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# Environmentally friendly syntheses of flavone derivatives from chalcones and the evaluation of their antimicrobial activity

Sumaiya Khan [1,*], Umme Aiman Liza [1], Afsana Mimi [1], Tama Kapasia [1], Md Aman Ullah Aman [1], A. H. M. Emon Ali [2], Mohammad Jahirul Alam [3] and Mohammad Mamun Hossain [1]

[1] *Department of Chemistry, Faculty of Mathematical and Physical Sciences, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh*
[2] *Department of Chemistry, University of Houston, 4302 University Dr, Houston, TX 77004, USA*
[3] *Earth and Atmospheric Science, University of Houston, 4302 University Dr, Houston, TX 77004, USA*

* *Corresponding author at: Department of Chemistry, Faculty of Mathematical and Physical Sciences, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh.*
*e-mail: sumaiya9@juniv.edu (S. Khan).*

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ABSTRACT

Polyphenolic flavonoid compounds are commonly found in colorful vegetables and fruits, as well as other foods such as coffee, tea, wine, beer, and chocolate. Recent studies have highlighted their potent antioxidant properties, which contribute significantly to various biological functions and overall health. Chalcones and flavones represent important subclasses of flavonoids. In addition to their natural occurrence, these compounds can also be synthesized in the laboratory using chemical methods. In this study, chalcones and flavones were synthesized through Claisen-Schmidt condensation. To produce flavone derivatives (4a-e) from their corresponding chalcones (3a-e), microwave irradiation (MWI) and conventional heating (CH) methods were employed. The MWI technique proved to be more eco-friendly and cost-effective and offers greater yields and reduced reaction time compared to the conventional method. The structures of the synthesized compounds were confirmed by ultraviolet (UV) spectroscopy, nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, and elemental analysis. Using Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa),* the antibacterial activities of the synthesized compounds were analysed. All synthesized flavones showed significant antibacterial activity but zero activity against Gram-negative bacteria, *Pseudomonas aeruginosa,* in different concentrations. Compound 4a showed highest activity 19 mm zone of inhibition against Gram-positive bacteria *Staphylococcus aureus* with concentration 128 µg/disc.

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## 1. Introduction

Gutiérrez-Grijalva and colleagues, in their article, discuss the structure-function relationships of known flavonoids, highlighting that flavonoids from the oregano family of medicinal plants exhibit varying functions based on specific changes in their flavonoid backbone structures [1]. Different subgroups of flavonoids are flavones, flavonols, and isoflavones [2]. The classification of isoflavones is implied on the attachment site of the two different rings containing isoflavones and the level of unsaturation and oxidation of another ring. In flavonoids, usually one ring is connected at the specific position of the other ring [3]. Flavonoids function as allelopathic substances, signalling molecules, phytoalexins, and detoxifying agents, and they also help defend against microorganisms and protect plants from various biotic and abiotic stresses [4]. Flavonoids are called stop cell development and work as anticancer drugs [5,6]. In enzyme systems, allow flavonoids to act as radicals are immediately oxidized by exogenous antioxidants to create less reactive species [7,8]. Flavonoids are important bioactive compounds widely used in nutraceuticals, pharmaceuticals, medicine, and cosmetics because of their diverse health-promoting properties. Because of their ability to promote imperative cellular enzyme activities and their activity against a carcinogen, oxidative agent [9-11]. Due to their critical presence as antioxidants, antiresorptive agents, and free radical scavengers, flavonoids offer a variety of positive effects [9]. Flavonoids such as quercetin, kaempferol, genistein, and daidzein contribute to the treatment of osteoporosis, one of the leading causes of bone density and reduction in joint inflammation by modulating the functions of osteoblasts (OB) and osteoclasts (OC) [12]. Isoflavones, anthocyanins, and cocoa flavan-3-ols also contribute to better vascular health [13]. Although vitamins C and E are commonly used as antioxidant supplements, flavonoids exhibit even greater antioxidant potential [14-16]. Flavonoids protect against dementia and other age-related neurodegenerative disorders [17,18] and Parkinson's and Alzheimer's disease [19,20]. The biological activity of chalcones appears to be largely influenced by their physicochemical characteristics [21].



