Research article

Synthesis and Anti-Plant Pathogenic Fungal Activity of Flavokawain-Derived Flavones and Related Flavones Against *Rhizoctonia solani*

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Abstract

Flavones are organic compounds in the flavonoid family that have a diverse range of biological functions. In this research, many flavones with various substituents were designed and synthesized from flavokawains A, B, and C, and their chalcone derivatives via an iodine-catalyzed oxidative cyclization process. All synthetic flavones were investigated for antifungal activities against *Rhizoctonia solani*, a plant pathogenic fungus. At 400 µg, most of the substances did not inhibit the tested species and *R. solani* growth was inhibited by only *o*-bromoflavone (**40**) by 74.88±0.91%. This indicated that the detrimental effect of flavones depends on the type and position of substituent, with the ortho bromo group showing the most promise. The molecular docking study on the succinate dehydrogenase (SDH) enzyme revealed that the bromophenyl moiety (ring B) is a key molecular substructure of the flavone fungicide. The findings of this study will be used to develop novel plant pathogenic fungicides.

Keywords

flavokawains;
flavones;
antifungal;
phytopathogen;
SAR;
Rhizoctonia solani

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1. Introduction

Plant disease is one of the world's most serious issues for farmers and agricultural producers of fruits, grains, and vegetables [1, 2]. This is an urgent and challenging issue that needs to be overcome. Overall, fungi and related organisms cause more plant diseases than other pests [2]. There are various ways to control plant pathogens, such as physical, biological, and chemical methods [3], and each method comes with its own set of advantages and disadvantages. Biological control has recently gained significant attention because it is safe to use and reduces the possibility of resistance. This type of control, however, has low efficacy, particularly when pathogen inoculum density is high or when used against a pre-existing infection [4].

Although chemical controls have raised concerns about making plant pathogens resistant to fungicides and toxic to health and the environment [5, 6], this method is still widely used because it is fast, effective, and relatively inexpensive [6, 7]. Currently, many research groups are still searching for new types of fungicides, including natural [8], semisynthetic [9], and synthetic compounds [10-14]. Various groups of organic compounds, such as benzoxazoles [10], chalcones and flavones [12], coumarins [11], quinolines [14], and triazoles [13] have been investigated against fungal plant pathogens. The modes of mechanism investigated differ depending on the chemical classes.

Flavones [15] are organic compounds in the flavonoid family whose main structure is 2-phenylchromen-4-one or 2-phenyl-1-benzopyran-4-one (Figure 1). This basic structure is composed of 15 carbons, with two aromatic hexagonal rings (A and B) connected by a heterocyclic pyran ring (ring C). Flavones and their derivatives have numerous biological functions, including antibacterial [16], anticancer [17], antifungal [18], and antiviral [19] properties. Apart from these activities, all natural flavones, such as trimethoxyflavone [20], methylenedioxy flavones [21, 22], flavone glycoside [23], isoginkgetin [24], and prenylated flavone [25], and synthetic flavones such as methylated flavone [12] showed anti-plant pathogenic fungal activity (Figure 1).

As mentioned above, some flavones are active against plant pathogens; however, thorough investigation of their structure activity relationships has rarely been studied. In this research, we are interested in the anti-plant pathogenic fungal activity of flavones derived from flavokawains and chalcone analogs (Figure 2) because previous reports have shown that these chalcones are effective fungicides [26, 27]. *Rhizoctonia solani*, a soil-borne plant pathogen, was used as a test species. This fungus is one of the most destructive pathogens that cause various plant diseases worldwide, such as damping-off, root rot, stem rot, and sheath blight in diverse plant species [28]. A molecular docking simulation was also performed to determine how active flavones could inhibit succinate dehydrogenase (SDH) [29], an ideal target enzyme that is normally used in the research and development of antifungal drugs [30, 31]. This preliminary study provided useful information for the development of flavones as plant pathogenic fungicides.

2. Materials and Methods

2.1 Chemicals and instrument

Xanthoxyline (**1**) was isolated from a crude ethyl acetate extract of dried fruits of *Zanthoxylum limonella* [32]. Propiconazole was purchased from Sigma-Aldrich (Missouri, USA). DMSO and all aldehydes were purchased from Sigma-Aldrich (Missouri, USA), and Tokyo Chemical Industry (TCI, Tokyo, Japan). Melting points and Infra-red (IR) spectra were recorded on a Gallenkamp melting point apparatus and a Perkin Elmer 8900 at the Department of Chemistry, School of Science, KMITL. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ-500R/S1 (500 MHz) at the

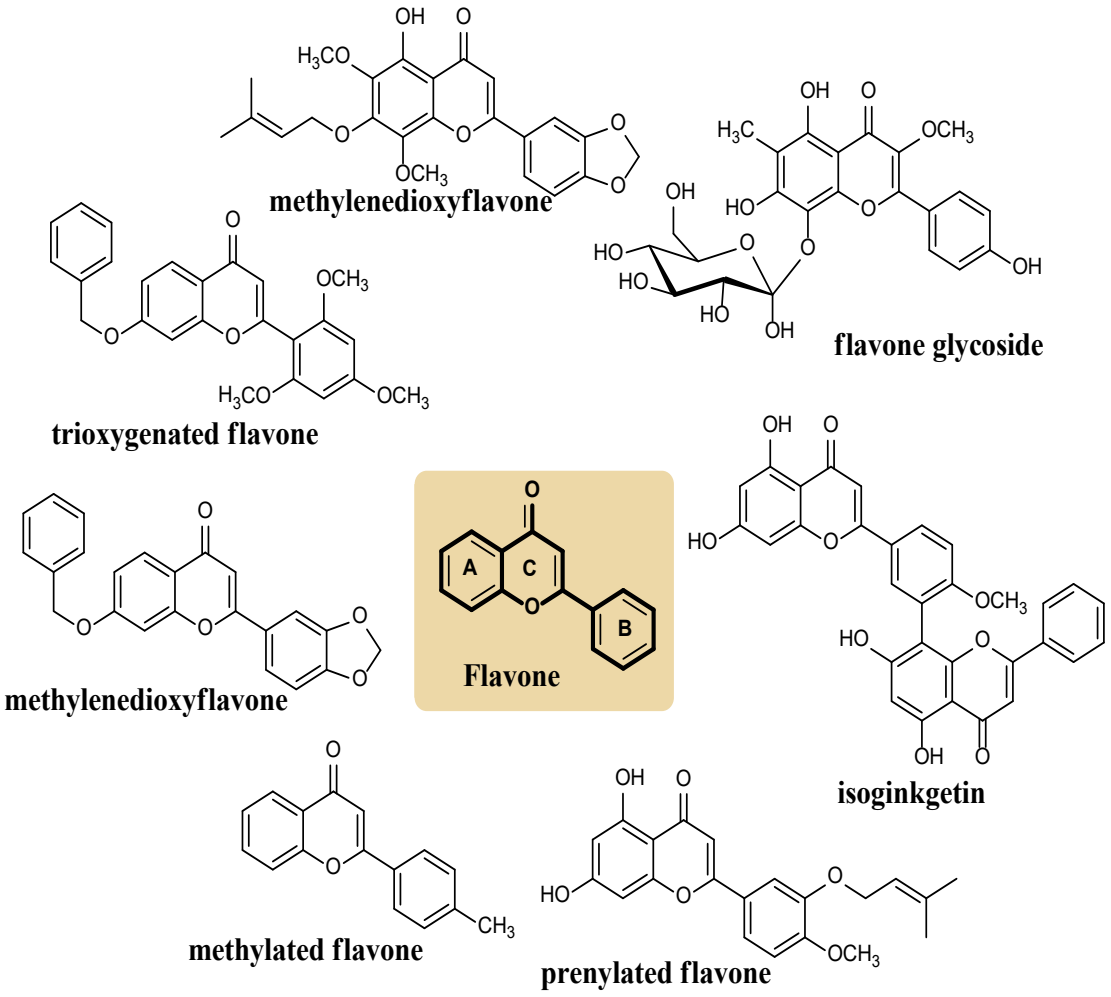

Figure 1. The core structure of flavone and some flavone fungicides

Scientific Instruments Center, School of Science, KMITL, using residual protonated chloroform ($CDCl_3$, 7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR), residual protonated dimethyl sulfoxide (DMSO-d_6, 2.50 ppm for ^1H NMR and 39.52 ppm for ^{13}C NMR), and residual protonated methanol (CD3OD, 3.31 ppm for ^1H NMR, and 49.00 ppm for ^{13}C NMR), as internal standards. High-resolution mass spectra (HRMS) were recorded on a Bruker Daltonics (micrOTOF) at the Faculty of Science, Mahidol University.

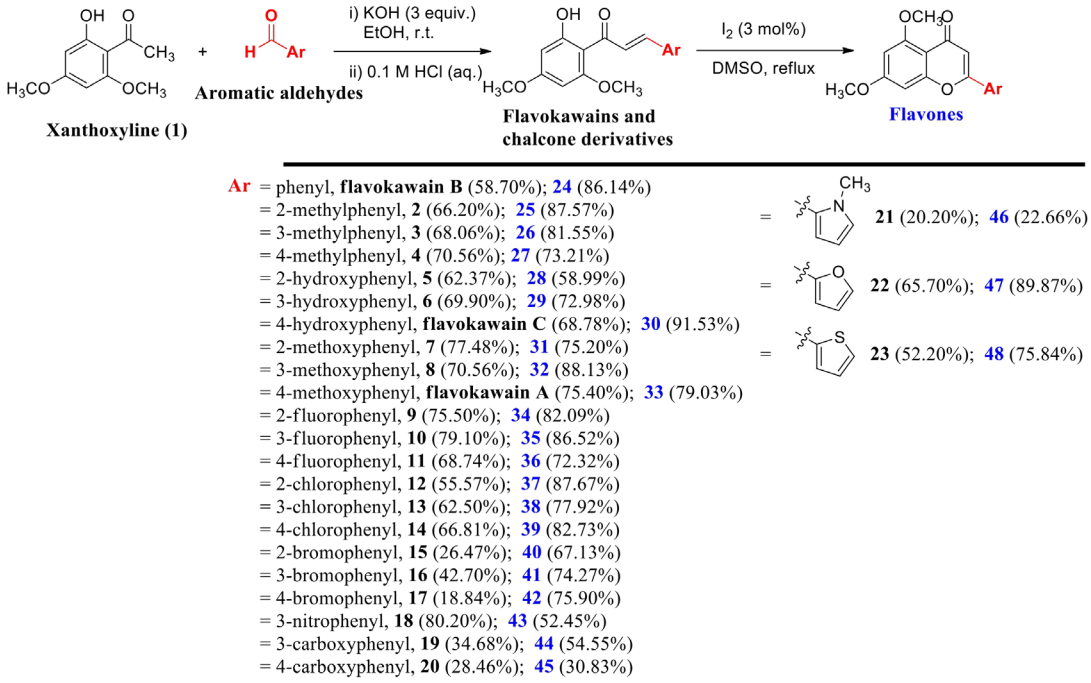

Figure 2. Synthesis of flavokawains, chalcones and flavone derivatives, the yields are given in parentheses.

2.2 Synthesis of flavokawains and chalcone derivatives

Flavokawains A, B, and C, as well as chalcones **2**, **8**, **9**, **16**, **18**, and **20**–**23** were prepared according to our previous report procedures [33]. Similarly, General procedure A was used to prepare chalcones **3**, **4**, **7**, **10**, **11**, **12**, **13**, **14**, **15**, **17**, and **19**, while General procedure B was used to prepare chalcones **5** and **6**.

2.2.1 General procedure A [33]

Xanthoxyline (**1**) (196.2 mg, 1.0 mmol) and aromatic aldehydes (1.1 mmol) were dissolved in ethanol (20 mL), and potassium hydroxide (168.3 mg, 3.0 mmol) was slowly added. The mixture was stirred at room temperature until the xanthoxyline was completely consumed (monitored by TLC), and then acidified with a 1 N HCl solution. The acidic solution was kept in the fume cupboard until the chalcone product precipitated out of it. The precipitate was filtered off and recrystallized from methanol to obtain the pure compounds.

2.2.2 General procedure B [33]

Xanthoxyline (**1**) (196.2 mg, 1.0 mmol) and potassium hydroxide (168.3 mg, 3.0 mmol) were ground with a mortar and pestle at room temperature. An aromatic aldehyde (1.1 mmol) was added to the mixture dropwise, and the mixture was ground until the reaction was complete (around 20 min, monitored by TLC). The mixture was then treated with 5 mL of cold distilled water before

being transferred to a 50-mL beaker and acidified with 1 N HCl (aq.). The precipitated solids were filtered, dissolved in methanol, and recrystallized from the methanol to obtain the pure chalcones.

*(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(m-tolyl)prop-2-en-1-one (**3**)*. Yield 68.06%. m.p. 80 – 81 °C (MeOH); R_f = 0.34 (10% EtOAc/hexane); IR (film) 2938, 1614 (C=O), 1558, 1414, 1337, 1238, 1207(C-O), 1155, 1111, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.31 (1H, s, OH), 7.89 (1H, d, *J* = 12.4 Hz, CH=CH), 7.77 (1H, d, *J* = 12.5 Hz, CH=CH), 7.45 – 7.39 (2H, m, ArH), 7.31 (1H, t, *J* = 6.1 Hz, ArH), 7.21 (1H, d, *J* = 6.0 Hz, ArH), 6.12 (1H, d, *J* = 1.9 Hz, ArH), 5.98 (1H, d, *J* = 1.9 Hz, ArH), 3.93 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.40 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.7 (C=O), 168.4 (C), 166.2 (C), 162.5 (C), 142.6 (CH), 138.5 (C), 135.5 (C), 130.9 (CH), 129.2 (CH), 128.7 (CH), 127.3 (CH), 125.4 (CH), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3), 21.4 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.1283, found 299.1284.

*(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(p-tolyl)prop-2-en-1-one (**4**)*. Yield 70.56%. ^1H NMR (500 MHz, $CDCl_3$) δ 14.35 (1H, s, OH), 7.87 (1H, d, *J* = 12.4 Hz, CH=CH), 7.77 (1H, d, *J* = 12.5 Hz, CH=CH), 7.50 (2H, d, *J* = 6.5 Hz, ArH), 7.21 (2H, d, *J* = 6.3 Hz, ArH), 6.11 (1H, d, *J* = 1.9 Hz, ArH), 5.96 (1H, d, *J* = 1.9 Hz, ArH), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.39 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.7, 168.4 (C), 166.1 (C), 162.5 (C), 142.5 (CH), 140.5 (C), 132.8 (C), 129.6 (2 × CH), 128.4 (2 × CH), 126.5 (CH), 106.3 (C), 93.8 (CH), 91.2 (CH), 55.8 (CH_3), 55.6 (CH_3), 21.5 (CH_3); The NMR data were in agreement with the literature [34].

*(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one (**5**)*. Yield 62.37%; m.p. 156 – 157 °C (MeOH); R_f = 0.22 (20% EtOAc/hexane); IR (film) 3400–3000 (br), 2943, 1620 (C=O), 1520, 1458, 1346, 1221, 1159, 1117, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.30 (1H, s, OH), 8.05 (1H, d, *J* = 15.8 Hz, CH=CH), 7.96 (1H, d, *J* = 15.7 Hz, CH=CH), 7.55 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 7.28 – 7.23 (1H, m, ArH), 6.98 (1H, t, *J* = 7.5 Hz, ArH), 6.86 (1H, d, *J* = 8.1 Hz, ArH), 6.13 (1H, d, *J* = 2.4 Hz, ArH), 5.98 (1H, d, *J* = 2.4 Hz, ArH), 5.60 (1H, s, OH), 3.92 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.9 (C=O), 168.3 (C), 166.2 (C), 162.5 (C), 155.0 (C), 137.3 (CH), 131.2 (CH), 129.2 (CH), 128.6 (CH), 122.8 (C), 121.1 (CH), 116.5 (CH), 106.4 (C), 93.8 (CH), 91.3 (CH), 55.8 (CH_3), 55.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{16}O_5Na$ $[M+Na]^+$: 323.0895, found 323.0895.

*(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (**6**)*. Yield 69.90%. m.p. 154 – 155 °C (MeOH); R_f = 0.19 (20% EtOAc/hexane); IR (film) 3500–3100 (br), 2981, 1632 (C=O), 1583, 1446, 1331, 1223, 1167, 1119, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.30 (1H, s, OH), 7.85 (1H, d, *J* = 15.6 Hz, CH=CH), 7.70 (1H, d, *J* = 15.6 Hz, CH=CH), 7.29 – 7.25 (1H, m, ArH), 7.17 (1H, d, *J* = 7.7 Hz, ArH), 7.08 – 7.05 (1H, m, ArH), 6.87 (1H, dd, *J* = 8.0, 2.5 Hz, ArH), 6.11 (1H, d, *J* = 2.4 Hz, ArH), 5.96 (1H, d, *J* = 2.3 Hz, ArH), 5.24 (1H, s, OH), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.6 (C=O), 168.4 (C), 166.3 (C), 162.5 (C), 155.9 (C), 141.9 (CH), 137.2 (C), 130.1 (CH), 127.9 (CH), 121.3 (CH), 117.2 (CH), 114.6 (CH), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{16}O_5Na$ $[M+Na]^+$: 323.0895, found 323.0896.

*(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**7**)*. Yield 77.48%. ^1H NMR (500 MHz, $CDCl_3$) δ 14.41 (1H, s, OH), 8.15 (1H, d, *J* = 15.8 Hz, CH=CH), 7.97 (1H, d, *J* = 15.8 Hz, CH=CH), 7.61 (1H, ddd, *J* = 7.7, 3.5, 1.1 Hz, ArH), 7.38 – 7.33 (1H, m, ArH), 6.98 (1H, t, *J* = 7.5 Hz, ArH), 6.93 (1H, d, *J* = 8.2 Hz, ArH), 6.11 (1H, d, *J* = 2.4 Hz, ArH), 5.96 (1H, d, *J* = 2.4 Hz, ArH), 3.91 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 193.0 (C=O), 168.3 (C), 166.0 (C), 162.5 (C), 158.6 (C), 137.8 (CH), 131.3 (CH), 128.7 (CH), 127.8 (CH), 124.5 (C), 120.7 (CH), 111.1 (CH), 106.4 (C), 93.7 (CH), 91.2 (CH), 55.7 (CH_3), 55.5 (CH_3), 55.5 (CH_3); The NMR data were in agreement with the literature [35].

*(E)-3-(3-fluorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**10**)*. Yield 79.10%. m.p. 112 – 113 °C (MeOH); R_f = 0.37 (10% EtOAc/hexane); IR (film) 3010, 2941, 1618 (C=O), 1582, 1489, 1418, 1341, 1213 (C-O), 1157, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.20

(1H, s, OH), 7.86 (1H, d, *J* = 15.6 Hz, CH=CH), 7.69 (d, *J* = 15.6 Hz, CH=CH), 7.40 – 7.32 (2H, m, ArH), 7.30 – 7.26 (1H, m, ArH), 7.10 – 7.03 (1H, m, ArH), 6.10 (1H, d, *J* = 2.3 Hz, ArH), 5.96 (1H, d, *J* = 2.3 Hz, ArH), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.3 (C=O), 168.4 (C), 166.4 (C), 163.0 (d, *J* = 246.4 Hz, C), 162.5 (C), 140.6 (CH), 137.9 (d, *J* = 7.6 Hz, C), 130.4 (d, *J* = 8.2 Hz, CH), 128.8 (CH), 124.4 (CH), 116.8 (d, *J* = 21.5 Hz, CH), 114.2 (d, *J* = 21.7 Hz, CH), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{14}FO_4$ $[M-H]^+$: 301.0876, found 301.0878.

(E)-3-(4-Fluorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ***(11)***. Yield 68.74%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.27 (1H, s, OH), 7.82 (1H, d, *J* = 15.6 Hz, CH=CH), 7.73 (d, *J* = 15.6 Hz, CH=CH), 7.61 – 7.54 (2H, m, ArH), 7.12 – 7.05 (2H, m, ArH), 6.11 (1H, t, *J* = 3.6 Hz, ArH), 5.95 (1H, t, *J* = 4.8 Hz, ArH), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.4 (C=O), 168.4 (C), 166.3 (C), 163.6 (d, *J* = 289.9 Hz, C), 162.8 (C), 141.0 (CH), 131.8 (C), 130.1 (d, *J* = 8.4 Hz, 2 × CH), 127.2 (CH), 116.0 (d, *J* = 21.9 Hz, 2 × CH), 106.2 (C), 93.8 (CH), 91.3 (CH), 55.8 (CH_3), 55.6 (CH_3); The NMR data were in agreement with the literature [34].

(E)-3-(2-Chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ***(12)***. Yield 55.57%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.21 (1H, s, OH), 8.14 (1H, d, *J* = 15.6 Hz, CH=CH), 7.86 (1H, d, *J* = 15.6 Hz, CH=CH), 7.71 – 7.66 (1H, m, ArH), 7.45 – 7.39 (1H, m, ArH), 7.33 – 7.27 (2H, m, ArH), 6.10 (1H, d, *J* = 2.4 Hz, ArH), 5.95 (1H, d, *J* = 2.4 Hz, ArH), 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.3 (C=O), 168.4 (C), 166.4 (C), 162.5 (C), 137.8 (CH), 135.3 (C), 133.8 (C), 130.6 (CH), 130.2 (CH), 130.0 (CH), 127.8 (CH), 127.0 (CH), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.8 (CH_3), 55.6 (CH_3); The NMR data were in agreement with the literature [34].

(E)-3-(3-Chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ***(13)***. Yield 62.50%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.18 (1H, s, OH), 7.86 (d, *J* = 15.6 Hz, CH=CH), 7.67 (1H, d, *J* = 15.6 Hz, CH=CH), 7.56 (1H, s, ArH), 7.48-7.42 (1H, m, ArH), 7.38 – 7.30 (2H, m, ArH), 6.11 (1H, d, *J* = 2.1 Hz, ArH), 5.96 (1H, d, *J* = 2.1 Hz, ArH), 3.92 (3H, s, OCH_3), 3.84 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.2 (C=O), 168.4 (C), 166.4 (C), 162.5 (C), 140.4 (CH), 137.5 (C), 134.8 (C), 130.1 (CH), 129.8 (CH), 128.9 (CH), 127.8 (CH), 126.6 (CH), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3); The NMR data were in agreement with the literature [36].

(E)-3-(4-Chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ***(14)***. Yield 66.81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.22 (1H, s, OH), 7.85 (1H, d, *J* = 15.6 Hz, CH=CH), 7.71 (1H, d, *J* = 15.6 Hz, CH=CH), 7.55 – 7.49 (2H, m, ArH), 7.39 – 7.35 (2H, m, ArH), 6.11 (1H, d, *J* = 2.4 Hz, ArH), 5.96 (1H, d, *J* = 2.4 Hz, ArH), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.3 (C=O), 168.4 (C), 166.4 (C), 162.5 (C), 140.7 (CH), 135.8 (C), 134.1 (C), 129.4 (2 × CH), 1 (2 × CH), 128.0 (CH), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3); The NMR data were in agreement with the literature [34].

(E)-3-(2-Bromophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ***(15)***. Yield 26.47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.21 (1H, s, OH), 8.10 (1H, d, *J* = 15.5 Hz, CH=CH), 7.81 (1H, d, *J* = 15.5 Hz, CH=CH), 7.67 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 7.62 (1H, dd, *J* = 8.0, 1.1 Hz, ArH), 7.34 (1H, dd, *J* = 11.2, 3.9 Hz, ArH), 7.21 (1H, td, *J* = 7.8, 1.6 Hz, ArH), 6.10 (1H, d, *J* = 2.3 Hz, ArH), 5.95 (1H, d, *J* = 2.4 Hz, ArH), 3.89 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.2 (C=O), 168.4 (C), 166.4 (C), 162.5 (C), 140.4 (CH), 135.6 (C), 133.5 (CH), 130.8 (CH), 130.2 (CH), 127.8 (CH), 127.6 (CH), 125.8 (C), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3); The NMR data were in agreement with the literature [37].

(E)-3-(4-Bromophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one ***(17)***. Yield 18.84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.22 (1H, s, OH), 7.86 (1H, d, *J* = 15.6 Hz, CH=CH), 7.68 (1H, d, *J* = 15.6 Hz, CH=CH), 7.56 – 7.49 (2H, m, ArH), 7.46 – 7.43 (2H, m, ArH), 6.10 (1H, d, *J* = 2.4 Hz, ArH), 5.95 (1H, d, *J* = 2.3 Hz, ArH), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 192.3 (C=O), 168.4 (C), 166.4 (C), 162.4 (C), 140.8 (CH), 134.5 (C), 132.1

(2 × CH), 129.6 (2 × CH), 128.1 (CH), 124.2 (C), 106.3 (C), 93.8 (CH), 91.3 (CH), 55.9 (CH_3), 55.6 (CH_3); The NMR data were in agreement with the literature [37].

*(E)-3-(3-(2-Hydroxy-4,6-dimethoxyphenyl)-3-oxoprop-1-en-1-yl)benzoic acid (**19**)*. Yield 34.68%. m.p. 190 – 191 °C (MeOH); R_f = 0.31 (60% EtOAc/hexane); IR (film) 2949, 1695, 1632 (C=O), 1576, 1420, 1348, 1269, 1219 (C-O), 1161, 1115, 744 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 13.33 (1H, s, *J* = 3.5 Hz, OH), 8.20 (1H, d, *J* = 1.2 Hz, ArH), 7.99 (2H, ddd, *J* = 5.0, 3.3, 1.2 Hz, ArH), 7.79 (1H, d, *J* = 12.5 Hz, CH=CH), 7.69 (1H, d, *J* = 12.6 Hz, CH=CH), 7.59 (1H, t, *J* = 6.2 Hz, ArH), 6.15 (2H, dd, *J* = 10.0, 1.8 Hz, ArH), 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.34 (1H, s, COOH); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 192.2 (C=O), 166.9 (C=O), 165.7 (C), 165.5 (C), 161.9 (C), 141.0 (CH), 135.3 (C), 132.2 (CH), 131.7 (C), 130.9 (CH), 129.5 (CH), 129.3 (CH), 128.7 (CH), 106.4 (C), 93.9 (CH), 91.2 (CH), 56.3 (CH_3), 55.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{15}O_6$ [M-H]+: 327.0874, found 327.0877.

2.3 Synthesis of flavones from flavokawains and chalcones

Similar to a reported procedure [38], to a solution of chalcone (1.0 mmol) in DMSO (3 mL), 1 mL of 0.03 M I_2 in DMSO was added. The mixture was heated at reflux for 2 h (monitored by TLC). Then the mixture was poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by flash column chromatography (EtOAc/ hexane) to obtain the flavone product.

*5,7-Dimethoxy-2-phenyl-4H-chromen-4-one (**24**)*. Yield = 86.14%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.84 (2H, m, ArH), 7.53 – 7.47 (3H, m, ArH), 6.68 (1H, s, CH=), 6.57 (1H, d, *J* = 2.3 Hz, ArH), 6.38 (1H, d, *J* = 2.3 Hz, ArH), 3.96 (3H, s, OCH_3), 3.91 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.6 (C=O), 164.0 (C), 160.9 (C), 160.6 (C), 159.9 (C), 131.5 (C), 131.1 (CH), 128.9 (2 × CH), 125.9 (2 × CH), 109.3 (C), 109.0 (CH), 96.2 (CH), 92.8 (CH), 56.4 (CH_3), 55.7 (CH_3); The NMR data were in agreement with the literature [39, 40].

*5,7-Dimethoxy-2-o-tolyl-4H-chromen-4-one (**25**)*. Yield = 87.57%. m.p. 93 – 94 °C (MeOH); R_f = 0.27 (70% EtOAc/hexane); IR (film) 3067, 2939, 1641 (C=O), 1604, 1456, 1419, 1215 (C–O), 1159, 1103, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.47 (1H, m, ArH), 7.40 – 7.35 (1H, m, ArH), 7.28 (2H, t, *J* = 5.8 Hz, ArH), 6.47 (1H, d, *J* = 1.8 Hz, ArH), 6.38 (1H, d, *J* = 1.8 Hz, ArH), 6.32 (1H, s, CH=), 3.95 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.46 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.5 (C=O), 164.0 (C), 163.1 (C), 160.9 (C), 160.1 (C), 136.6 (C), 132.2 (C), 131.1 (CH), 130.4 (CH), 129.0 (CH), 126.1 (CH), 113.3 (CH), 109.0 (C), 96.1 (CH), 92.6 (CH), 56.4 (CH_3), 55.7 (CH_3), 20.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_4Na$ $[M+Na]^+$: 319.0941, found 319.0957.

*5,7-dimethoxy-2-m-tolyl-4H-chromen-4-one (**26**)*. Yield = 81.55%. m.p. 76 – 77 °C (MeOH); R_f = 0.14 (70% EtOAc/hexane); IR (film) 2941, 2841, 1641 (C=O), 1607, 1458, 1421, 1337, 1217 (C-O), 1159, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.64 (2H, m, ArH), 7.37 (1H, dd, *J* = 10.1, 4.0 Hz, ArH), 7.30 (1H, d, *J* = 6.1 Hz, ArH), 6.65 (1H, s, CH=), 6.57 (1H, d, *J* = 1.8 Hz, ArH), 6.36 (1H, d, *J* = 1.8 Hz, ArH), 3.95 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.43 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.7 (C=O), 164.0 (C), 160.9 (C), 160.8 (C), 159.9 (C), 138.7 (C), 132.0 (CH), 131.4 (C), 128.8 (CH), 126.5 (CH), 123.1 (CH), 109.2 (C), 108.9 (CH), 96.1 (CH), 92.8 (CH), 56.4 (CH_3), 55.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_4Na$ $[M+Na]^+$: 319.3070, found 319.0946.

*5,7-dimethoxy-2-o-tolyl-4H-chromen-4-one (**27**)*. Yield = 73.21%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.72 (2H, m, ArH), 7.30 – 7.27 (2H, m, ArH), 6.64 (1H, s, CH=), 6.56 (1H, d, *J* = 2.3 Hz, ArH), 6.36 (1H, d, *J* = 2.3 Hz, ArH), 3.95 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 2.42 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.7 (C=O), 163.9 (C), 160.8 (2 × C), 159.8 (C), 141.7

(C), 129.6 (2 × CH), 128.6 (C), 125.8 (2 × CH), 109.2 (C), 108.4 (CH), 96.1 (CH), 92.8 (CH), 56.4 (CH_3), 55.7 (CH_3), 21.5 (CH_3); The NMR data were in agreement with the literature [12].

*2-(2-Hydroxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**28**)*. Yield = 58.99%. m.p. 254 – 255 °C (MeOH); R_f = 0.17 (80% EtOAc/hexane); IR (film) 3500-3300 (br), 2940, 1628 (C=O), 1451, 1421, 1215 (C-O), 1161, 1122, 818 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.66 (1H, s, OH), 7.90 (1H, dd, *J* = 7.9, 1.7 Hz, ArH), 7.39 – 7.33 (1H, m, ArH), 7.04 (1H, dd, *J* = 6.5 Hz, ArH), 6.99 (1H, t, *J* = 5.9 Hz, ArH), 6.90 (1H, s, CH=), 6.82 (1H, d, *J* = 1.8 Hz, ArH), 6.49 (1H, d, *J* = 1.8 Hz, ArH), 3.89 (3H, s, OCH_3), 3.83 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.9 (C=O), 163.7 (C), 160.2 (C), 159.3 (C), 157.5 (C), 156.4 (C), 132.2 (CH), 128.2 (CH), 119.4 (CH), 117.4 (C), 116.9 (CH), 112.5 (CH), 108.2 (C), 96.1 (CH), 93.3 (CH), 56.1 (CH_3), 56.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$: 321.2798, found 321.0732.

*2-(3-Hydroxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**29**)*. Yield = 72.98%. m.p. 242 – 243 °C (MeOH); R_f = 0.11 (60% EtOAc/hexane); IR (film) 3600-3300 (br), 2932, 1640 (C=O), 1458, 1423, 1207 (C-O), 1159, 1117, 845 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.96 (1H, s, OH), 7.42 (1H, ddd, *J* = 7.8, 1.6, 0.9 Hz, ArH), 7.39 – 7.36 (1H, m, ArH), 7.31 (1H, t, *J* = 7.9 Hz, ArH), 6.97 (1H, ddd, *J* = 8.1, 2.4, 0.9 Hz, ArH), 6.81 (1H, d, J = 2.3 Hz, ArH), 6.61 (1H, s, CH=), 6.49 (1H, d, *J* = 2.3 Hz, ArH), 3.88 (3H, s, OCH_3), 3.81 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 175.8 (C=O), 164.0 (C), 160.5 (C), 159.9 (C), 159.4 (C), 158.2 (C), 132.3 (H), 130.3 (CH), 118.7 (C), 116.8 (CH), 112.7 (CH), 108.5 (C), 108.4 (CH), 99.7 (C), 96.5 (CH), 93.5 (CH), 56.3 (CH_3), 56.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$: 321.2798, found 321.2588.

*2-(4-Hydroxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (**30**)*. Yield = 91.53%. ^1H NMR (500 MHz, DMSO-d_6) δ 10.21 (1H, s, OH), 7.91 – 7.84 (2H, m, ArH), 6.93 – 6.87 (2H, m, ArH), 6.82 (1H, d, *J* = 2.3 Hz, ArH), 6.58 (1H, s, CH=), 6.48 (1H, d, *J* = 2.3 Hz, ArH), 3.89 (3H, s, OCH_3), 3.82 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 175.7 (C=O), 163.6 (C), 160.5 (C), 160.2 (C), 160.1 (C), 159.1 (C), 127.8 (2 × CH), 121.4 (C), 115.8 (2 × CH), 108.3 (C), 106.1 (CH), 96.2 (CH), 93.3 (CH), 56.1 (CH_3), 55.9 (CH_3); The NMR data were in agreement with the literature [41, 42].

*5,7-Dimethoxy-2-(2-methoxyphenyl)-4H-chromen-4-one (**31**)*. Yield = 75.20 %. m.p. 171 – 172 °C (MeOH); R_f = 0.13 (60% EtOAc/hexane); IR (film) 3076, 2839, 1630 (C=O), 1603, 1491, 1456, 1248 (C–O), 1159, 1115, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (1H, dd, *J* = 7.8, 1.7 Hz, ArH), 7.44 (1H, ddd, *J* = 8.4, 7.5, 1.7 Hz, ArH), 7.11 – 7.05 (1H, m, ArH), 7.02 (1H, d, *J* = 8.4 Hz, ArH), 7.00 (1H, s, CH=), 6.53 (1H, d, *J* = 2.3 Hz, ArH), 6.36 (1H, d, *J* = 2.3 Hz, ArH), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 178.1 (C=O), 163.9 (C), 160.8 (C), 160.1 (C), 158.0 (C), 157.9 (C), 132.0 (CH), 128.9 (CH), 120.6 (CH), 120.5 (C), 114.1 (CH), 111.6 (CH), 109.2 (C), 95.9 (CH), 92.7 (CH), 56.4 (CH_3), 55.7 (CH_3), 55.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$: 335.0890, found 335.0918.

*5,7-Dimethoxy-2-(3-methoxyphenyl)-4H-chromen-4-one (**32**)*. Yield = 88.13%. m.p. 139 – 140 °C (MeOH); R_f = 0.32 (70% EtOAc/hexane); IR (film) 3078, 2939, 1637 (C=O), 1601, 1489, 1454, 1267 (C–O), 1157, 1112, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (1H, dt, *J* = 6.3, 1.0 Hz, ArH), 7.43 – 7.37 (2H, m, ArH), 7.07 – 7.02 (1H, m, ArH), 6.67 (1H, s, CH=), 6.57 (1H, d, *J* = 1.8 Hz, ArH), 6.38 (1H, d, *J* = 1.8 Hz, ArH), 3.96 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.7 (C=O), 164.1 (C), 160.9 (C), 160.5 (C), 159.9 (C), 159.9 (C), 132.9 (C), 130.0 (CH), 118.4 (CH), 116.9 (CH), 111.3 (CH), 109.3 (CH), 96.2 (CH), 92.8 (CH), 56.4 (CH_3), 55.8 (CH_3), 55.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$: 335.0890, found 335.0916.

*5,7-Dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (**33**)*. Yield = 79.03%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.76 (2H, m, ArH), 7.00 – 6.94 (2H, m, ArH), 6.56 (1H, s, CH=), 6.53 (1H, d, *J* = 1.8 Hz, ArH), 6.34 (1H, d, *J* = 1.8 Hz, ArH), 3.93 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.7 (C=O), 163.8 (C), 162.0 (C), 160.8 (C),

160.6 (C), 159.7 (C), 127.5 (2 x CH), 123.7 (C), 114.3 (2 × CH), 109.1 (C), 107.5 (CH), 96.0 (CH), 92.7 (CH), 56.3 (CH_3), 55.68 (CH_3), 55.4 (CH_3); The NMR data were in agreement with the literature [43].

*2-(2-Fluorophenyl)-5,7-dimethoxy-4H-chromen-4-one (**34**)*. Yield = 82. 09%. m.p. 146 – 147 °C (MeOH); R_f = 0.47 (70% EtOAc/hexane); IR (film) 3078, 2941, 1638 (C=O), 1603, 1490, 1452, 1213 (C–O), 1159, 1113, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (1H, t, *J* = 1.7 Hz, ArH), 7.77 (1H, ddd, *J* = 7.9, 1.8, 1.0 Hz, ArH), 7.63 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, ArH), 7.37 (1H, t, *J* = 7.9 Hz, ArH), 6.65 (1H, s, CH=), 6.59 (1H, d, *J* = 2.3 Hz, ArH), 6.39 (1H, d, *J* = 2.3 Hz, ArH), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.4 (C=O), 160.3 (d, *J* = 122.7 Hz, C), 164.0 (C), 160.8, (C), 159.8 (C), 156.0 (d, *J* = 4.0 Hz, C), 132.4 (d, *J* = 9.1 Hz, CH), 128.7 (d, *J* = 1.9 Hz, CH), 124.4 (d, *J* = 4.0 Hz, CH), 119.9 (d, *J* = 10.1 Hz, C), 116.8 (d, *J* = 22.5 Hz, CH), 113.8 (d, *J* = 11.6 Hz, CH), 109.1 (C), 96.1 (CH), 92.6 (CH), 56.3 (CH_3), 55.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}FO_4Na$ $[M+Na]^+$: 323.0690, found 323.0725.

*2-(3-Fluorophenyl)-5,7-dimethoxy-4H-chromen-4-one (**35**)*. Yield = 86.52%. m.p. 137 – 138 °C (MeOH); R_f = 0.19 (60% EtOAc/hexane); IR (film) 3070, 2943, 1641 (C=O), 1603, 1489, 1450, 1269 (C–O), 1159, 1113, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.60 (1H, m, ArH), 7.58 – 7.53 (1H, m, ArH), 7.45 (1H, td, *J* = 6.4, 4.6 Hz, ArH), 7.21 – 7.16 (1H, m, ArH), 6.64 (1H, s, CH=), 6.55 (1H, d, *J* = 1.8 Hz, ArH), 6.36 (1H, d, *J* = 1.8 Hz, ArH), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.4 (C=O), 164.2 (C), 163.9 (C), 162.0 (C), 160.3 (d, *J* = 445.8 Hz, C), 159.14 (d, *J* = 6.6 Hz, C), 133.7 (d, *J* = 24.8 Hz, C), 130.6 (d, *J* = 25.1 Hz, CH), 121.6 (CH), 118.02 (d, *J* = 68.0 Hz, CH), 112.93 (d, *J* = 76.1 Hz, CH), 109.5 (CH), 109.2 (C), 96.3 (CH), 92.7 (CH), 56.37 (CH_3), 55.76 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}FO_4Na$ $[M+Na]^+$: 323.0690, found 323.0725.

*2-(4-Fluorophenyl)-5,7-dimethoxy-4H-chromen-4-one (**36**)*. Yield = 72.32%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.84 (2H, m, ArH), 7.21 – 7.15 (2H, m, ArH), 6.62 (1H, s, CH=), 6.56 (1H, d, *J* = 2.3 Hz, ArH), 6.39 (1H, d, *J* = 2.3 Hz, ArH), 3.96 (3H, s, OCH_3), 3.91 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.5 (C=O), 164.5 (d, *J* = 200.8 Hz, C), 164.1 (C), 161.0 (C), 159.8 (C), 159.7 (C), 128.1 (d, *J* = 8.9 Hz, 2 × CH), 127.8 (d, *J* = 3.4 Hz, C), 116.2 (d, *J* = 22.1 Hz, 2 × CH), 109.2 (C), 108.9 (d, *J* = 1.7 Hz, CH), 96.2 (CH), 92.8 (CH), 56.4 (CH_3), 55.8 (CH_3); The NMR data were in agreement with the literature [40].

*2-(2-Chlorophenyl)-5,7-dimethoxy-4H-chromen-4-one (**37**)*. Yield = 87.67%. m.p. 143 – 144 °C (MeOH); R_f = 0.24 (60% EtOAc/hexane); IR (film) 3067, 2939, 1643 (C=O), 1605, 1456, 1419, 1215 (C–O), 1159, 1115, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 7.5, 1.9 Hz, ArH), 7.50 (1H, dd, *J* = 8.0, 1.3 Hz, ArH), 7.41 (1H, td, *J* = 7.7, 1.9 Hz, ArH), 7.37 (1H, td, *J* = 7.5, 1.4 Hz, ArH), 6.49 (1H, s, CH=), 6.49 (1H, d, *J* = 2.4 Hz, ArH), 6.37 (1H, d, *J* = 2.3 Hz, ArH), 3.95 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.2 (C=O), 164.1 (C), 160.9 (C), 160.2 (C), 159.9 (C), 132.8 (C), 131.5 (C), 131.5 (CH), 130.7 (CH), 130.5 (CH), 127.0 (CH), 114.3 (CH), 109.2 (C), 96.3 (CH), 92.7 (CH), 56.4 (CH_3), 55.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}ClO_4Na$ $[M+Na]^+$: 339.0395, found 339.0433.

*2-(3-Chlorophenyl)-5,7-dimethoxy-4H-chromen-4-one (**38**)*. Yield = 77.92%. m.p. 161 – 162 °C (MeOH); R_f = 0.21 (60% EtOAc/hexane); IR (film) 3073, 2941, 1641 (C=O), 1607, 1458, 1422, 1269 (C–O), 1161, 1120, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.86 (1H, m, ArH), 7.72 (1H, ddd, *J* = 7.7, 1.7, 1.2 Hz, ArH), 7.47 (1H, ddd, *J* = 8.0, 2.0, 1.2 Hz, ArH), 7.45 – 7.40 (1H, m, ArH), 6.66 (1H, s, CH=), 6.58 (1H, d, *J* = 2.3 Hz, ArH), 6.38 (1H, d, *J* = 2.3 Hz, ArH), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.3 (C=O), 164.2 (C), 160.9 (C), 159.8 (C), 159.1 (C), 135.1 (C), 133.3 (C), 131.1 (CH), 130.2 (CH), 126.0 (CH), 124.0 (CH), 109.6 (CH), 109.2 (C), 96.4 (CH), 92.8 (CH), 56.4 (CH_3), 55.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}ClO_4Na$ $[M+Na]^+$: 339.0395, found 339.0433.

*2-(4-Chlorophenyl)-5,7-dimethoxy-4H-chromen-4-one (**39**)*. Yield = 82.73%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.76 (2H, m, ArH), 7.47 – 7.43 (2H, m, ArH), 6.62 (1H, s, CH=), 6.54

(1H, d, *J* = 1.8 Hz, ArH), 6.36 (1H, d, *J* = 1.8 Hz, ArH), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.4 (C=O), 164.1 (C), 160.9 (C), 159.7 (C), 159.5 (C), 137.3 (C), 129.9 (C), 129.2 (2 × CH), 127.1 (2 × CH), 109.1 (CH), 109.1 (C), 96.2 (CH), 92.7 (CH), 56.4 (CH_3), 55.8 (CH_3); The NMR data were in agreement with the literature [40].

2-(2-Bromophenyl)-5,7-dimethoxy-4H-chromen-4-one ***(40)***. Yield = 67.13%. m.p. 144 – 145 °C (MeOH); R_f = 0.15 (60% EtOAc/hexane); IR (film) 3066, 2939, 1647 (C=O), 1607, 1458, 1412, 1215 (C–O), 1159, 1115, 764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, dd, *J* = 6.4, 1.0 Hz, ArH), 7.53 (1H, dd, *J* = 6.1, 1.4 Hz, ArH), 7.41 (1H, td, *J* = 6.0, 0.9 Hz, ArH), 7.34 (1H, td, *J* = 6.2, 1.4 Hz, ArH), 6.49 (1H, d, *J* = 1.8 Hz, ArH), 6.42 (1H, s, CH=), 6.38 (1H, d, *J* = 1.8 Hz, ArH), 3.95 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.2 (C=O), 164.1 (C), 161.1 (C), 160.9 (C), 160.1 (C), 133.8 (CH), 133.7 (C), 131.6 (CH), 130.8 (CH), 127.5 (CH), 121.8 (C), 114.2 (CH), 109.2 (C), 96.3 (CH), 92.7 (CH), 56.4 (CH_3), 55.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}BrO_4Na$ $[M+Na]^+$: 382.9889, found 382.9890.

2-(3-Bromophenyl)-5,7-dimethoxy-4H-chromen-4-one ***(41)***. Yield = 74.27%. m.p. 158 – 159 °C (MeOH); R_f = 0.38 (70% EtOAc/hexane); IR (film) 2940, 2841, 1643 (C=O), 1607, 1458, 1420, 1333, 1217 (C-O), 1161, 824 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (1H, t, *J* = 1.7 Hz, ArH), 7.77 (1H, ddd, *J* = 7.9, 1.8, 1.0 Hz, ArH), 7.63 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, ArH), 7.37 (1H, t, *J* = 7.9 Hz, ArH), 6.65 (1H, s, CH=), 6.59 (1H, d, *J* = 2.3 Hz, ArH), 6.39 (1H, d, *J* = 2.3 Hz, ArH), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.3 (C=O), 164.2 (C), 160.9 (C), 159.8 (C), 159.0 (C), 134.0 (CH), 133.5 (C), 130.4 (CH), 128.9 (CH), 124.5 (CH), 123.1 (C), 109.63 (CH), 109.2 (C), 96.4 (CH), 92.8 (CH), 56.4 (CH_3), 55.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}BrO_4Na$ $[M+Na]^+$: 382.9889, found 382.9898.

2-(4-Bromophenyl)-5,7-dimethoxy-4H-chromen-4-one ***(42)***. Yield = 75.90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.68 (2H, m, ArH), 7.63 – 7.59 (2H, m, ArH), 6.62 (1H, s, CH=), 6.53 (1H, d, *J* = 1.8 Hz, ArH), 6.36 (1H, d, *J* = 1.8 Hz, ArH), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.3 (C=O), 164.1 (C), 160.8 (C), 159.7 (C), 159.5 (C), 132.1 (2 × CH), 130.4 (C), 127.3 (2 × CH), 125.7 (C), 109.2 (C), 109.1 (CH), 96.2 (CH), 92.7 (CH), 56.4 (CH_3), 55.8 (CH_3). The NMR data were in agreement with the literature [40].

5,7-Dimethoxy-2-(3-nitrophenyl)-4H-chromen-4-one ***(43)***. Yield = 52.45%. m.p. 198 – 199 °C (MeOH); R_f = 0.16 (80% EtOAc/hexane); IR (film) 3069, 2976, 1663 (C=O), 1614, 1526, 1340, 1217 (C–O), 1165, 1101, 816 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (1H, t, *J* = 1.9 Hz, ArH), 8.35 (1H, ddd, *J* = 8.2, 2.3, 0.9 Hz, ArH), 8.14 (1H, ddd, *J* = 7.9, 1.7, 1.0 Hz, ArH), 7.70 (1H, t, *J* = 8.0 Hz, ArH), 6.74 (1H, s, CH=), 6.61 (1H, dd, *J* = 3.3, 1.4 Hz, ArH), 6.40 (1H, d, *J* = 2.3 Hz, ArH), 3.96 (3H, s, OCH_3), 3.94 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 176.9 (C=O), 164.4 (C), 160.9 (C), 159.7 (C), 157.7 (C), 148.7 (C), 133.4 (C), 131.4 (CH), 130.1 (CH), 125.5 (CH), 120.8 (CH), 110.3 (CH), 109.2 (C), 96.6 (CH), 92.8 (CH), 56.5 (CH_3), 55.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{13}BrO_4Na$ $[M+Na]^+$: 350.0635, found 350.0638.

3-(5,7-dimethoxy-4-oxo-4H-chromen-2-yl)benzoic acid ***(44)***. Yield = 54.55%. m.p. 252 – 253 °C (MeOH); R_f = 0.08 (80% EtOAc/hexane); IR (film) 3700-3200 (br), 2945, 1708, 1638 (C=O), 1475, 1420, 1204 (C-O), 1161, 829 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.34 (1H, brs, COOH), 8.49 (1H, t, *J* = 1.3 Hz, ArH), 8.29 – 8.26 (1H, m, ArH), 8.13 – 8.09 (1H, m, ArH), 7.68 (1H, t, *J* = 6.3 Hz, ArH), 6.88 (1H, d, *J* = 1.8 Hz, ArH), 6.82 (1H, s, CH=), 6.52 (1H, d, *J* = 1.8 Hz, ArH), 3.92 (3H, s, OCH_3), 3.83 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.6, 166.7, 163.9 (C), 160.3 (C), 159.3 (C), 158.7 (C), 132.0 (CH), 131.7 (C), 131.5 (C), 130.3 (CH), 129.6 (CH), 126.3 (CH), 109.0 (CH), 108.4 (C), 96.6 (CH), 93.3 (CH), 56.1 (CH_3), 56.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_4H$ $[M-H]^+$: 327.3081, found 327.0861.

4-(5,7-Dimethoxy-4-oxo-4H-chromen-2-yl)benzoic acid ***(45)***. Yield = 30.83%. m.p. 258 – 259 °C (MeOH); R_f = 0.17 (70% EtOAc/hexane); IR (film) 3500-3200 (br), 2922, 1709, 1638 (C=O), 1497, 1414, 1283, 1219 (C-O), 1163, 854 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (2H, d, *J* = 8.6 Hz, ArH), 8.07 (2H, d, *J* = 8.3 Hz, ArH), 6.88 (2H, m, ArH, CH=), 6.53 (1H, d, *J* = 2.2

Hz, ArH), 3.91 (3H, s, OCH_3), 3.84 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 175.6 (C=O), 166.7 (C=O), 164.0 (C), 160.3 (C), 159.2 (C), 158.5 (C), 134.8 (C), 133.0 (C), 129.8 (2 × CH), 126.1 (2 × CH), 109.5 (CH), 108.5 (C), 96.5 (CH), 93.4 (CH), 56.2 (CH_3), 56.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$: 349.0648, found 349.0683.

5,7-Dimethoxy-2-(1-methyl-1H-pyrrol-2-yl)-4H-chromen-4-one ***(46)***. Yield = 22.66%. m.p. 188 – 189 °C (MeOH); R_f = 0.22 (90% EtOAc/hexane); IR (film) 2936, 2841, 1630 (C=O), 1603, 1458, 1415, 1339, 1219 (C-O), 1159, 835 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.01 – 6.97 (1H, m, ArH), 6.87 (1H, dd, *J* = 3.2, 1.4 Hz, ArH), 6.70 (1H, d, *J* = 1.8 Hz, ArH), 6.52 (1H, d, *J* = 1.8 Hz, ArH), 6.37 (1H, s, CH=), 6.20 (1H, dd, *J* = 3.2, 2.2 Hz, ArH), 3.97 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.90 (3H, s, NCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 179.8 (C=O), 166.4 (C), 162.0 (C), 160.9 (C), 158.8 (C), 131.2 (CH), 125.2 (C), 116.2 (CH), 110.0 (CH), 109.1 (C), 107.1 (CH), 97.3 (CH), 94.1 (CH), 56.6 (2 × CH_3), 37.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{16}O_5Na$ $[M+Na]^+$: 308.2844, found 308.0896.

2-(Furan-2-yl)-5,7-dimethoxy-4H-chromen-4-one ***(47)***. Yield = 89.87%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (1H, dd, *J* = 1.7, 0.7 Hz, ArH), 7.02 (1H, dd, *J* = 3.5, 0.6 Hz, ArH), 6.58-6.56 (2H, m, ArH), 6.50 (1H, d, *J* = 2.3 Hz, ArH), 6.35 (1H, d, *J* = 2.3 Hz, ArH), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.0 (C=O), 164.0 (C), 160.9 (C), 159.4 (C), 152.7 (C), 146.2 (C), 145.3 (CH), 112.2 (C), 112.0 (C), 109.4 (C), 107.0 (CH), 96.1 (CH), 92.8 (CH), 56.4 (CH_3), 55.7 (CH_3); The NMR data were in agreement with the literature [40].

5,7-Dimethoxy-2-(thiophen-2-yl)-4H-chromen-4-one ***(48)***. Yield = 75.84%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, dd, *J* = 3.7, 1.1 Hz, ArH), 7.51 (1H, dd, *J* = 4.9, 1.0 Hz, ArH), 7.14 (1H, dd, *J* = 5.0, 3.8 Hz, ArH), 6.53 (1H, s, CH=), 6.51 (1H, d, *J* = 2.2 Hz, ArH), 6.35 (1H, d, *J* = 2.1 Hz, ArH), 3.94 (3H, s, OCH_3), 3.90 (3H, s, OCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 177.1 (C=O), 164.0 (C), 160.8 (C), 159.5 (C), 156.4 (C), 134.9 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 109.2 (C), 107.7 (CH), 96.2 (CH), 92.8 (CH), 56.4 (CH_3), 55.8 (CH_3). The NMR data were in agreement with the literature [40].

2.4 *In vitro* antifungal activity of synthesized chalcones and flavones

The antifungal activity of synthesized flavones was evaluated, using a previously described method [44]. *Rhizoctonia solani* was grown on PDA plates at 30°C for four days. