Utilization of monosodium glutamate (MSG) for the synthesis of 1,8-dioxoacridine and polyhydro-quinoline derivates with SiO2-AA-glutamate catalyst and antioxidant ability test

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Abstract. Derivatives of 1,8-dioxoacridine and polyhydro-quinoline compounds are active compounds that have several beneficial bioactivities. The purpose of this research is to synthesize 1,8-dioxoacridine and polyhydro-quinoline derivatives supported by SiO2-AA-Glu as the catalyst and test their antioxidant activity. The reaction was conducted at the optimum condition with ethanol solvent at boiling point temperature (78 °C) for 60 min with a catalyst concentration of 3 % mol with a yield of 88.16 %. Analysis of formation products was confirmed using FTIR, UV-Vis Spectrophotometer, and GC-MS. The results of the analysis produced three 1,8-dioxoacridine and polyhydro-quinoline derivatives, namely 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (compound 1), 9-(4-hydroxy-phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (compound 2), and 7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (compound 3). Compound 2 shows the best activity as an antioxidant compared to the other two compounds with an IC50 value of 83.72 ppm.

Keywords: 1,8-dioxoacridine, polyhydro-quinoline, SiO2-AA-Glu catalyst, antioxidant

1. Introduction
The acridine compound was first discovered in the 19th century [1]. The structure of this compound has similarities with 1,4-dihydropyridines (DHP) which is an analog of nicotinamide adenine dinucleotide (NADH) [2-6]. Research on the development of 1,8-dioxoacridine derivatives is still under investigation. Based on previous research reports, the compound 1,8-dioxoacridine has beneficial bioactivity in the health field. Among them, antimicrobial, carbonic anhydrase inhibitors for glaucoma treatment, anti-tumors, fungicides, as anti-multidrug-resistant, cytotoxic, and cardiovascular disease [7-9].

The use of catalysts in the synthesis of 1,8-dioxoacridine compounds was carried out to streamline the reaction. In this study, synthesized SiO2-AA-glutamate made from monosodium glutamate (msg) was used to support the reaction. The use of msg as a catalyst is possible because of the dual properties as acids and bases of the structure [10]. In this study, the modification of msg was conducted to improve its capabilities. Heterogeneous catalyst SiO2-AA-Glu has advantages compared to homogeneous catalysts which are more effective, non-corrosive, easily separated from the product produced, and can be reused.
2. Materials and method

2.1. Chemical reagents and instrumentation
In this research, the tools needed for synthesis and analysis structure were glassware, magnetic stirrer, thermometer, filter paper, TLC, stirring hot plate IKA C-MAG HS 7 shaker Julabo SW22. The analytical instruments used were the Fourier Transform Infrared (FTIR) IRPrestige-21 Shimadzu Spectrophotometer, the Shimadzu UV-Vis UV-2450 Spectrophotometer, and the GC-MS 6890 spectroscopy. The materials used in this study were ethyl acetate, n-hexane, SiO\textsubscript{2}, Monosodium Glutamate (MSG) Viet Shen brand, sodium alginate, ammonium acetate, variations of aldehydes (benzaldehyde, hydroxy benzaldehyde), dimedone, ethyl acetoacetate, aquadest, ethanol 96 %, HCl 1 M, DPPH.

2.2. Synthesis of glutamic acid from monosodium glutamic
Monosodium Glutamate (MSG) was weighed as much as 2.5 g and placed in a beaker then added with 15 mL of HCl or CH\textsubscript{3}COOH 1 M. The mixture was stirred for 10 min at 70 °C. The precipitated sludge was filtered and recrystallized with ethanol 96 %. The synthesized product was characterized by TLC, FTIR and UV-Vis spectrophotometer.

2.3. Synthesis of SiO\textsubscript{2}-AA-Glu catalyst
Two beakers were prepared and the first beaker was filled with 1 g of sodium alginate dissolved in 20 mL of distilled water. The second beaker was filled with 1 g of glutamic acid that has been synthesized, then each beaker was added with 3 g of silica and stirred. Then, 3 mL of 1M HCl was added to form sediments. The sediment was then heated to vaporize H\textsubscript{2}O and washed with distilled water to neutral pH. After that, the product was dried and formed 4.8 g of white powder SiO\textsubscript{2}-AA-Glu and characterized by FTIR.