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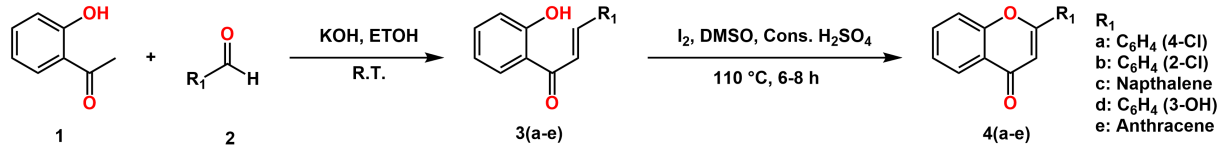
**Table 1.** Comparison between microwave irradiation (MWI) and the conventional heating method (CH) of the synthesized compounds.

| Compound | Method | Reaction time | Solvent (mL) | Yield (%) |
|---|---|---|---|---|
| 3a | MWI | 10 min | 16 | 81.20 |
| | CH | 26 hours | 20 | 75.50 |
| 3b | MWI | 8 min | 18 | 76.50 |
| | CH | 20 hours | 22 | 70.44 |
| 3c | MWI | 6 min | 15 | 75.40 |
| | CH | 27 hours | 20 | 70.90 |
| 3d | MWI | 9 min | 18 | 76.90 |
| | CH | 40 hours | 21 | 72.30 |
| 3e | MWI | 10 min | 17 | 92.20 |
| | CH | 36 hours | 22 | 87.21 |
| 4a | MWI | 6 min | 5 | 94.10 |
| | CH | 8 hours | 6 | 93.00 |
| 4b | MWI | 10 min | 5 | 86.40 |
| | CH | 6 hours | 7 | 82.80 |
| 4c | MWI | 12 min | 6 | 93.70 |
| | CH | 8 hours | 7 | 92.80 |
| 4d | MWI | 10 min | 5 | 89.30 |
| | CH | 9 hours | 8 | 86.20 |
| 4e | MWI | 8 min | 6 | 94.60 |
| | CH | 10 hours | 7 | 92.10 |




**Scheme 1.** Synthesis of compounds 3a-e and 4a-e.

Chalcones have therapeutic uses dating back to prehistoric times that are comparable to the many years of use of plants and herbs to cure various diseases [22]. For these reasons, chalcone synthesis is a primary objective for the synthesis of flavones and flavanones. Chalcones are also natural aromatase inhibitors [23,24]. The involvement of flavonoids in modulating the expression of the nodulation gene is one of the well-studied functions of interaction between plants and bacteria [25,26]. The bioactivity and possible adverse developmental effects of most flavonoids in living organisms are not yet fully understood [27]. During the past two decades, microwave irradiation (MW) has attracted significant interest in the field of organic synthesis for research purposes [28-32]. Therefore, we designed a synthetic plan to synthesize some potential flavone with different substitute methods, both conventional heating method, and microwave method for comparison (Table 1). The content of all flavonoids was determined by differential UV spectrophotometry. Then NMR was used to characterize the compounds obtained. The antibacterial property of all synthesized new flavones was measured against Gram-positive bacteria and Gram-negative bacteria with standard ciprofloxacin to investigate the antibacterial potential. The aim of this research is to synthesize and characterize different substituted flavones and find the most active flavones against different Gram-positive and Gram-negative bacteria.

## 2. Experimental

### *2.1. Analytical apparatus*

The melting points of the synthesized compounds were measured using a Fisher-Johns electrothermal melting point instrument. The FT-IR-Plus (Shimazu IR Prestige-21) spectrophotometer was used to collect infrared spectra from KBr pellets. $^1$H NMR spectra were obtained using a 400 MHz Bruker-Avance spectrometer with $CDCl_3$ as the solvent. The measurements were carried out at the Wazed Miah Science Research Center at Jahangirnagar University in Savar, Dhaka, Bangladesh. Chemical shift (ppm) measurements were made downfield from the TMS and given a value of zero ppm. 60 $GF_{254}$ (Merck) silica gel sheets with a thickness of 0.25 nm were used for thin layer chromatography (TLC). TLC pots were observed under ultraviolet light and then developed further by placing the plates in an iodine chamber. Column chromatography was frequently used to purify crude products. The stationary phase, Kiessel gel 100, 70-230 mesh, ASTM (Merck) was used to create the chromatographic column using the slurry method.

### *2.2. Synthesis*

#### *2.2.1. Synthesis of chalcone derivatives 3a-e*

##### *2.2.1.1. Microwave heating method*

In a round bottom flask, an ethanolic solution of substituted benzaldehyde of 2.05 mmol (for example, compound 4a, 4-chlorobenzaldehyde, 288.02 mg) was added with 2′-hydroxy-acetophenone (278.8 mg, 2.05 mmol) and an ethanolic solution of KOH (517.52 mg, 9.25 mmol). The reacting components were then subjected to microwave irradiation (10 seconds × 70 times, with 1-minute intervals between irradiations) for a total of 6-14 minutes. The progression of the reaction was tracked by thin-layer chromatography employing *n*-hexane: ethyl acetate (6:1, v:v) as the mobile phase. After the reaction was complete, the mixture was neutralized with 5% diluted hydrochloric acid and extracted using ethyl acetate. The solvent was then evaporated under reduced pressure, and the resulting chalcones (3a-e) were purified by recrystallization from the crude product (Scheme 1).

##### *2.2.1.2. Conventional method*

An ethanolic solution of KOH (517.52 mg, 9.25 mmol, 20mL) was prepared and chilled in an ice bath. In the next step, 2′-hydroxyacetophenone (278.8 mg, 2.05 mmol) was added to the mixture. Subsequently, the substituted benzaldehyde (for compound 4a, 4-chlorobenzaldehyde, 288.02 mg, 2.05 mmol) was dissolved in ethanol in a 100 mL beaker and placed in an ice bath. The chilled solution of substituted benzaldehyde was gradually added to the solution of 2′-hydroxyacetophenone and

was stirred at a maximum temperature of 25 °C for 26 hours. The progression of the reaction was tracked by thin-layer chromatography using and *n*-hexane: ethyl acetate (6:1, v:v) as the mobile phase (for compound, 4a, $R_f$ = 0.575). When the reaction was completed, the mixture of dilute HCl (5%) was added for neutralization and the solid mass found was filtered off. Recrystallization was used to separate the crude material from the ethanol. Nice crystals of chalcone (3a-e) were obtained (Scheme 1). The comparative analysis of microwave and conventional methods is shown in Table 1.

3-(4-Chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**3a**): Color: Yellow. Yield: 75.5%. M.p.: 155-157 °C. FT-IR (KBr, ν, $cm^{-1}$): 3442 (OH) (br, phenol), 1637 (C=O) (ketone), 1577 (C=C) (alkene), 1560 (C=C) (aromatic), 1205 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.77 (s, 1H, Ar-OH), 7.93 (d, 1H, $J_o$ = 8 Hz, Ar-H), 7.88 (d, 1H, $J_{trans}$ = 15.6 Hz, =C-H), 7.66-7.61 (m, 3H, Ar-H), 7.53 (t, 1H, $J_o$ = 8.4 Hz, Ar-H), 7.44 (d, 2H, $J_o$ = 8.4 Hz, Ar-H), 7.06 (d, 1H, $J_{trans}$ = 15.6 Hz, =C-H), 6.98 (t, 1H, $J_o$ = 7.2 Hz, Ar-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 327 (0.521).

3-(2-Chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**3b**): Color: Yellow. Yield: 70.44%. M.p.: 147-149 °C. FT-IR (KBr, ν, $cm^{-1}$): 3412 (OH) (br, phenol), 2922 (C-H) (aromatic), 2852 (olefinic), 1637 (C=O) (ketone), 1558 (C=C) (alkene), 1541 (C=C) (aromatic), 1155 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.74 (s, 1H, Ar-OH), 8.33(d, 1H, $J_{trans}$ = 15.6 Hz, =C-H), 7.94 (dd, 1H, $J_o$ = 8.4Hz, $J_m$ = 1.6Hz, Ar-H), 7.80 (d, 1H, $J_o$ = 8.6 Hz, Ar-H), 7.78 (d, 1H, $J_o$ = 8.6Hz, Ar-H), 7.65 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.50-7.48 (m, 3H, Ar-H), 7.40 (d, 1H, $J_o$ = 8.4Hz, Ar-H), 7.28 (d, 1H, $J_{trans}$ = 15.6Hz, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 316 (0.594).

