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Research Article

SYNTHESIS AND ANTIOXIDANT EVALUATION OF 3-BROMO-FLAVONE

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ABSTRACT

Objective: The objective of the study was to obtain a flavone derivative compound through N-bromosuccinimide (NBS) reducing the reaction. The antioxidant activity of the synthetic compound was then assayed by the 2,2-diphenyl-1-picrylhydrazyl method.

Methods: Chalcone (3 mmol) as intermediate precursor was suspended with dimethyl sulfoxide and reacted with NBS (3 mmol), stirred at room temperature for 25 min and diluted in cold water. The synthesis of flavone derivatives resulted in yellow crystalline powder, freely soluble in methanol and ethanol, renamed 60% with a melting point of 87.7°C. Detection by thin-layer chromatography using hexane:chloroform (2:1) showed single spot with Rf = 0.38 which is different from the Rf value of the starting compound (chalcone, 0.66 and 0.78).

Results: The results of the characterization of the synthesized compound using ultraviolet-visible and Fourier transform-infared showed the group characteristic containing C=C (1604.77 and 1639.49 cm^{-1}), C=O (1681.93 cm^{-1}), C-O-C (1242.16 cm^{-1}), Ar-H (3032.1 and 3062.96 cm^{-1}), and C-Br (663.51 cm^{-1}) at maximum absorption of wavelength 253 nm.

Conclusion: The synthesis of flavone using NBS resulted in 3-bromo-flavone with a weak antioxidant activity.

Keywords: Antioxidant, chalcone, flavone, n-bromosuccinimide, synthesis.

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INTRODUCTION

Flavones are a class of natural compounds that are widely distributed in plants and have biological activity, such as antioxidant, inhibition of HIV-1 proteinase, and anticancer [1]. Flavones are flavonoids that have a strong activity to protect the body from reactive oxygen species (ROS). Free radicals and ROS are produced, either normally or induced by exogenous damage that is can damage cells and tissues [2].

Synthesis of flavone derivatives can be carried out using ortho hydroxyacetophenone or its derivatives and benzoic acid derivatives [3]. Synthesis of flavone derivatives can also be performed by the N-Bromosuccinimide (NBS) reducing the reaction. NBS is a catalyst, oxidant, and selective bromination reagent [4]. NBS, as a bromine source, is easier and safer to handle than bromine [4]. Therefore, the synthesis of flavone derivative through NBS reducing reaction is performed to obtain better synthesis results.

The aim of this work is to synthesize the flavone derivative through NBS reducing reaction and its antioxidant activity assay using 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. The role of synthetic compounds as antioxidant agents is important for future drug development.

EXPERIMENTAL

DPPH and L-ascorbic acid were purchased from Sigma-Aldrich Ltd. (St Lois, USA). NBS and *o*-hydroxyacetophenone were obtained from the collection of Pharmaceutical Chemistry Laboratory of Hasanuddin University (Indonesia). Ethanol, methanol, chloroform, hexane, demineralized water, dimethyl sulfoxide (DMSO), and sodium hydroxide were purchased from Merck. Indonesia. All chemicals and solvents were of analytical or pharmaceutical grade. Column chromatography was performed using silica gel (60–120 mesh) from Merck. Melting points were determined using a KRÜSS Optronic apparatus. Ultraviolet-visible (UV-Vis) spectra were recorded in the range λ 200–400 nm with Shimadzu. Infared (IR) data were collected on a IRPrestige-21 using a KBr pellet. ^{1}H-NMR spectra were recorded with a 500 MHz Bruker Advance spectrometer, and δ are given in ppm and referenced to the residual solvent peaks (1H, δ 7.26 for $CDCl_3$).

Synthesis of 3-bromo-flavone

A mixture of o-hydroxyacetophenone (0.1 mol), ethanol (5 mL), NaOH 50% (5 mL), and benzaldehyde (0.1 mol) was stirred at room temperature for 60 min. The reaction mixture was diluted with ice cold water; the product formed is then filtered and extracted with chloroform. The filtrate was evaporated and recrystallized with ethanol; light yellow crystals were obtained (chalcone). A mixture of chalcone (3 mmol), DMSO (3 mL), and NBS (3 mmol) was stirred at room temperature for 25 min, refluxed 20–25 min. The mixture was cooled, diluted with ice-cold water and filtered. The filtrate was evaporated and crystallized with ethanol. The reactions were monitored by thin-layer chromatography (TLC) and purified by column chromatography using hexane:chloroform (1:2) eluent. The product obtained was characterized by melting point, spectrophotometry UV-Vis, Fourier transform (FT)-IR, and ^{1}H-NMR.