2.4. Synthesis of 1,8-dioxoacridine derivatives
Aldehyde compounds (1 mmol), dimedone (2 mmol), ammonium acetate (1.5 mmol) and SiO\textsubscript{2}-AA-Glu catalyst were mixed (figure 1). The mixture was heated in an oil bath and under reflux conditions. The reaction process was monitored using TLC (Ethyl acetate:n-hexane = 3:7). Then, the solvent was evaporated to get the product. The product was purified by recrystallization using ethanol 96 %. Product characterization analysis was performed with (FTIR), UV-Vis spectrophotometer and GCMS.

2.5. Antioxidant activity test
The sample solution was prepared in a series concentrations of 500, 300, 200 100, 50, 10 and 5 ppm in a methanol solvent. Then, 2 mL each solution was reacted with 1mL DPPH 0.1 mM. The reaction mixture was then incubated at room temperature for 30 min. After that, the absorbance of the solution was measured at a wavelength of 518 nm using a UV/Vis spectrophotometer. Radical scavenging activity was expressed as a percent of inhibition which can be calculated with the following formula:

\[
\%\text{inhibition} = \left(\frac{\text{absorbance of control} - \text{absorbance of sample}}{\text{absorbance of control}}\right) \times 100\%
\]

![Figure 1. Reaction scheme for the synthesis of 1,8-dioxoacridine derivatives.](image-url)
The percentage of inhibition was then plotted with a logarithmic line to get IC_{50} with the x-axis as concentration (ppm) and the y-axis as a percent of inhibition [11-12].

3. Results and discussion

Synthesis of glutamic acid using the acidification method is considered the most effective because it can properly substitute Na^{+} ions to H^{+} ions. HCl acid is an acid that can be well hydrolyzed in solution because it is a strong acid. To see its characteristics, an analysis with FTIR was carried out to find out the functional groups of compounds. Figure 2a shows a comparison between the FTIR spectrum of glutamic acid and monosodium glutamic. Both FTIR spectra show peaks in wave numbers broadened around 2750–3250 cm\(^{-1}\) which is O-H stretching vibrations, but the O-H peak of MSG is different from glutamic acid due to the influence of ionic substituents found in MSG. In the wavenumber between 3500 and 3300 cm\(^{-1}\) indicate the existence of N-H primary vibrations. The N-H peak of glutamic acid is indicated by the overlapping with the O-H peak so that it covers the N-H peak. In addition, there is also a stretching vibration C=O at wavenumber 1750 cm\(^{-1}\) with strong intensity and C-H at 3000 cm\(^{-1}\).

Characterization using UV-Vis spectrophotometry (figure 2b) showed the maximum wavelength of glutamic acid was 262 nm. However, in MSG there is an increase in wavelength uptake to 267 (rightward shift), which is called the bathochromic shift due to the auxochrome substitution of O-H with O-Na. MSG yield obtained from the synthesis is 92.88 %.

SiO\(_2\)-AA-Glu catalyst is a heterogeneous catalyst based on green chemistry. In this catalyst structure, sodium alginate which is reacted with glutamic acid forms hydrogen bonds that are bound to oxygen groups with oxygen and nitrogen in the catalyst structure. SiO\(_2\) acts as a binder between sodium alginate and glutamic acid. The addition of HCl aims to cut the alginate polymer bonds to form sediments consisting of catalyst layers which are then dried to form powders. The catalyst yield obtained by 96 %. The characterization of SiO\(_2\)-AA-Glu with FTIR (figure 3) produced several absorptions, including O-H stretching vibrations of carboxylic acid at wave number 3445 cm\(^{-1}\), vibrations of stretching carbonyl (C =O) at wave number 1627 cm\(^{-1}\) and stretching vibration of Si-O-Si at wave number 1097 cm\(^{-1}\).