1-(2-Hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (**3c**): Color: Yellow. Yield: 70.9%. M.p.: 137-139 °C. FT-IR (KBr, ν, $cm^{-1}$): 3444 (OH) (br, phenol), 3053 (C-H) (aromatic), 2916 (C-H) (olefinic), 1695 (C=O) (ketone), 1571 (C=C) (alkene), 1558 (C=C) (aromatic), 1159 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.89 (s, 1H, Ar-OH), 8.37 (d, 1H, $J_m$ = 2 Hz, Ar-H), 8.14 (d, 1H, $J_m$ = 2 Hz, Ar-H), 8.10 (d, 1H, $J_{trans}$ = 15.2 Hz, =C-H), 8.02 (s, 1H, Ar-H), 8.00 (d, 1H, $J_o$ = 12 Hz $J_m$ = 1.6 Hz, Ar-H), 7.98 (d, 1H, $J_o$ = 9.2 Hz, Ar-H), 7.98-7.92 (m, 5H, Ar-H), 7.88 (m, 1H, $J_o$ = 8.4 Hz, Ar-H), 7.63 (d, 1H, $J_{trans}$ = 15.2 Hz, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 332 (0.226).

1-(2-Hydroxyphenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**3d**): Color: Yellow. Yield: 72.3%. M.p.: 130-132 °C. FT-IR (KBr, ν, $cm^{-1}$): 3361 (OH) (br, phenol), 1637 (C=O) (ketone), 1577 (C=C) (alkene), 1554.63 (C=C) (aromatic), 1151 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.80 (s, 1H, Ar-OH), 12.71(s, 1H, Ar-OH), 7.99 (dd, 1H, $J_o$ = 8.4 Hz, $J_m$ = 1.6 Hz, Ar-H), 7.95 (d, 1H, $J_{trans}$ = 15.6 Hz, =C-H), 7.69 (d, 1H, $J_o$ = 8.6 Hz, Ar-H), 7.53 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.31-7.26 (m, 4H, Ar-H), 7.16 (s, 1H, Ar-H), 7.08 (d, 1H, $J_{trans}$ = 15.6 Hz, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 295 (0.629).

3-(Anthracen-9-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**3e**): Color: Yellow. Yield: 87.21%. M.p.: 220-222 °C. FT-IR (KBr, ν, $cm^{-1}$): 3055 (C-H) (aromatic), 1635 (C=O) (ketone), 1575 (C=C) (alkene), 1558 (C=C) (aromatic), 1157 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.88 (s, 1H, Ar-OH), 8.96 (dd, 1H, $J_o$ = 8.4 Hz, $J_m$ = 1.6 Hz, Ar-H), 8.64 (d, 1H, $J_{trans}$ = 15.6 Hz, =C-H), 8.53 (s, 1H, Ar-H), 8.32 (d, 2H, $J_m$ = 1.6 Hz Ar-H), 8.05 (d, 2H, $J_o$ = 8.4 Hz, Ar-H), 7.84 (t, 1H, $J_o$ = 8.4 Hz, Ar-H), 7.57 (m, 6H, Ar-H), 7.45 (d, 1H, $J_{trans}$ = 15.6 Hz, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 329(0.565).

### *2.2.2. Synthesis of flavone derivatives (4a-e) from chalcones (3a-e)*

#### *2.2.2.1. Microwave irradiation method*

Synthesized chalcone, 0.440 mmol (for example, compound 3a, 112.2 mg) was dissolved in 5-7 mL of DMSO and stirred with 2-4 drops of conc. $H_2SO_4$ for 15 minutes at 110 °C. After 15 minutes of stirring at 110 °C, a catalytic amount of $I_2$ (10 mol %) was carefully added. The reacting components were then subjected to microwave irradiation (10 seconds × 70 times, with 30-second intervals between irradiations) for a total of 6-14 minutes. The progression of the reaction was tracked by thin-layer chromatography employing *n*-hexane: ethyl acetate (6:1, v:v) as the mobile phase. After the mixture was cooled, water was slowly introduced to drive the formation of a solid crude flavone derivative. The crude precipitate was washed with a 20% aqueous sodium thiosulfate combination and then dried. An ethyl acetate and *n*-hexane solvent mixture was used to recrystallize the crude solid. Finally, the titled pure flavones (4a-e) were obtained as a crystalline solid (Scheme 1).

