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2009-2016 trends

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The SJR indicator measures the scientific influence of the average article in a journal, it expresses how central to the global scientific discussion an average article of the journal is. The above trend is for 2009-2016 during which journal was indexed with Scopus. Cites per Doc. (2y) measures the scientific impact of an average article published in the journal, it is computed using the same formula that journal impact factor™ (Thomson Reuters).
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Synthesis of N’-(2-Methoxybenzylidene)-4-Hydroxy Benzohydrazide and N’-(4-Nitrobenzylidene)-4-Hydroxy Benzohydrazide, in Silico Study and Antibacterial Activity

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Faculty of Pharmacy Airlangga University, Dharmawangsa Dalam Street, Surabaya 60286-Indonesia.

ABSTRACT
In this study, synthesized N’-(2-methoxybenzylidene)-4-hydroxybenzohydrazide and N’-(4-nitrobenzylidene)-4-hydroxybenzohydrazide in two step reaction by using methylparaben as starting material has been performed. Methylparaben was treated with hydrazine hydrate to obtain 4-hydroxybenzohydrazide. The reaction was carried out by microwave irradiation resulting 91 % yield. The obtained compound was then reacted with 2-methoxybenzaldehyde or 4-nitrobenzaldehyde to accomplish the target molecule, N’-(2-methoxybenzylidene)-4-hydroxybenzohydrazide and N’-(4-nitrobenzylidene)-4-hydroxybenzohydrazide in 55% and 72% yield respectively. Identification of N’-(2-methoxybenzylidene)-4-hydroxy benzo hydrazide and N’-(4-nitrobenzylidene)-4-hydroxybenzohydrazide was performed by FT-IR, MS, 1H-NMR, and 13C-NMR spectroscopy. In silico study was done with receptor pdb 1C14. The N’-(4-nitrobenzylidene)-4-hydroxybenzohydrazide exhibited antimicrobial activity against Escherichia coli (MIC=31.3 ppm), Bacillus subtilis (MIC=500 ppm). Antimicrobial activity of N’-(2-methoxybenzylidene)-4-hydroxybenzohydrazide against Bacillus subtilis (MIC=31.3 ppm) and MIC= 500 ppm against Escherichia coli.

Keywords: Synthesis, N’-Benzylidene-4-hydroxybenzohydrazide derivatives, microwave, antibacterial.

INTRODUCTION
New drugs invention and development is crucial in the pharmaceutical industry. The application of conventional methods in developing new drugs such as through organic reactions which require high temperature has been widely practiced. Traditional heater equipment which are commonly used are sand-bath, oil-bath, and heating mantle. These techniques take much time to react the samples and may cause temperature differences on the samples. Moreover, heated reaction flask surface may cause localized overheating which results products, reagents, and substrate decomposition in prolonged heating. Therefore, new reaction methods which are expected to be able to perform quicker synthesis with higher product percentage and quality should be proposed. One of new synthesis methods is conducted by microwave irradiation. This technique is applied in new drugs development1-3. Hydrazide derivatives are widely used in new drug development for its biological activity and various clinical applications such as anticancer4, antitumor5, antimicrobial6, antifungal7,8, antiHIV9, and antituberculosis10. In some literature, it is mentioned that hydrazide derivatives have pharmacological activities (i.e. anticancer, anticonvulsant, antiinflammation, antibacterial, and antioxidant) are related to −CONHN=CN functional group in its molecular structure10. Although hydrazide derivatives can be synthesized with conventional11 and microwave irradiation methods in this research, we attempt to conduct synthesis reaction by applying microwave irradiation. This method is chosen because it takes shorter time and it’s able to result higher percentage product. The products are more eco-friendly because no toxic solvents are used in this process. Moreover, optimization of 4-hydroxybenzohydrazide derivatives were using microwave irradiation reaction method has not been conducted. Based on the background explained above, the problem proposed in this research is whether microwave irradiation can be used to synthesize 4-hydroxybenzohydrazide compound and its derivatives. Synthesis of 4-hydroxybenzohydrazide derivatives used methyl paraben as starting material. This research is expected to be able to provide new understanding of condensation reaction through the application of microwave irradiation to synthesize 4-hydroxybenzohydrazide derivatives. The compounds are tested antibacterial activity against Bacillus subtilis (Gram positive) and Escherichia coli (Gram negative). The scheme of synthesis reaction is presented in Figure 1.

