ORIGINAL ARTICLE

Synthesis of antioxidant and antimicrobial bioactive compounds based on the quinoline-hydrazone and benzimidazole structure

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ABSTRACT

Quinoline and its derivatives are known to have various biological activities such as antibacterial and antioxidant. Therefore, this study aims to synthesize quinoline moiety from isatin and ethyl acetoacetate by Pfitzinger reaction under acidic conditions. The benzimidazole derivative was synthesized from quinoline and o-phenylenediamine by a solvent-less reaction, while the hydrazone derivative was formed by the reaction with hydrazine hydrate and aromatic aldehyde. In addition, 4-hydroxybenzaldehyde was used as an aromatic aldehyde. The four compounds formed were characterized by thin-layer chromatography (TLC), melting point measurement, Fourier-transform infrared, liquid chromatography–mass spectrometry, and ultraviolet-visible spectrophotometry. They were also evaluated for their antioxidant and antimicrobial activities using the 2,2-diphenyl-1-picrylhydrazyl assay and the disc diffusion method, respectively. All compounds showed weak antioxidant activity compared to ascorbic acid; the quinoline-hydrazone derivative showed the best antioxidant activity with IC_{50} = 843.52 ppm, while the IC_{50} value for quinoline-benzimidazole was 4784.66 ppm. All synthesized compounds have not been confirmed to be effective against *Staphylococcus aureus* and *Escherichia coli* bacteria in a concentration range of 75–1000 ppm. The bioactive compounds based on the quinoline-hydrazone and benzimidazole structures have been successfully synthesized and tested for their activity as antioxidant and antimicrobial agents.

Key words: Antimicrobial, antioxidant, benzimidazole, hydrazine, quinoline

INTRODUCTION

The increasing threat to the health system that raises by the severe global threat of antimicrobial resistance (AMR) has become a great concern. Antibiotic-resistant bacterial infections are expected to affect up to 2 million people in the US each year. During the COVID-19 pandemic, one of the main contributors to considerable antibiotic resistance in clinical settings is Gram-negative bacteria.[1] In 2019, *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* are the pathogens that caused 3.57 million deaths related to AMR and 929.000 deaths attributed to AMR.[2] Various treatments have been

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developed to overcome the bacterial resistance problem, such as creating molecules with new modes of action that avoiding any potential cross-resistance with existing treatments. Heterocyclic molecules are desirable targets for medicinal chemists to develop novel antimicrobials.[3] One of the important heterocyclic compounds that are frequently examined due to its wide biological activity is quinoline. Its derivatives reportedly have antimicrobial, antioxidant, anticancer, anti-inflammation, and antimalarial activity.[4] Modification of the quinoline structure has been attempted to improve its biological activity; for example, aminophosphonate derivatives have moderate antioxidant activity.[5] In addition, the 4-amino-6-ether quinoline derivative has great antibacterial activity against resistive positive-gram bacteria.[6]

Quinoline structure is mainly synthesized using the Skraup, Doubler-von Miller, or Combes Methods but they have some disadvantages such as occurring in highly acidic conditions, being highly exothermic, and requiring an oxidant.[7] Meanwhile, the Pfitzinger reaction offers a more efficient and simple way to build a quinoline structure.[7] The reaction converts isatin, an indole heterocyclic molecule, and α-menthylene carbonyl, in the presence of a base, into quinoline-4-carboxylic acid.[8] Reports suggested that benzimidazole and hydrazone derivatives of quinoline possess antibacterial and antioxidant potential.[9-11] Quinoline hydrazones structure containing $R_1R_2C{=}NNH_2$ functional group which gives this compound both polar and nonpolar properties. This functional group is also helpful for bacterial cell penetration, and eventually leading to bacterial death.[12] The Benzimidazole group has a similar structure with a purine base of DNA, making it beneficial in drug development. Therefore, this study aims to synthesize quinoline-hydrazone and quinoline-benzimidazole derivatives from isatin as well as evaluate their antibacterial and antioxidant activities.