#### *2.2.2.2. Conventional method*

In a round bottom flask, 0.440 mmol of chalcone (for example, compound 3a, 112.2 mg) was taken and dissolved in 5-7 mL of DMSO and mixed with 2-4 drops of conc. $H_2SO_4$ with stirring for 15 minutes at 110 °C. Subsequently, a catalytic amount of $I_2$ (10 mol %) was carefully added and the resulting mixture was refluxed at 110 °C for approximately 8 hours. The progression of the reaction was tracked by thin-layer chromatography using *n*-hexane: ethyl acetate (6:1, v:v, for compound 4a, $R_f$ value = 0.26) as mobile phase. After cooling the mixture, water was slowly introduced to drive the formation of solid crude flavone derivative. The crude precipitate was washed with the combination of 20% aqueous sodium thiosulfate and then dried. An ethyl acetate and *n*-hexane solvent mixture was used to recrystallize the crude solid. Finally, the titled flavone (4a-e) was obtained as a crystalline solid (Scheme 1). The comparative analysis of the microwave and conventional methods is shown in Table 1.

2-(4-Chlorophenyl)-4*H*-chromen-4-one (**4a**): Color: Off white. Yield: 93.0%. M.p.: 205-207 °C. FT-IR (KBr, ν, $cm^{-1}$): 3061 (C-H) (aromatic), 2916 (olefinic), 1639 (C=O) (ketone), 1591 (C=C) (alkene), 1489(C=C) (aromatic),1091 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.27 (d, 1H, $J_o$ = 8.0 Hz, $J_m$ = 1.6 Hz, Ar-H), 7.91 (d, 2H, $J_o$ = 8.0 Hz, Ar-H), 7.74 (td, 1H, $J_o$ = 8.0 Hz, $J_m$ = 1.6 Hz, Ar-H), 7.59 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.55 (d, 2H, $J_o$ = 8.0 Hz, Ar-H), 7.47 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 6.86 (s, 1H, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 304 (0.220).

2-(2-Chlorophenyl)-4*H*-chromen-4-one (**4b**): Color: Off white. Yield: 82.8 %. M.p.: 166-169 °C. FT-IR (KBr, ν, $cm^{-1}$): 3066 (C-H) (aromatic), 1654 (C=O) (ketone), 1544 (C=C) (alkene), 1465 (C=C) (aromatic), 1128 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.28 (dd, 1H, $J_o$ = 8.0 Hz, $J_m$ = 1.6 Hz, Ar-H), 7.94 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.78 (dd, 1H, $J_o$ = 8.0 Hz, $J_m$ = 1.6 Hz, Ar-H), 7.75 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.52 (m, 1H, Ar-H), 7.38 (m, 1H, Ar-H), 7.05 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 6.67 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 6.70 (s, 1H, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 309 (0.641).

2-(Naphthalen-1-yl)-4*H*-chromen-4-one (**4c**): Color: Off white. Yield: 92.8%. M.p.: 160-162 °C. FT-IR (KBr, ν, $cm^{-1}$): 3068(C-H) (aromatic), 1631 (C=O) (ketone), 1595 (C=C) (alkene), 1460 (C=C) (aromatic), 1130 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.41(t, 1H, $J_o$ = 8.0 Hz, Ar-H), 8.31 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 8.01 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.97 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.94 (d, 2H, $J_o$ = 8.0 Hz, Ar-H), 7.76 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.71 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.63 (m, 2H, Ar-H), 7.51 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.10 (s, 1H, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 325 (0.588).

2-(3-Hydroxyphenyl)-4*H*-chromen-4-one (**4d**): Color: Off white. Yield: 86.2%. M.p.: 90-92 °C. FT-IR (KBr, ν, $cm^{-1}$): 3444 (OH) (br, phenol), 1614 (C=O), (ketone), 1591 (C=C) (alkene), 1481 (C=C) (aromatic), 1130 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.60 (s, 1H, Ar-OH), 8.29 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.77 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.63 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.55 (s, 1H, Ar-H), 7.53 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.48 (t, 1H, $J_o$= 8.0 Hz, Ar-H), 7.42 (t, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.10 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 7.00 (s, 1H, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 307 (0.522).

**Table 2.** Assessment of the antibacterial properties of flavones using the disc diffusion technique.

| Compounds | Inhibition zone (mm) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *E. coli* | | | *P. aeruginosa* | | | *S. aureus* | | |
| | 256 µg/disc | 128 µg/disc | 64 µg/disc | 256 µg/disc | 128 µg/disc | 64 µg/disc | 256 µg/disc | 128 µg/disc | 64 µg/disc |
| 4a | 12 | 8 | 0 | 0 | 0 | 0 | 10 | 19 | 8 |
| 4c | 14 | 12 | 0 | 0 | 0 | 0 | 16 | 14 | 9 |
| 4d | 14 | 9 | 0 | 0 | 0 | 0 | 12 | 9 | 0 |
| 4e | 12 | 13 | 0 | 0 | 0 | 0 | 14 | 11 | 9 |
| Positive control (Ciprofloxacin 5 µg/disc) | 28 | 28 | 29 | 25 | 23.5 | 25 | 23 | 24 | 20 |
| Negative control (100% $CHCl_3$) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