Antioxidant Activity Assay Using a DPPH Method

The stock solution of DPPH 32 ppm in methanol was prepared. The various concentrations of compounds (40, 60, 80, and 100 ppm) were prepared with 200, 300, 400, and 500 µL, respectively, add with 1 mL solution of DPPH and methanol up to 5 mL. L-ascorbic acid in ethanol was used as a positive control (standard compound) with range concentration 2–5 ppm. The absorbance (A) was measured at 515 nm using UV/Vis spectrometer, after 30 min incubation in the dark and at room temperature. The percentage of radical scavenging activity was calculated based on the following equation:

$$\% \text{ Inhibition} = \left(\frac{(A_{control} - A_{sample})}{A_{\text{control}}} \right) \times 100\% \quad [1]$$

Antioxidant activity index (AAI) was calculated as follows: AAI = (final concentration of DPPH in the reaction)/50% inhibitory concentration (IC_{50}), where the final concentration of the reaction was 32 ppm. The

concentration for 50% inhibition (IC_{50}) was calculated by the linear regression equation. Scherer and Godoy established the following criteria of AAI values: poor activity < 0.5< moderate < 1.0< strong < 2.0< very strong [5].

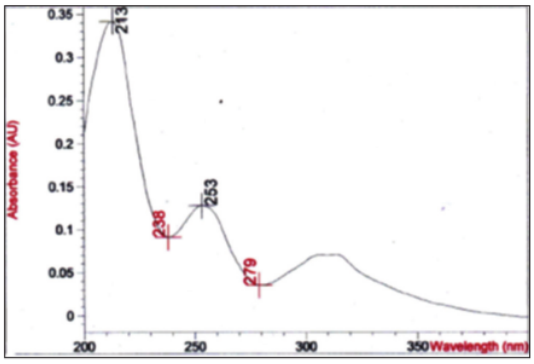


Figure 1: Ultraviolet-visible spectra of 3-bromo-flavone

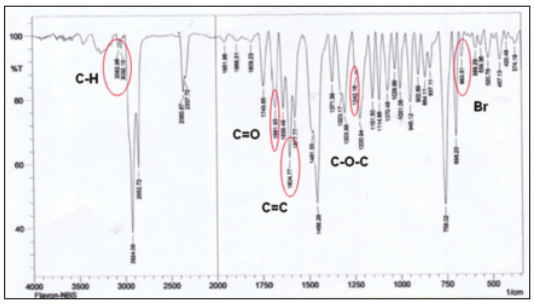
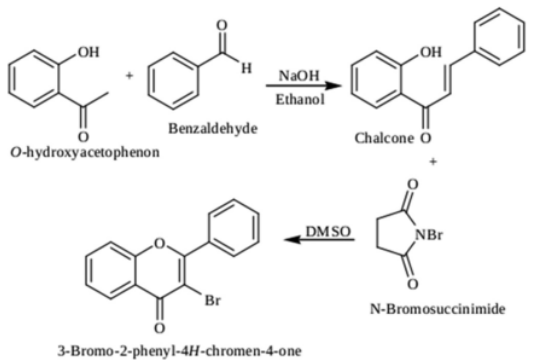


Figure 2: Infrared spectra of 3-bromo-flavone



Scheme 1: Synthesis of 3-bromo-flavone

RESULTS AND DISCUSSION

Synthesis results

The synthesis of flavone derivatives resulted in yellow crystalline powder, freely soluble in methanol and ethanol (melting point of 87.7°C). Detection by TLC using hexane:chloroform (2: 1) showed a single spot with Rf = 0.38, which differed from the Rf value of the starting compound (chalcone, 0.66 and 0.78).

The characterization of the synthesized compound using UV-Vis and FT-IR showed the group characteristic containing C=C (1604.77 and 1639.49/cm), C=O (1681.93/cm), C-O-C (1242.16 cm^{-1}), Ar-H (3032.1 and 3062.96 cm^{-1}), and C-Br (663.51 cm^{-1}) at maximum absorption of wavelength 253 nm (Fig. 1 and 2).