MATERIALS AND METHODS

Materials

The chemicals used in this study were isatin, ethyl acetoacetate, ortho-phenylenediamine, hydrazine hydrate, 4-hydroxybenzaldehyde, ethanol, ethyl acetate, n-hexane, 2,2-diphenyl-1-picrylhydrazyl (DPPH), dimethyl sulfoxide (DMSO), acetone, chloroform, and nutrient agar. All of the chemicals (Merck and Sigma-Aldrich analytical grade) were utilized without additional purification. Amoxicillin and ascorbic acid were obtained from the pharmacy, while *E. coli* and *S. aureus* bacterial suspensions were obtained from the Biochemistry Laboratory of the Department of Chemistry, Universitas Indonesia.

Synthesis of quinoline derivative

The quinoline derivative compound was synthesized using the reported method.[7] Isatin (1 mmol) was dissolved in a 5% potassium hydroxide (KOH) solution composed of ethanol/water, 1:1, 5 mL, followed by 30 min of stirring the mixture. Shortly afterward, a few drops of concentrated HCl were added until the pH = 2–3. The mixture was also added with 2 mmol of ethyl acetoacetate and 0.1 mmol $AlCl_3$, and stirred for another 2 h. The precipitate was obtained and then recrystallized from hot ethanol after being filtered and rinsed with cold water. The compound was identified by thin-layer chromatography (TLC), melting point analysis, and also characterized by Fourier-transform infrared (FTIR), ultraviolet-visible (UV-Vis) spectroscopy, and liquid chromatography–mass spectrometry (LC-MS).

Synthesis of quinoline-benzimidazole derivative

The quinoline-benzimidazole derivative was synthesized from the previous quinoline derivative based on the adaptation of the reported method.[13] The synthesized quinoline derivative (1 mmol) and o-phenylenediamine (1 mmol) were mixed and pounded using a mortar and pestle at room temperature, then heated for 1 h at 140°C. The molten mixture was then added to ice-cold water once it had cooled to room temperature. The precipitate obtained was then recrystallized from hot ethanol after being filtered and washed with cold water. The compound was identified by TLC, melting point analysis, and characterized by FTIR, UV-Vis spectroscopy, and LC-MS.

Synthesis of quinoline-hydrazone derivatives

The quinoline-hydrazone derivative was synthesized through the Quinoline-hydrazide intermediate reported by a previous study.[14,15] The synthesized quinoline derivative (10 mmol) was dissolved in ethanol of 10 mL, while hydrazine hydrate 10 mL was added to the solution. Subsequently, the mixture was refluxed for 4 h, cooled at room temperature, and the hydrazide crystals appeared, then, the solid obtained was recrystallized from hot ethanol after being filtered and washed with cold water.

Quinoline-hydrazide (1 mmol) was dissolved in ethanol 8 mL and 4-hydroxybenzaldehyde (1 mmol) was added, followed by two drops of glacial acetic acid. The mixture was then agitated for 30 min at room temperature; after that, the precipitate was filtered and recrystallized from ethanol. The products were identified by TLC, melting point analysis, and characterized by FTIR, UV-Vis spectroscopy, and LC-MS.

Antioxidant study (2,2-diphenyl-1-picrylhydrazyl assay)

DPPH radical scavenging experiment was used to evaluate the synthetic compound's antioxidant properties. The DPPH stock solution was prepared by dissolving a certain amount of DPPH radical in ethanol 25 mL to reach a 1 mM DPPH concentration. The stock solution was diluted by ethanol to 0.1 mM and used for the test. The series concentrations of 100 ppm to 1000 ppm were prepared by dissolving each

compound and ascorbic acid control in a certain amount of ethanol. Each sample solution of 0.5 mL was added with 0.1 mM DPPH solution (0.5 mL), homogenized, and incubated for 30 min in a dark place. Afterward, the sample's absorbance was measured at 517 nm.[16] The radical inhibition percentage was calculated from the absorbance and control (0.05 mM DPPH) using the equation below.

$$\%\text{inhibition} = \frac{A_c - A_s}{A_c} \times 100\%$$

A_c and A_s are the absorbance of the control and the sample at 517 nm, respectively.

The IC_{50} value for each compound was determined by interpolation of the inhibition percentage-concentration curve. IC_{50} is an expression of antioxidant activity, which is defined as the minimum analyte concentration to decrease 50% of the initial DPPH concentration.[15]

Antibacterial study

Disk diffusion was used to conduct the antibacterial investigation against Gram-negative *E. coli* and *S. aureus* (Gram-positive). The bacteria were incubated in the sterile nutrient broth at 37°C for 24 h, separately, then bacterial suspension absorbance was measured at 625 nm. It is important to note that the absorbance used for the test is only in the range of 0.08–0.13 (0.5 McFarland).[17] Furthermore, the bacterial suspension of 0.1 mL was inoculated to a sterile liquid agar medium in the petri dish and then allowed to harden. For the test, a series of concentrations between 62.5 ppm and 1000 ppm for the compound and amoxicillin was made by dissolving a certain amount of the sample in DMSO. Some 6 mm paper disc that contains sample solution and negative control (DMSO) was placed on the inoculated agar medium. The disc was then incubated for 24 h at 37°C, and the inhibitory zone was measured by measuring the diameter of the clear zone surrounding the disc paper.

RESULTS

The synthesis of quinoline-benzimidazole and quinoline-hydrazone derivatives showed good prospects, as demonstrated in the FTIR, UV-Vis, and LCMS characterization results in Table 1.

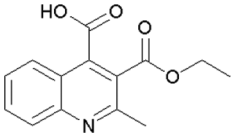
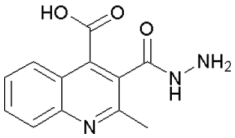
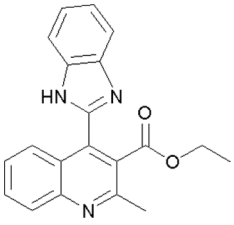
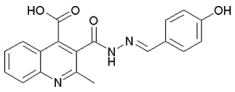
The antimicrobial activity test against *E. coli* and *S. aureus* using the disk diffusion technique revealed no inhibition zone on any sample in the concentration of 75–1000 ppm. Meanwhile, the antioxidant activity test of the products was carried out by DPPH radical scavenging. The results showed that the quinoline-hydrazone derivative has stronger antioxidant activity than benzimidazole. Table 2 shows the antioxidant and antimicrobial activity of the synthesized products.

DISCUSSION

Synthesis and characterization of quinoline derivative

The quinoline-4-carboxylic acid derivative was synthesized by the Pfitzinger reaction of isatin and ethyl acetoacetate in a water-based medium. The reaction was catalyzed by