The evaluation of the ability of SiO\(_2\)-AA-Glu as a catalyst was carried out by synthesizing 1,8-dioxoacridine and polyhydro-quinoline derivatives. Two 1,8-dioxoacridine compounds were synthesized by reacting benzaldehyde (compound 1)/4-hydroxybenzaldehyde (compound 2), dimesione, and ammonium acetate. While the synthesis of polyhydro-quinoline derivative was carried out by reacting dimesione, benzaldehyde, ammonium acetate and ethyl acetacetate (compound 3). The three synthesized compounds were analyzed by functional group vibration, maximum wavelength,
Table 1. Characterization data and yield of 1,8-dioxoacridine and polyhydro-quinoline derivatives.

| No | Product | Characterization data | Yield (%) | Photo |
|----|---------|------------------------|-----------|-------|
| 1  | ![Chemical Structure](image1) | Yellowish white powder. IR (cm⁻¹): 3201 (N-H stretching), 1495 (N-H bending), 2996 (C-H sp³), 2902 (C-H sp³), 1404 (C-N), 15140 (C=C), and 1623 (C=O). UV-Vis (nm): 266. MS (m/z): 349 | 88.16 | ![Photo](image2) |
| 2  | ![Chemical Structure](image3) | Yellow powder. IR (cm⁻¹): 3234 (N-H stretching), 1485 (N-H bending), 2987 (C-H sp³), 2900 (C-H sp³), 1413 (C-N), 1506 (C=C), and 1664 (C=O). UV-Vis (nm): 265. MS (m/z): 364.9 | 85.11 | ![Photo](image4) |
| 3  | ![Chemical Structure](image5) | Yellowish white powder. IR (cm⁻¹): 3252 (N-H stretching), 1514 (N-H bending), 3001 (C-H sp³), 2930 (C-H sp³), 1423 (C-N), 1572 (C=C), and 1744 (C=O). UV-Vis (nm): 364. MS (m/z): 339.2. | 71.07 | ![Photo](image6) |

and molecular weight by FTIR, UV-Vis spectrophotometer, and GCMS. The results of analysis with these instruments, it was found that 1,8-dioxoacridine and polyhydro-quinoline derivatives have been successfully synthesized as 3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (compound 1), 9-(4-Hydroxy-phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (compound 2), and 7,7-Dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (compound 3). Product characterization and yield data are illustrated in table 1.

The optimum conditions for the reaction to obtain the optimum yield as shown in table 1 was carried by varying the reaction conditions. Determination of the optimum reaction conditions was carried out...
by synthesizing compound 1 by varying the reaction temperature, reaction time, catalyst concentration, and type of solvent (table 2). The optimum conditions obtained for the synthesis of compound 1 in this study were with ethanol solvent at boiling point temperature (78 °C) for 60 min with a catalyst concentration of 3 % mol with a yield 88.16 %. In green chemistry, it would be more beneficial to use water as a solvent (entry 11) in this reaction. This is caused by the high yield produced, more environmentally friendly, and requires lower costs.

Experimental evidence in support of the formation of 1,8-dioxoacridine and polyhydro-quinoline derivatives through FTIR obtained several specific peaks. Figure 4a shows the absorption at 3201 cm\(^{-1}\) which is N-H stretching vibration, 1495 cm\(^{-1}\) is N-H bending vibration, 2996 cm\(^{-1}\) is the absorption of C-H sp\(^2\) stretching vibration (benzene ring), while 2902 cm\(^{-1}\) is of C-H sp\(^3\) stretching vibration. In addition, there is a peak at 1404 cm\(^{-1}\) is as stretching vibration of C-N, 15140 cm\(^{-1}\) is stretching vibration of C = C, and 1623 cm\(^{-1}\) is the absorption of carbonyl groups (C = O). UV-Vis Spectrophotometer analysis (figure 4b) showed the maximum wavelength of compound 1 was 266 nm. Peak compound 1 shifts to the right (bathochromic shift) compared with its precursors.