3-bromo-flavone

3-bromoflavone was obtained as a yellow powder. Mp: 87.7°C; ^{1}HNMR (500 MHz, CD_3OD, TMS): 7.86 ppm (doublet, *J* = 1.9 Hz, 1H), 7.49 ppm (doublet, *J* = 7, 25 Hz, 2H), 7.43 ppm (triplet, *J* = 7 Hz, 1.65 Hz, 6.35 Hz, 3H), 7.38–7.37 ppm (multiplet, 1H), and 7.00–6.97 ppm (multiplet, 2H).

Characterization results

In the beginning process of synthesis of flavone derivatives, we used a chalcone as an intermediate precursor. The chalcone was obtained from the condensation reaction between *o*-hydroxyacetophenone and benzaldehyde in an alkaline known as Claisen-Schmidt aldol condensation reaction. In the formation of aldolic reactions, a compound can form an enolate that serves as a nucleophile, whereas the addition of another carbonyl acts as an electrophile. Nucleophiles undergo α-substitution reaction while electrophiles undergo electrophilic addition. The OH^- ions in NaOH will deprotonate hydrogen-α to a more acidic *o*-hydroxyacetophenone, thus forming the enolate ions and ethanol as a proton donor.

Cyclization of chalcone into corresponding flavones was carried out using DMSO [3]. The presence of NBS also plays a role to accelerate the formation of cyclization. In addition, NBS is a source of bromonium ions (Br^+) which will be readily attached to the flavone ring. The derivative compound obtained was assumed as 3-bromoflavone (Scheme 1).

The antioxidant activity of the synthesis of flavone derivatives through the NBS reducing reaction was carried out using free radical capture method through DPPH. The DPPH method was chosen because it requires a small sample, simple, easy, fast, and sensitive to evaluate the antioxidant activity of a compound. In this method, DPPH acts as a free radical model that will bind to antioxidant compounds. Antioxidants can respond to DPPH radicals by various mechanisms, including hydrogen atom transfer and single electron transfer (SET), or a combination of both. The obtained flavone derivative compound has a bromine atom that acts as a SET [6-10].

Quantitative antioxidant activity was performed using UV-Vis spectrophotometer. This quantitative test was performed to determine the absorption of DPPH remaining after the addition of the compound

Table 1: Value of the antioxidant activity index of 3-Bromo flavone

Compound	Concentration (µg/mL^1)	Log concentration	Percentage inhibition	IC_{50} (µg/mL^1)	Total AAI*
3-Bromo flavone	40	1.602	25.921	71.419	0.448
	60	1.778	38.754		
	80	1.903	60.355		
	100	2	63.659		
Ascorbic acid (standard)	2	0.301	16.010	5.088	6.289
	3	0.477	30.114		
	4	0.602	36.722		
	5	0.699	51.842		

*AAI: Final concentration of DPPH in the reaction/IC_{50}, where the final concentration of DPPH was 32 µg/mL^1. DPPH: 2,2-diphenyl-1-picrylhydrazyl, IC_{50}: 50% inhibitory concentration, AAI: Antioxidant activity index

in the synthesis process. If a compound has activity as an antioxidant, it will decrease the absorbance value of DPPH at 515 nm wavelength. The decrease in the absorbance of DPPH was measured against absorbance of control, i.e., the absorbance of DPPH in methanol without the addition of test material. The decrease in DPPH absorbance is indicated by the degradation of DPPH color from purple to yellow. The DPPH color degradation process is directly proportional to the concentration of the test material added.

The IC_{50} was determined by the DPPH absorbance value and the DPPH inhibition of radical inhibition (% inhibition). The IC_{50} value of the synthetic compound was 71.419 ppm, while the IC_{50} value of L-ascorbic acid as control was 5.088 ppm. The AAI value for the synthesis of flavone derivatives by NBS reducing reaction was 0.448 (AAI <0.5) meaning that it has a weak antioxidant activity. L-ascorbic acid has a very strong antioxidant activity because the value of AAI >2 was 6.289 (Table 1).

CONCLUSION

In this work, we synthesized 3-bromo-flavone, which has a Weak antioxidant activity. The compound was a yellow crystalline powder and has a melting point at 87.7°C in the maximum absorption of wavelength at 253 nm.

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AUTHOR'S CONTRIBUTIONS

The authors declare that this work done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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