Table 1: Analysis of synthesized compound

Compound	Molecular structure	Characterization result	Yield (%)
Quinoline derivative*		White Powder, $C_{14}H_{13}NO_4$, mp: 182.3°C–183°C IR: 1734 cm-1 (C=O), 1662 cm-1 (C=C), 1085 cm-1 (C-O), and 2990 cm-1 (C-H sp3) UV-vis (nm): 210, 239	50.5
Quinoline hydrazide*		Dark Brown Powder, $C_{12}H_{11}N_3O_3$ IR: 1568 cm-1 (N-H), 1725 cm-1 (C=O), 2986 cm-1 (C-H sp3), 3198 cm-1 (C-H sp2), 3345 cm-1 (N-H), and 2400–3500 cm-1 (O-H acid) UV-vis (nm): 233	61.2
Quinoline benzimidazole		Yellow Powder, $C_{20}H_{19}N_3O_2$, mp: 244.7°C IR: 3480 cm-1 (N-H), 3057 cm-1 (C-H sp2), 2930 cm-1 (C-H sp3), 1754 cm-1 (C=O), 1622 cm-1 (C=N), 1369 cm-1 (C-O), and 772 cm-1 (C-H o-benzene) UV-vis (nm): 278, 326	7.6
Quinoline hydrazone		Pale Brown Powder, $C_{19}H_{15}N_3O_4$, mp: 177.4°C IR: 3406 cm-1 (O-H phenol), 2400-3500 cm-1 (O-H acid), 3313 cm-1 (N-H), 3120 cm-1 (C-H sp2), 2985 cm-1 (C-H sp3), 1727 cm-1 (C=O), and 1608 cm-1 (C=C) UV-vis (nm): 235, 327	22.9

*Precursors for the next step of synthesis reaction. UV-vis: Ultraviolet–visible, IR: Infrared

$AlCl_3$ as a lewis acid. In general, the reaction occurs in two steps, firstly, in the presence of KOH isatin will be hydrolyzed into isatinate (2-aminophenylglyoxylate) anion. Afterward, HCl provides acidic conditions to the reaction, and the quinoline moiety is formed after the condensation of isatinic acid and ethyl acetoacetate.[7] This condensation step is catalyzed by $AlCl_3$, presumably through the formation of a bond with an oxygen atom in the carbonyl group. The process culminates in quinoline derivative 3-(ethoxycarbonyl)-2-methylquinoline-4-carboxylic acid that was confirmed by FTIR and UV-Vis spectrophotometry. Furthermore, the synthesized quinoline derivative was used for synthesizing the quinoline-hydrazide derivative. The nucleophilic substitution reaction between quinoline and hydrazine forms the hydrazide derivative. Hydrazide formation gives the quinoline derivative a more reactive amine group. The hydrazide derivative is an intermediate for synthesizing the quinoline-hydrazone. Figure 1 shows the scheme of the quinoline and quinoline-hydrazide derivative formation reaction.

FTIR spectrum in Figure 2a and b confirmed the formation of quinoline and quinoline-hydrazide derivatives, while the analysis of synthesized compounds is shown in Table 1.

Table 2: Antioxidant and antimicrobial activity of synthesized products

Compound	DPPH scavenging activity IC_{50} - value (ppm)	Susceptibility zone	
		Escherichia coli	*Staphylococcus aureus*
Quinoline-benzimidazole	4784	-	-
Quinoline-hydrazone	843.5	-	-
Ascorbic acid	11	Not measured	
Amoxicillin	Not measured	+++	++++

DPPH: 2,2-diphenyl-1-picrylhydrazyl, IC_{50}: Half-maximal inhibitory concentration, +++: Good antibacterial activity, ++++: Great antimicrobial activity

