenol derivatives **2a-b**. The reaction was carried out in the presence of Eaton regents, a catalyst and a dehydrating agent for 3 h and heated at 353±3 K. The resulting precipitate was filtered and washed with water to afford solid (Fig. 1). The synthesized compounds were obtained in excellent yields (81–87.5 %).

2.2. General Procedure for the Synthesis of Compounds 3a-c

A mixture of salicylic acid (0.55 g, 5 mmol), phloroglucinol (0.63 g, 5 mmol) and Eaton's reagent (5 ml) was stirred and heated at 353±3 K for 3 h. The mixture was allowed to cool down to room temperature, poured into cooled water and stirred for 1 h. The resulting precipitate was filtered and washed with water to afford solid. This method was also used to synthesize other hydroxyxanthones – 3,4,6-trihydroxyxanthone (**3b**), a mixture of resorcylic acid (0.80 g, 5.2 mmol) and pyrogallol (0.63 g, 5 mmol), as well as for 1,3,6-trihydroxyxanthone (**3c**), a mixture of resorcylic acid (0.80 g, 5.2 mmol) and phloroglucinol (0.63 g, 5 mmol).

2.3. Antioxidant Assay

A solution of 0.05 mM DPPH was prepared by dissolving 1.97 mg DPPH in 100 ml of methanol and stored in the dark place at 277 K [30]. A solution of xanthone (**3a-c**) was prepared in 6.25; 12.5 and 25 ppm in methanol. 500 µl of the solution of the compound was added to 2 ml of 0.05 mM DPPH, respectively. The mixture was shaken well and stored in a dark place at room temperature. After 30 min the absorbance of the mixture was measured at 515 nm using UV spectrophotometer, which then was compared with the corresponding absorbance of the standard quercetin concentration. For measuring free radical scavenging activity (RSA) or as inhibition percentage against the stable DPPH, the following formula was used:

$$Inhibition = \frac{(A\ DPPH - A\ Sample)}{A\ DPPH} \cdot 100$$

where A is the measured absorbance of DPPH or sample.

Linear regression $y = mx + b$ gives a meaning that concentration is abscissa x and RSA (percentage of inhibition) is ordinate y. IC_{50} indicates the concentration of the compounds with 50 % of radical scavenging activity. IC_{50} is inversely proportional to the antioxidant activity. Accordingly, the smaller the IC_{50} value, the greater the antioxidant activity.

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2.4. Toxicity Evaluation

Vero cell line (normal African green monkey kidney epithelial cells) for the toxicological studies was obtained from the toxicology laboratory, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Cultures with approximately $3\cdot10^3$ cells/ml were suspended in RPMI 1640 medium, containing FBS (fetal bovine serum), penicillin, and streptomycin. The cells were inoculated into 96 well microplates and were incubated in a CO_2 incubator for 24 h. After that the samples dissolved in DMSO (dimethyl sulfoxide) were added. Samples in various concentrations were diluted with addition of PBS (phosphoric buffer solution) which pH was around 7.30–7.65 and then added to the cells in a microplate. The mixture was then shaken and stored again in CO_2 incubator for 48 h. In this assay, DMSO was used as the negative control while *cis*-platin was used as the positive control. After 48 h the MTT reagent was added to the cells and the mixture was incubated for 4 h. After that SDS was added and the mixture was shaken well. Incubation of the cells was then resumed in 24 h. MTT color changed from yellow to purple indicating the mitochondria of the cells that were still alive and it could be quantified with a spectrophotometer at the wavelength (λ) of 550 nm. The data were calculated as the percentage of toxicity using the following formula [31]. 50 % cytotoxic concentration (CC_{50}) was defined as the cytotoxic concentration of the compounds by regression analysis.

$$\%\ toxicity = 100 - \frac{Absorbance\ test}{Absorbance\ control} \cdot 100 \cdot$$

3. Results and Discussion

3.1. Synthesis of Xanthone Compounds

The structures of investigated compounds were confirmed by ^{1}H NMR, mass spectrometry and FTIR analysis. The spectroscopic data of hydroxyxanthones **3a-c** are presented as follows:

1,3-dihydroxy-9H-xanthen-9-one **(3a).** Red solid (0.97 g, 85.5 %), m.p. 596–596.8 K. FTIR (KBr, ν; cm^{-1}): 3448 (OH), 1612 (C=O), 1458 (C–C aromatic), 1296 (C–O–C). ^1H NMR (CD_3OD; 500 MHz) δ (ppm): 6.30 (1H, s), 6.36 (1H, s), 7.41 (1H, d, J = 8 Hz), 7.50 (2H, t), 7.78 (2H, t), 8.30 (1H, d J=6.5), MS (EI) m/z: 228 (M+1).

3,4,6-trihydroxy-9H-xanthen-9-one **(3b).** Yellowish red solid (1.07 g, 87.5 %), m.p. 511–514 K. FTIR (KBr, ν; cm^{-1}): 3425 (OH), 1620 (C=O), 1504 (C–C aromatic), 1242 (C–O–C). 1H NMR (500 MHz, CDCl3) d (ppm): 7.37 (2H ,d, J = 8.5 Hz), 6.41 (2H, d, J = 8.4 Hz), 6.35 (s, 1H). HRESI-MS calcd. for $C_{13}H_8O_5$, [M+H]+ 245.0421, found 245.0411.

1,3,6-trihydroxy-9H-xanthen-9-one **(3c).** Yellowish solid (81 %), 595–596 K (Dec.). FTIR (KBr, ν; cm^{-1}): 3163 (OH), 1612 (C=O), 1465 (C–C aromatic), 1296 (C–O). ^1H NMR (DMSO; 500 MHz) δ (ppm): 8.02–8.04 (1H, dd, J = 8.75 Hz), 6.92-6.95 (1H, dd, J = = 8.75 Hz), 6.64 (1H, s), 6.36 (1H, s), 6.21 (1H, s). MS (EI) m/z: 244 (M).

All series of hydroxyxanthones were produced by reacting acid derivatives, such as salicylic acid **1a** and resorcylic acid **1b** with phenol derivatives, such as phloroglucinol **2a** and pyrogallol **2b** as shown in Fig. 1. Former synthesis path [32] shows that there is a possibility for related benzophenone to be formed if $POCl_3/ZnCl_2$ is used. This may lower the overall yield of the synthesized xanthones. An alternative method has been reported to overcome these limitations. There has been a modification reaction which can provide a high yield of xanthones without producing any benzophenones. The modification is conducted using Eaton's reagent as a catalyst and condensing agent instead of $POCl_3/ZnCl_2$. Eaton's reagent is a mixture of phosphorus pentoxide and methane sulfonic acid. Eaton's reagent provides a better product of xanthone with minimum detectable amount of benzophenone, beside it can initiate a faster reaction and higher yield compared to the reaction without Eaton's reagent [33].

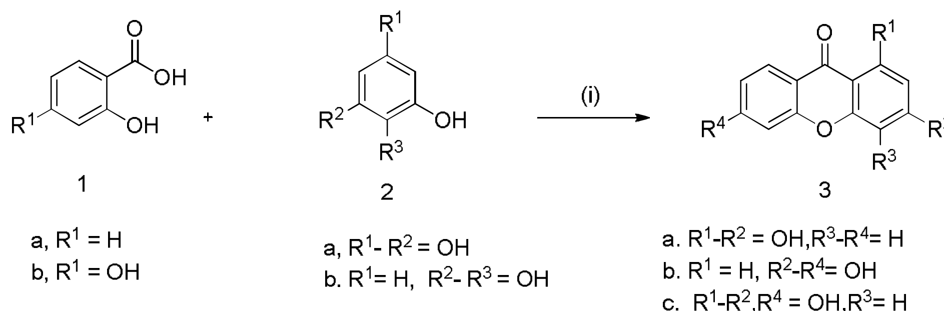

Fig. 1. General procedure for preparation of hydroxyxanthones **3a-c**. Reagents and conditions: Eaton's reagent ($P_2O_5/MeSO_3H$), 353±3 K, 3h, refluxes

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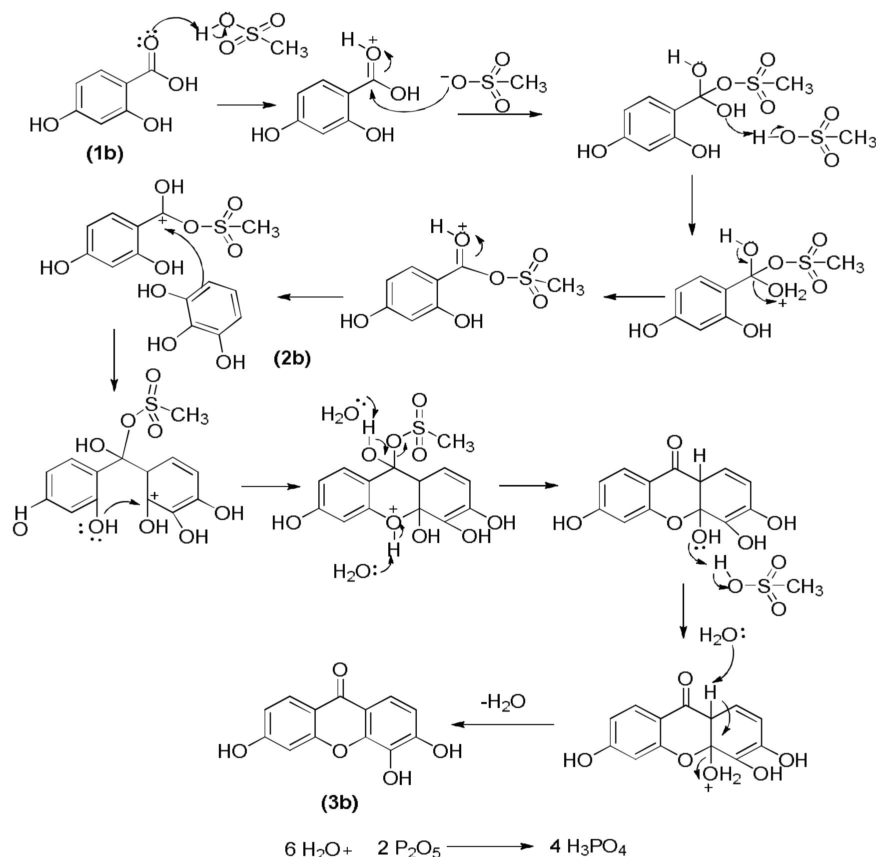

Fig. 2. Proposed mechanism describing catalysis and dehydration process by Eaton's reagents on the synthesis of 3,4,6-trihydroxyxanthone

The proposed mechanism for cyclodehydration reaction of acid derivatives and derivatives of phenol to obtain **3a-c** is presented in Fig. 2. This mechanism describes the function of Eaton's reagent in detail as a catalyst (methane sulfonic acid) and dehydrating agent. Essentially, this reaction consists of a protonation and deprotonation, which stops with the loss of water molecules. The role of Eaton's reagent as a catalyst involves the protonation and deprotonation, and as the dehydrating agent it is to absorb water molecules that are formed during the cyclodehydration reaction.

3.2. DPPH Radical Scavenging Activity

The antiradical activity of the hydroxyxanthones is measured by the ability of the compound to scavenge DPPH free radicals and this was compared with the standard quercetin and ascorbic acid. Table 1 below presents the IC_{50} (50% inhibitory showed that the IC_{50} varied between 79.77, 22.01 and 25.75 μg/ml depending on the number of hydroxy group on xanthone scaffold). According to [34], the antioxidant strength is divided into four levels, which are: very strong ($IC_{50} < 50$ μg/ml), strong (IC_{50} = 50–100 μg/mL), moderate (IC_{50} = 101–150 μg/ml), and weak (IC_{50} = 250–500 μg/m).

Antioxidant activity of hydroxyxanthones **3a-c** was tested by DPPH method with quercetin and ascorbic acid as positive controls. DPPH (1,1-diphenyl-2-dipicrylhydrazyl) assay is a rapid, simple, and inexpensive method that is commonly used to study the antioxidant activities of the tested compounds. The antioxidant activity of the tested compounds is expressed as the inhibition rate (%) with reference to the two reference standards. Polyphenolic compounds are classified as anti-oxidants based on the electron donating (labile H atoms) ability to form radicals. Radical scavenging activity depends not only on the rate of the labile H atom abstraction from the phenol molecules by DPPH radicals but also on the stability of the formed phenolic radical [35].

The antioxidant properties of hydroxyxanthones **3a-c** are calculated from the decreasing absorbance of DPPH. DPPH is a nitrogen radical of purple color. The presence of the antioxidants could cause a decline in the intensity of the purple color to yellow [36-38]. Antioxidant assay of **3a-c** shows IC_{50} of 79.77; 22.02 and 25.75 μg/ml, respectively, and IC_{50} of quercetin and ascorbic acid as the controls are 18.86 and 11.79, respectively. Jun *et al.* [39] suggested a standard of antioxidant activity of compounds to be based on the IC_{50}.

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The compound is classified as very strong antioxidant if it has $IC_{50} < 50$ and strong when IC_{50} level is 50–100 μg/ml [34]. Therefore, hydroxyxanthones **3a-c** could be described as strong antioxidants.