MATERIALS AND METHODS
All chemicals were used in this study from commercial sources. Methyl paraben, hydrazine hydrate, 2-methoxybenzaldehyde, 4-nitrobenzaldehyde ethanol 95%, chloroform, ethyl acetate, acetone, hexane, KBr, silica gel 60 GF254 were purchased from Merck. Glassware commonly used in the chemical synthesis laboratories, Sanyo microwave EM-S 400 Watt, Spectrophotometer

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Preparation of 4-hydroxybenzohydrazide (I) with microwave irradiation\textsuperscript{12,13}

Methyl paraben (10 mmol) and hydrazine hydrate (50 mmol) were stirred until homogeneous. The mixture was put in the microwave on 160 Watt power for 2-8 minutes while stirring every 2 minutes. The progress of the reaction was monitored by TLC. The mixture was cooled to room temperature and then added to 20-30 ml of ice water, filtered, washed with ethanol. Crystals were recrystallized with absolute ethanol. The purity tests were done by melting point and thin layer chromatography (TLC) using three different eluents. Identifications were carried out by FT-IR, and \(^1\)H-NMR spectroscopy.

Preparation of \(N'-(2\text{-methoxybenzilidene})-4\text{-hydroxybenzohydrazide}\) and \(N'-(4\text{-nitrobenzilidene})-4\text{-hydroxybenzohydrazide}\)\textsuperscript{12,13}

4-Hydroxybenzohydrazide (10 mmol) and benzaldehyde (20 mmol) were dissolved in ethanol (12 ml). Ethanol was evaporated until exhausted. The mixture was put in the microwave on 320 Watt power for 2 minutes (for synthesis IIb), and on 160 Watt power for 4 minutes (for synthesis IIa). The mixture was cooled to room temperature, then added to 20-30 ml of ice water, filtered, washed with ethanol. Crystals were crystallized with absolute ethanol. The purity tests were done using melting point and thin layer chromatography using three different eluents. Identifications were carried out by FT-IR, MS, \(^1\)H-NMR, and \(^{13}\)C-NMR spectroscopy.

Antibacterial Activity

Antibacterial activity was done by well diffusion method\textsuperscript{14-16}. In this method, The wells are filled with test compounds. Petri plate was labeled with the name of the culture, sample and standard at the bottom of the plate. Inoculums were standardized by adjusting the turbidity of culture, sample and standard at the bottom of the plate. Antimicrobial activity was carried out by thin layer chromatography indicated one stone. Three of eluents were chloroform:ethanol (1:1), chloroform:acetone (1:2) and acetone:ethyl acetate (2:1), m.p. 255-256°C. IR (KBr in cm\(^{-1}\)): 1620 (-C=O amide), 3318 (-OH phenolic), 1590 and 1467 (-C=C- aromatic), 1534 (C=N), 3005 (C=C-H), 850 (para substitution on benzene), 3197 (-NH\(_2\)). \(^1\)H-NMR (DMSO-d\(_6\), \(\delta\) ppm): 6.74-6.72 (d, \(J=8.4\) Hz, 2H, C\(\text{H}_3\)-), 7.65-7.62 (d, \(J=9.2\) Hz, 2H, C\(\text{H}_3\)-), 8.99 (s, 1H, OH), 11.33 (1H, NH), 8.24 (2H, NH\(_2\)).

Characterization of \(N'-(2\text{-methoxybenzilidene})-4\text{-hydroxybenzohydrazide}\) (IIa)\textsuperscript{21,22}

Obtained in 55% yield as white needle-shaped crystals. Characterization of \(N'-(4\text{-nitrobenzilidene})-4\text{-hydroxybenzohydrazide}\) (IIb)\textsuperscript{21,22}

Obtained in 72% yield as yellow needle-shaped crystals. Characterization of \(N'-(4\text{-nitrobenzilidene})-4\text{-hydroxybenzohydrazide}\) (IIb)\textsuperscript{21,22}

Obtained in 72% yield as yellow needle-shaped crystals. Characterization of \(N'-(4\text{-nitrobenzilidene})-4\text{-hydroxybenzohydrazide}\) (IIb)\textsuperscript{21,22}

Obtained in 72% yield as yellow needle-shaped crystals.