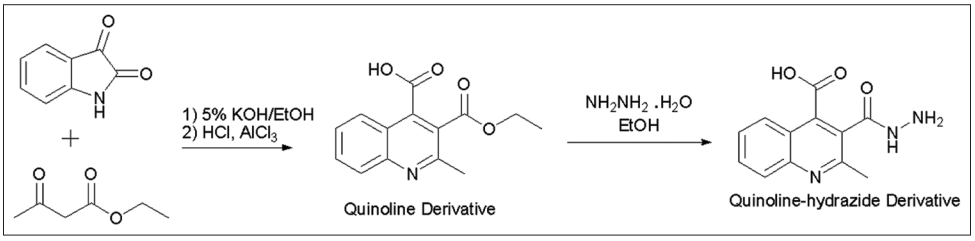


Figure 1: Formation of quinoline derivative and quinoline-hydrazide derivative

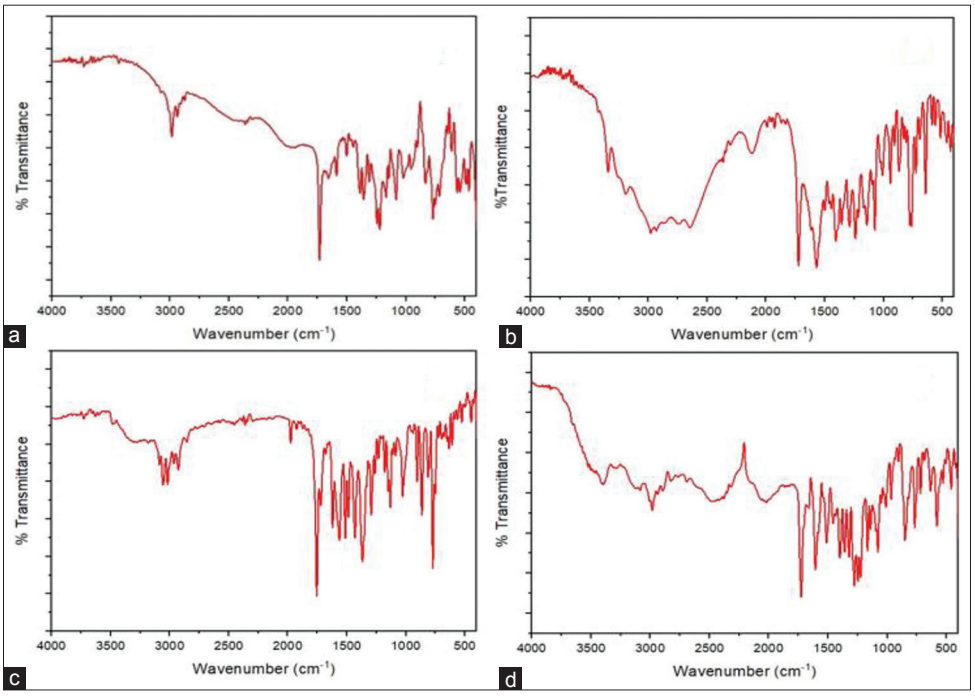


Figure 2: FTIR spectrum of quinoline derivative. (a) Quinoline-hydrazide derivative. (b) Quinoline-benzimidazole derivative. (c) And quinoline-hydrazone derivative (d)

Synthesis and characterization of the quinoline-benzimidazole derivative

The quinoline-benzimidazole derivative was synthesized by the solvent-less reaction between quinoline and ortho-phenylenediamine, as shown in Figure 3. The product obtained was ethyl 4-(1H-benzimidazol-2-yl)-2-methylquinoline-3-carboxylate, confirmed by the FTIR, UV-Vis, and LC-MS characterization. Figure 2c shows the infrared (IR) spectrum band of the synthesized compound, while its analysis results are presented in Table 1. UV-Vis spectrum of quinoline-benzimidazole shows a bathochromic shift compared to its precursor. This phenomenon is due to extended π-conjugation. The mass spectrum in Figure 4 shows molecular ion at m/z = 331 and base peak at m/z = 286. The molecular ion corresponds to the predicted molecular mass of the quinoline-benzimidazole derivative, while the peak at m/z = 258 corresponds to the fragment of the molecular ion.

Quinoline-benzimidazole derivatives' mass spectra and proposed fragmentation are shown in Figure 4.