Based on the above mechanism, there is a difference in radical stability of each hydroxyxanthone, as we know the mechanism of reaction between antioxidant and DPPH depends on the structural conformation of the antioxidant. This causes the difference in the value of the formed antioxidants: compounds **3b** having 3-hydroxyl on xanthone core will generate three species working to stabilize radicals while the **3a** compound produces two species that can stabilize radicals. Some compounds react very quickly with DPPH, reducing the number of DPPH molecules which are equal to the number of the hydroxyl groups [40]. Comparison of the tested compounds concludes that the number and position of the hydroxyl group could influence the antioxidant activity (presented as IC_{50}) as listed in Table 1.

3.3. The Toxicity Evaluation

The toxicity effect of hydroxyxanthones **3a-c** on Vero cell line was evaluated by MTT assay.

Table 1

IC_{50} values of some hydroxyxanthones and standard

Compound	IC_{50}, μg/ml*
3a	79.77 ± 0.005
3b	22.01 ± 0.050
3c	25.75 ± 0.050
Quercetin	18.86 ± 0.007
Ascorbic acid	11.79 ± 0.021

Note: * determined in CH_3OH solvent. Data are represented as mean ± S.D.

Table 2

CC_{50} values of some hydroxyxanthones toward Vero cell line

Compound	CC_{50}, μg/ml*
3a	484.65 ± 36.57
3b	612.87 ± 49.68
3c	> 2000

Note: * data are represented as mean ± S.D.

To be able to use new compounds as commercial antioxidants, we have to investigate or evaluate their selective toxicity toward normal cells. The normal cell line used in this research is Vero cells line. Vero cells have been chosen for toxicity tests because Vero cells are cells derived from normal kidney cells of mature African green apes (*cercophitecus aethiops*) that have morphology such as fibroblasts. Thus, it can indirectly represent some of the cells contained in the human body.

MTT assay can be used to measure toxicity, proliferation or activation. This method determines the number of living cells based on changes in MTT solution whose color changes from yellow to purple due to the use of formazan crystal. The color change indicates that mitochondria of the living cells are still active. MTT is absorbed into the living cells and is broken through the oxidation reaction by nicotinamide adenine dinucleotide, as an enzyme in the mitochondrial respiratory chain was changed into formazan, which is not soluble in water. Purple color intensity was directly proportional to the amount of metabolism in active cells. The darker the color, the higher the absorbance value, the more living the cell [41, 42]. This goal should be attained with little or no effect on normal cells. The toxicity was measured by the MTT assay against a Vero cell line and **3a-c** were found to have no effect on normal cell line with CC_{50} values of 484.65, 612.87 and more than 2000 μg/ml, respectively, as listed in Table 2. The highest CC_{50} value indicates that the hydroxyxanthones compound has no selectivity against normal cells and has potential to be developed into a commercial antioxidant.

4. Conclusions

The search for new compounds that are effective and safe to be used as antioxidants has been facing challenges. Series of hydroxyxanthones (**3a-c**) have been synthesized by a simple method – cyclodehidration, which gave excelent yield. Compounds **3b** and **3c** exhibit a very strong antioxidant activity. The results suggest that a correlation exists between antioxidant activity and the position as well as number of hydroxyl substituents present on the xanthones core. All compounds are proven to be effective and safe to be developed as commercial antioxidants.

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ОДНОСТАДІЙНИЙ СИНТЕЗ І ОЦІНКА АНТИОКИСНЮВАЛЬНОЇ АКТИВНОСТІ ТА ТОКСИЧНОСТІ ДЕЯКИХ ГІДРОКСИКСАНТОНІВ

Анотація. *За допомогою одностадійої реакції циклодегідрування похідних гідроксибензенової кислоти (саліцилова або резорцилова кислота) з флороглюціном або пірогалолом у присутності реагенту Ітона ($P_2O_5/MeSO_3H$) одержано нові сполуки гідроксиксантону. Для визначення інгібуючої концентрації (IC_{50}) синтезованих сполук їх антиокиснювальну активність перевірено за допомогою 2,2-дифеніл-1-пікрилгідразилу. Цитотоксичність отриманих сполук оцінено МТТ-тестом на лінії клітин Vero. Встановлено, що положення та кількість гідроксильних груп можуть суттєво вплинути на потенційну антиокиснювальну активність приготовлених сполук. Показано, що синтезовані сполуки гідроксиксантону можна класифікувати як сильні антиоксиданти та їх можна використовувати в промисловості.*

Ключові слова*: антиоксидант, гідроксиксантони, 2,2-дифеніл-1-пікрилгідразил, реагент Ітона.*

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