RESULTS AND DISCUSSION

Synthesis of 4-hydroxybenzohydrazide derivatives using condensation reaction were carried in two reaction phases. The first phase was conducted reaction methyl paraben with hydrazine hydrate with microwave irradiation 160 Watt power for 2-8 minutes to produce 4-hydroxybenzohydrazide. It was done by the nucleophilic substitution reaction\textsuperscript{15}. The second phase was conducted to produce 4-hydroxybenzohydrazide derivatives using the condensation reaction method. This method was chosen for its practicality and not requiring toxic solvent. Besides, the method took a relatively short time (about 8 minutes). The reaction was carried out without toxic solvent. Therefore, this reaction conformed to eco-chemistry because lacking of toxic solvent and energy saving\textsuperscript{9,20}. 4-Hydroxybenzohydrazide derivatives were synthesized by reacting 4-hydroxy benzohydrazide and 2-methoxybenzaldehyde or 4-nitrobenzaldehyde. Ethanol was used as solvent, then evaporated to run out.

In Silico Study

To estimate the antimicrobial activity of derivatives of 4-hydroxybenzohydrazide, in silico study was done with receptor pdb 1C14 program MVD 5.0 (Mollegro Virtual Docker). 1C14 is a receptor model of inhibitor triclosan.
The synthetic compounds were evaluated for antibacterial activity against Gram positive (*Bacillus subtilis*) and Gram negative (*Escherichia coli*). Antibacterial activities against *Escherichia coli* of the compounds as well as reference drug are summarized in Table 1. The results indicated that N'-((2-methoxybenzylidene)-4-hydroxybenzohydrazide and N'-(4-nitrobenzylidene)-4-hydroxybenzohydrazide have had activities against *E. coli*. Results of minimal inhibitory concentration (MIC) of N'-((2-methoxybenzylidene)-4-hydroxybenzohydrazide and N'-(4-nitrobenzylidene)-4-hydroxybenzohydrazide have MIC against *E. coli* (Gram negative) bigger than N'-(2-methoxybenzylidene)-4-hydroxybenzohydrazide. Antibacterial activities against *Bacillus subtilis* of the compounds as well as reference drug are summarized in Table 2. Results indicated that N'-((2-methoxybenzylidene)-4-hydroxybenzohydrazide and N'-(4-nitrobenzylidene)-4-hydroxybenzohydrazide had activity against *Bacillus subtilis*. Results of minimal inhibitory concentration (MIC) of N'-((2-methoxybenzylidene)-4-hydroxybenzohydrazide was 31.3 ppm and N'-(4-nitrobenzylidene)-4-hydroxybenzohydrazide was 500 ppm. N'-(2-methoxybenzylidene)-4-hydroxybenzohydrazide had MIC against *B. subtilis* (Gram positive) bigger than N'-(4-nitrobenzylidene)-4-hydroxybenzohydrazide. The antibacterial activity of the target compounds due to the phenolic group (HO-CH<sub>3</sub>)<sup>23</sup> and the azometin group (-HN=N=CH-)<sup>26</sup>. Variations of the target compound antibacterial activity against different bacteria (Gram positive/Gram negative) is influenced by electronic, steric, and lipophilicity of compounds. In silico test lipophilicity factors not included, so it can give different results<sup>24</sup>.

**CONCLUSION**

It can be concluded that N'-2-methoxybenzylidene-4-hydroxybenzohydrazide and its derivatives can be synthesized from the methyl paraben as starting material by microwave irradiation (160-320 Watt power for 2-8 minutes). The yields were obtained between 55-72%. The preliminary biological tests indicated that N'-(4-nitrobenzylidene)-4-hydroxybenzohydrazide has effective activity against *Escherichia coli* (MIC=31.3 ppm), and
Table 2: Antibacterial activity against *E.coli* of the test compounds.

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<th>Inhibition zone (mm)</th>
<th>Amoxicillin</th>
<th>Control negative</th>
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<td>Concentration (ppm)</td>
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<tr>
<td>I</td>
<td>31.3 62.5 125 250 500 1000</td>
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<td>14.5±0.67</td>
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<tr>
<td>IIb</td>
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</tr>
</tbody>
</table>

(-) No inhibition zone, n=3 replications.

Table 3: Antibacterial activity against *Bacillus subtilis* of the test compounds.

<table>
<thead>
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<th>Control negative</th>
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<td>- - - - - - - -</td>
<td>12.0±0.33 10.0±0.50 14.5±0.67</td>
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<tr>
<td>IIb</td>
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(-) No inhibition zone, n=3 replications.

N’-(2-methoxybenzylidene)-4-hydroxybenzohydrazide has effective activity against *Bacillus subtilis* (MIC=31.3 ppm).

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**REFERENCES**


16. Namasivayam N, Theivarasu C. Synthesis of substituted piperidine-4-ones with dichlorocyclooctadiene palladium (II) and antimicrobial activity, International Journal of