### Table 2. Optimization of the reaction condition for the synthesis of compound 1.

| Entry | Catalyst | Time (min) | Temp. (°C) | Solvent | % yield |
|-------|----------|------------|------------|---------|---------|
| 1     | 0        | 60         | 78         | Ethanol | 40.45 % |
| 2     | 1        | 60         | 78         | Ethanol | 61.63 % |
| 3     | 2        | 60         | 78         | Ethanol | 74.12 % |
| 4     | 3        | 60         | 78         | Ethanol | 88.16 % |
| 5     | 5        | 60         | 78         | Ethanol | 85.55 % |
| 6     | 10       | 60         | 78         | Ethanol | 84.11 % |
| 7     | 3        | 45         | 78         | Ethanol | 85.00 % |
| 8     | 3        | 30         | 78         | Ethanol | 72.12 % |
| 9     | 3        | 60         | 50         | Ethanol | 65.20 % |
| 10    | 3        | 60         | Room temperature | Ethanol | 62.20 % |
| 11    | 3        | 60         | 70         | water   | 75.15 % |
| 12    | 3        | 60         | 78         | Ethanol | 85.11 % |
| 13    | 3        | 60         | 78         | Ethanol | 86.75 % |

![Figure 4. FTIR (a) dan UV-Vis, and (b) spectra of compound 1.](image)
Figure 5. Mass spectrum of compound 1.

| Sample                  | IC_{50} (ppm) |
|-------------------------|---------------|
| Compound 1              | 90.37         |
| Compound 2              | 83.72         |
| Compound 3              | 95.77         |
| Benzaldehyde            | 715.68        |
| 4-Hydroxybenzaldehyde   | 135.31        |

Table 3. Antioxidant activity test of 1,8-dioxoacridine and polyhydro-quinoline derivatives.

The determination of molecular structure from the aspect of molecular weight has been carried out using GCMS. Based on the results of the peak on chromatogram obtained from the chromatographic process, there is a peak with m/z 349. This peak was then analyzed with a mass spectrum as shown in figure 5. Compound 1 with the molecular formula C_{23}H_{27}NO_{2} has a molecular weight of 349 g/mol which is appropriate with the results of the analysis of this instrument. Some important fragments found in the mass spectrum of compound 1 are m/z 272. In this condition, it is estimated that compound 1 loses the benzene ring.

DPPH compounds are free radicals that are stable due to electron delocalization. The delocalization causes the purple color in the DPPH solution. The mechanism of the antioxidant activity of a compound is by donating hydrogen atoms to DPPH radicals. The DPPH radical compound will change to its yellow form after receiving the hydrogen atom from the antioxidant compound. The antioxidant activity value is determined as the IC_{50} value, which states the minimum concentration needed to inhibit 50 % of free radical activity. IC_{50} values of each product are shown in table 3. The addition of the O-H group which is a differentiator of compound 2 with compound 1, makes compound 2 has a better antioxidant bioactivity than compound 1.
4. Conclusion
In summary, the utilization of monosodium glutamate (MSG) for the synthesis of 1,8-dioxoacridine and polyhydro-quinoline derivates were successfully synthesized using SiO$_2$-AA-Glu as a catalyst. The determination and characterization of products were analyzed by FTIR, Uv-Vis, and GC-MS and showed the properties of the target compound. The analysis identified that the compound formed was 1,8-dioxoacridine and polyhydro-quinoline derivates namely 3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (compound 1), 9-(4-Hydroxy-phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (compound 2), and 7,7-Dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester (compound 3). The best condition of the reaction was carried out with ethanol solvent at boiling point temperature (78 °C) for 60 min with a catalyst concentration of 3 % mol with a yield of 88.16 %. Compound 2 shows the best activity as an antioxidant compared to the other two compounds with an IC$_{50}$ value of 83.72 ppm.

Acknowledgments
This research was financially supported by Directorate General of Higher Education (DIKTI), Republic of Indonesia through Penelitian Dasar Unggulan Perguruan Tinggi (PDUPT) 2019 with contract No. NKB-1586/UN2R3.1/HKP.05.00/2019.

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