Synthesis and characterization of quinoline-hydrazone derivative

The quinoline-hydrazide derivative was reacted with one equivalent of 4-hydroxybenzaldehyde to form quinoline-hydrazone. The formation of the product was identified by TLC after the reaction was completed, as shown

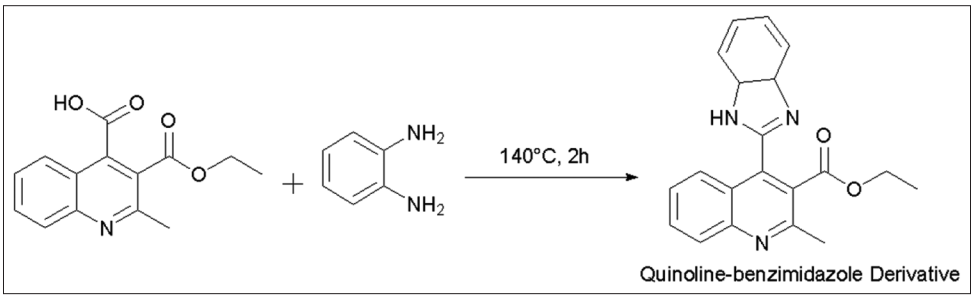


Figure 3: Formation of quinoline-benzimidazole derivative

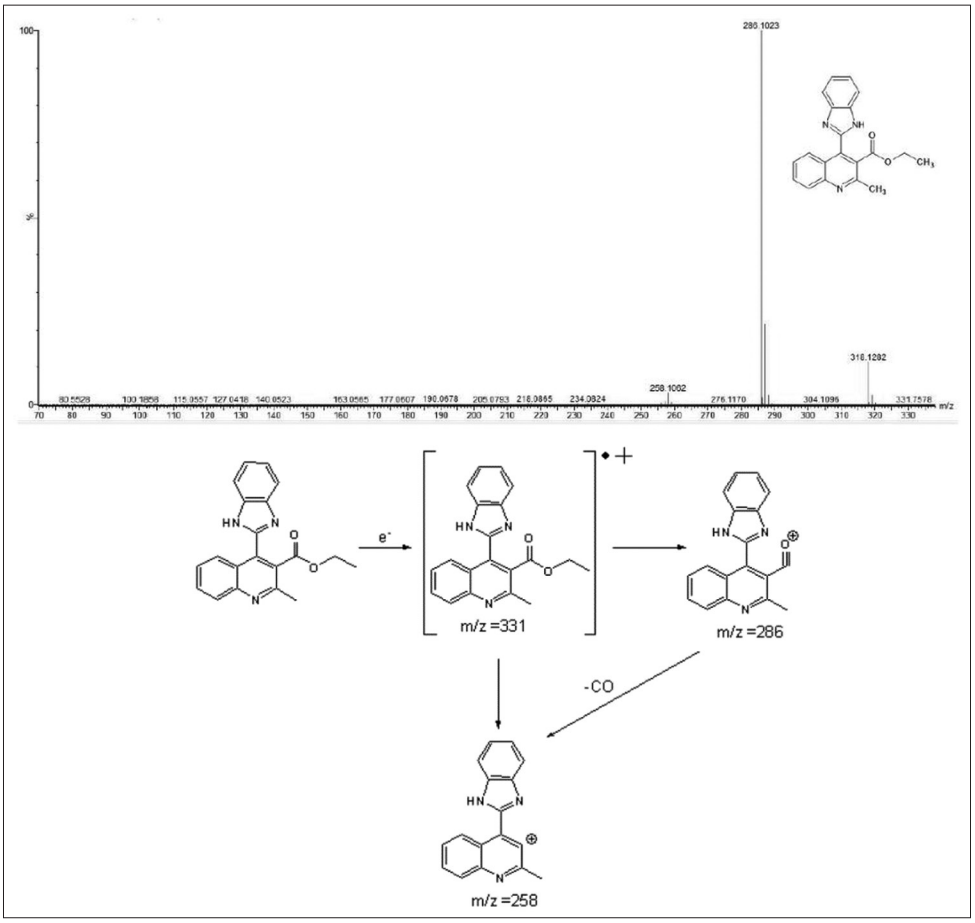


Figure 4: Mass spectrometry and proposed quinoline-benzimidazole derivative fragmentation

in Figure 5. The synthesized quinoline-hydrazone derivative was characterized by FTIR, UV-Vis spectrophotometry, and LC-MS. The quinoline-hydrazone derivative was identified as 3-{(2E)-2-[(4-hydroxyphenyl) methylidene] hydrazinecarbonyl}-2-methylquinoline-4-carboxylic acid.

The IR absorption peak confirmed the formation of the quinoline-hydrazone derivative, as shown in Figure 2d, while the analysis results of the synthesized compound are presented in Table 1. UV-vis spectrum shows bathochromic shift due to extended π-conjugation and the existence of-OH auxochrome group. The mass spectrum of the quinoline-hydrazone derivative in Figure 6 shows molecular ion at m/z = 349 and base peak at m/z = 141. Peaks at m/s = 304, 244, and 226 are due to further fragmentation of the molecular ion.

The mass spectra and suggested fragmentation of the derivatives of quinoline and benzimidazole are shown in Figure 6 below.

Antioxidant and antibacterial activity study

The antioxidant analysis in this study was based on the colorimetric measurement of DPPH radical scavenging. DPPH assay for antioxidant activity analysis is commonly used because it is simple, effective, and quick. A stable molecular product will be created by the antioxidant molecule by giving the DPPH radical an electron or a hydrogen atom.[18] The linear regression analysis of DPPH radical scavenging activity of each product is shown in Figure 7, and the IC50 can be seen in Table 2. Compounds with a lower IC_{50} value have higher antioxidant activity. Based on the results, the quinoline-hydrazone derivative has stronger antioxidant activity than benzimidazole. This is caused by the-OH group in the structure of the quinoline-hydrazone derivative. The number of-OH groups in phenolics positively correlate with DPPH radical scavenging ability.[19] The capacity of the hydroxyl group to donate hydrogen to the DPPH radical may be the cause of the antioxidant activity of the molecule. However, its

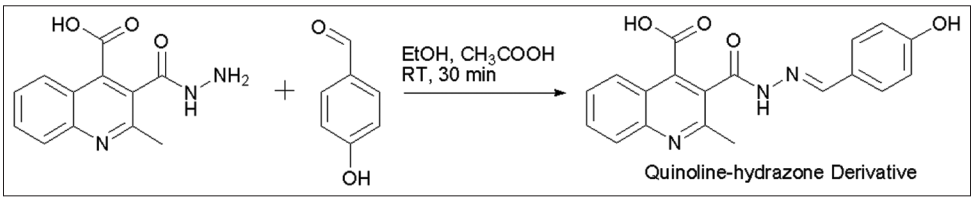


Figure 5: Formation of quinoline-hydrazone derivative

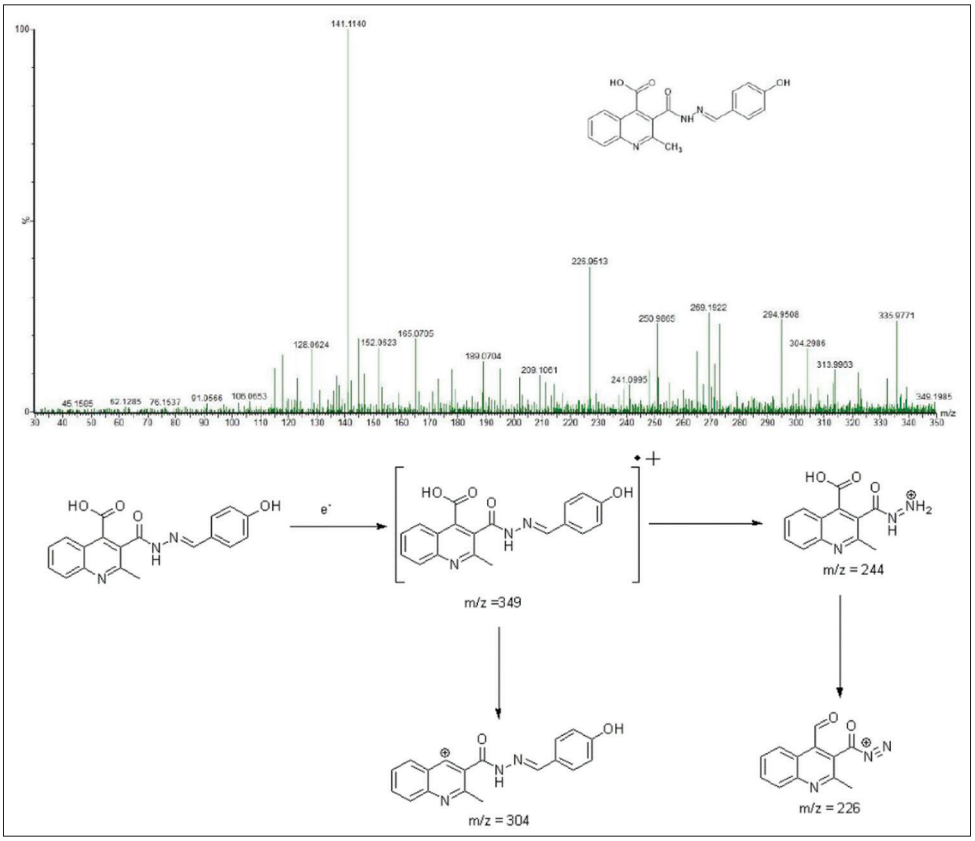


Figure 6: Mass spectrometry and proposed quinoline-benzimidazole derivative fragmentation

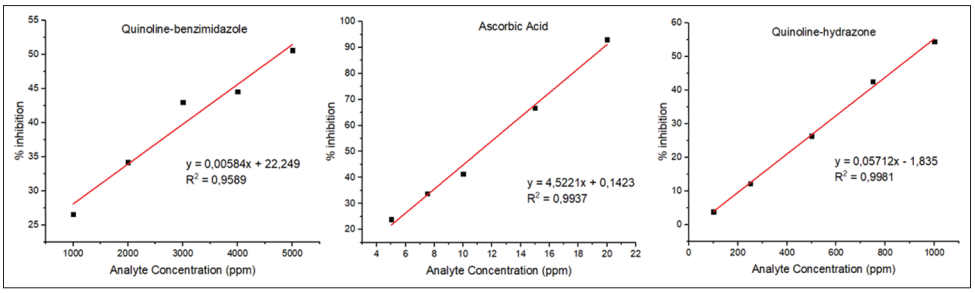


Figure 7: Linear regression analysis of 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity of synthesized products

antioxidant activity is very weak based on the high IC_{50} value.

The antimicrobial activity of the products was evaluated by the disk diffusion method against *E. coli* and *S. aureus*. After 24 h of incubation, there was no antimicrobial activity observed on all products. No susceptibility zone was observed on any tested sample concentration from 75 to 1000 ppm. This is probably caused by the absence of hydrophobic substituent, methoxy group next to the phenolics, or fluoro substituent at the quinoline scaffold.[11,20,21] Meanwhile, the positive control showed great antimicrobial activity, specifically on Gram-positive bacteria.

CONCLUSION

Quinoline hydrazone and benzimidazole derivatives were synthesized with the Pfitzinger reaction, although with a relatively low yield. This synthesis route is through the formation of 3-(ethoxycarbonyl)-2-methylquinoline-4-carboxylic acid from isatin. The structure of the products was interpreted by FTIR, UV-Vis spectroscopy, and LC-MS. Furthermore, the antioxidant activity was evaluated by DPPH assay. The synthesized quinoline-hydrazone derivative has higher activity with IC_{50} = 843.5 ppm, but no antimicrobial activity was observed in all synthesized products. Future modifications are required to increase the biological activity and effectiveness of the synthesis of the quinoline-benzimidazole and hydrazone derivatives.

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Conflicts of interest

There are no conflicts of interest.

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