2-(Anthracen-9-yl)-4*H*-chromen-4-one (**4e**): Color: Yellowish white. Yield: 92.1%. M.p.: 235-237 °C. FT-IR (KBr, ν, $cm^{-1}$): 3061 (C-H) (aromatic), 1647 (C=O) (ketone), 1571 (C=C) (alkene), 1463 (C=C) (aromatic), 1134 (C-O). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.67 (s, 1H, Ar-H), 8.41 (d, 1H, $J_o$ = 8.0 Hz, Ar-H), 8.11 (d, 2H, $J_o$ = 8.0 Hz, Ar-H), 7.98 (d, 2H, $J_o$ = 8.0 Hz, Anthracene-H), 7.76 (t, 1H, $J_o$ = 8.0 Hz, Anthracene-H), 7.57-7.50 (m, 6H, Anthracene-H), 6.72 (s, 1H, =C-H). UV (DMSO, $\lambda_{max}$, nm, (log ε)): 391(0.427).

### *2.3. Bioactivity test*

The antibacterial activity of all synthesized compounds 4a-e was evaluated against *Pseudomonas. aeruginosa, Escherichia coli* and *Staphylococcus aureus* using the disc diffusion method [27,33]. The stock solution of the synthesized compounds was prepared in chloroform ($CHCl_3$). A single bacterial colony was inoculated into 4-5 mL of Mueller-Hinton broth at 37 °C until turbidity reached the 0.5 McFarland standard (approximately 2-6 hours). Using a sterile cotton swab, the surface of each agar plate was uniformly inoculated with the bacterial suspension. Sample solutions at concentrations of 1, 0.5, and 0.25 mg/mL were applied onto the disks and then incubated at 37 °C for 16-18 hours. After incubation, the zones of inhibition were analyzed in millimeters. Standard antibiotic discs (ciprofloxacin, 5 µg/disc) were used as positive controls, and chloroform discs were used as negative controls. The antibacterial activity results of all synthesized compounds are shown in Table 2. Antifungal activity was skipped due to the unavailability of antifungal assay facility.

## 4. Results and discussion

Flavonoids have a common structural backbone containing 15 carbon atoms in a C6-C3-C6 arrangement, with two six-membered rings and a three-carbon bridge [34]. These compounds are significant secondary metabolites with various structural forms. Additionally, 2-hydroxyacetophenone serves as a useful starting material for the synthesizing of various heterocyclic compounds [35,36].

### *4.1. Synthesis*

Using the microwave and conventional methods, all compounds are synthesized. The structure of all newly synthesized compounds was evaluated using spectroscopic techniques, including $^1$H NMR, IR, and UV analysis. In the $^1$H NMR spectrum, a singlet at δ 12.77 ppm confirms the phenolic OH proton in compound 3a. It showed two doublets at δ 7.90 and 7.86 ppm with a coupling constant of *J* value of 16 Hz that indicates the vinyl *trans-coupling* hydrogen of chalcone. Doublets were found to be at δ 7.66 and 7.44 ppm with coupling constant $J_o$ = 8.0 Hz and $J_o$ = 8.4 Hz for *para*-substituted. Compound 4a showed a singlet at δ 6.86 ppm which was a characteristic value for hydrogen of flavones and two doublets at δ 7.91 and 7.55 ppm for with a coupling constant $J_o$ value of 8.0 Hz for the *para* substituted aromatic ring. Two doublets were found at δ 8.27 ppm and δ 7.59 ppm with a coupling constant of $J_o$ = 8.0 Hz and $J_o$ = 8.4 Hz. In IR spectrum of compound 4a showed band at 3061 $cm^{-1}$ aromatic C-H bond, band at 2916 $cm^{-1}$ for olefinic C-H bond, band at 1639 $cm^{-1}$ for ketone C=O bond,1591 $cm^{-1}$ for olefinic C=C bond, 1489 $cm^{-1}$ for aromatic C=C bond, 1091 $cm^{-1}$ for C-O bond. Compound 4b showed a singlet at δ 6.70 ppm, which was a characteristic value for flavone hydrogen, and two doublets at δ 7.94 and 7.05 ppm with a $J_o$ coupling constant value of 8.0 Hz for the substituted aromatic ring. Two doublet of doublets were found at δ 8.28 and 7.78 ppm with coupling constant of $J_o$ = 8.0 Hz and $J_o$ = 1.6 and two multiplicity was found at δ 7.52 and 7.38 ppm. In IR spectrum of compound 4b showed band at 3066 $cm^{-1}$ aromatic C-H bond, band at 1654 $cm^{-1}$ for ketone C=O bond, 1544 $cm^{-1}$ for olefinic C=C bond, 1465 $cm^{-1}$ for aromatic C=C bond, 1128 $cm^{-1}$ for C-O bond. Compound 4c showed a singlet at δ 7.10 ppm and a triplet at δ 8.41 ppm and a doublet δ 8.31 ppm for a coupling constant $J_o$ value 8.0 Hz for the aromatic proton. Two doublets were found at δ 8.01 ppm and δ 7.97 ppm with a $J_o$ coupling constant of 8.0 Hz for aromatic proton. The doublet at δ 7.94 ppm, the triplet at δ 7.76 ppm, doublet at δ 7.71, multiplet at δ 7.63, and triplet at δ 7.51 are found for naphthalene hydrogens. In IR spectrum of compound 4c showed a band at 3044 $cm^{-1}$ broad aromatic C-H bond, band at 1631 $cm^{-1}$ for ketone C=O bond, 1595 $cm^{-1}$ for olefinic C=C bond, 1460 $cm^{-1}$ for aromatic C=C bond, 1130 $cm^{-1}$ for C-O bond. Compound 4d showed a singlet at δ 7.00 ppm for the olefinic =C-H proton, a doublet at δ 8.29 ppm and a triplet δ 7.77 ppm with the $J_o$ coupling constant = 8.0 Hz and one singlet at δ 7.55 for the meta substituted aromatic proton. Two doublets were found at δ 7.63 ppm and δ 7.53 ppm with a $J_o$ coupling constant value of 8.0 Hz for the aromatic proton. Two triplets are found at δ 7.42 ppm and δ 7.48 ppm for aromatic hydrogen. In IR spectrum of compound 4d showed a broadband at 3444 $cm^{-1}$ aromatic C-OH bond, a band at 1614 $cm^{-1}$ for the ketone C=O bond, 1591 $cm^{-1}$ for olefinic C=C bond, 1481 $cm^{-1}$ for the aromatic C=C bond, and 1130 $cm^{-1}$ for C-O bond. In $^1$H NMR spectrum for compound 4e, peak at δ 8.67 ppm singlet for one aromatic proton, peak at δ 8.41 ppm doublet with coupling $J_o$ = 8.0 Hz for one aromatic proton, peak at δ 8.11 ppm doublet with coupling $J_o$ = 8.0 Hz for two aromatic proton, peak at δ 7.98 ppm doublet with coupling $J_o$ = 8.0 Hz for two anthracene proton, peak at δ 7.76 ppm triplet with coupling $J_o$ = 8.0 Hz for one anthracene proton, peak at δ 7.57-7.50 ppm multiplicity for six anthracene protons , peak at δ 6.72 ppm singlet for olefinic =C-H proton. For compound 4e in the characteristic peak of the IR spectrum 3061 $cm^{-1}$ for the aromatic C-H bond, 1571 $cm^{-1}$ for the olefinic C=C bond, 1463 $cm^{-1}$ for the aromatic C=C bond, 1134 $cm^{-1}$ for the C-O bond.

### *4.2. Comparison of microwave and conventional methods*

The synthesis of different substituted chalcones was successfully carried out in a mixture of AcOH and $H_2SO_4$ under conventional heating; however, the yields were lower compared to those achieved by microwave-assisted synthesis. The cyclization of 2-hydroxychalcone under conventional conditions was achieved successfully with iodine as a catalyst in dimethyl sulfoxide (DMSO), although the achievement of satisfactory results required the use of a relatively large amount

of solvent. Chalcones (3a-e) were obtained in higher yields using the microwave method using minimum amount of solvent than with conventional heating, as illustrated in Table 1. Similarly, all other compounds 4a-e, identified as flavones, were obtained in higher yields, with their synthesis procedures described in detail in the experimental section (Scheme 1).

### *4.3. Antibacterial activity*

The activity against bacteria of synthesized compounds was evaluated against two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and one Gram-positive bacteria (*Staphylococcus aureus*) using the traditional Kirby-Bauer disk diffusion method (Paper disc method) [27,33]. Against both Gram-positive and Gram-negative bacteria, the synthesized flavones showed potential activity. Flavone 4a-e showed potential antibacterial activity against Gram-positive bacteria, *Staphylococcus aureus,* and Gram-negative bacteria, *Escherichia coli,* but did not show any activity against Gram-negative bacteria, *Pseudomonas aeruginosa* (Table 2). The highest antibacterial activity against *Staphylococcus aureus* was shown by synthesized flavone 4a in 128 µg/disc concentration. At the lowest concentration of 64 µg/disc, highest antibacterial activity was shown by flavones 4c and 4e showed the highest antibacterial activity against *Staphylococcus aureus*. Against Gram-negative bacteria, *Escherichia coli* synthesized flavone 4c showed the highest activity at a concentration of 256 µg/disc.

## 5. Conclusions

Flavonoids are a significant class of polyphenolic molecules broadly distributed in natural sources, such as fruits, vegetables, chocolate, and both alcoholic and non-alcoholic beverages, making them one of the most prominent classes of natural products. They are now recognized as vital agents in many pharmacological, nutraceutical, and therapeutic applications, primarily due to their capacity to regulate complex cellular enzyme activities and their notable antioxidant, antimutagenic, anti-inflammatory, and anti-carcinogenic properties. The flavone derivatives 4a-e were synthesized from their corresponding chalcones 3a-e using microwave irradiation and conventional heating techniques. Flavone compounds were prepared with limited amounts of DMSO, iodine, and trace sulphuric acid. MWI demonstrated greater environmental friendliness, time savings, and achieving higher yields compared to the conventional heating approach. The synthesized flavones showed enhanced antibacterial activity against both Gram-positive and Gram-negative bacteria. A complete characterization of the compounds was achieved through elemental analysis and UV, IR, and NMR spectroscopy.

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## Disclosure statement

Conflict of interest: Authors have no conflict of interest that has been declared.
Ethical approval: All ethical guidelines have been adhered to.
Sample availability: Samples of the compounds are available from Sumaiya Khan, Umme Aiman Liza, and Mohammad Mamun Hossain.

## CRediT authorship contribution statement

Conceptualization: Mohammad Mamun Hossain, Sumaiya Khan; Methodology: Sumaiya Khan, Mohammad Mamun Hossain; Validation: Sumaiya Khan, Umme Aiman Liza, Mohammad Mamun Hossain; Synthesis: Afsana mimi, Tama Kapasia; Formal Analysis: Sumaiya Khan, Umme Aiman Liza, Afsana mimi, Tama Kapasia, Md Aman Ullah Aman, Mohammad Mamun Hossain; Investigation: Sumaiya Khan, Umme Aiman Liza, Mohammad Mamun Hossain; Resources: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Data Correction: Sumaiya Khan, Umme Aiman Liza, Afsana mimi, Tama Kapasia, Md Aman Ullah Aman, A H M Emon Ali, Mohammad Jahirul Alam, Mohammad Mamun Hossain; Writing -Original Draft: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza, Tama Kapasia; Writing -Review and Editing: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza, Tama Kapasia; Visualization: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Funding acquisition: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Supervision: Mohammad Mamun Hossain, Sumaiya Khan; Project Administration: Mohammad Mamun Hossain, Sumaiya Khan.

## Funding

Jahangirnagar University, Savar, Dhaka, Bangladesh.
https://www.juniv.edu

## ORCID and Email

Sumaiya Khan
sumaiya9@juniv.edu
https://orcid.org/0000-0003-1473-7102
Umme Aiman Liza
aimanliza@juniv.edu
https://orcid.org/0009-0001-5971-7001
Afsana Mimi
afsana.chem45@gmail.com
https://orcid.org/0009-0003-5691-8195
Tama Kapasia
20190348412tama@juniv.edu
https://orcid.org/0009-0009-4398-4111
Md Aman Ullah Aman
aman.stu2017@juniv.edu
https://orcid.org/0009-0002-3567-389X
A. H. M. Emon Ali
emonchemistry42@gmail.com
https://orcid.org/0009-0003-1184-9026
Mohammad Jahirul Alam
malam22@cougarnet.uh.edu
https://orcid.org/0009-0007-8645-0414
Mohammad Mamun Hossain
chemamun@juniv.edu
https://orcid.org/0000-0002-7712-2482

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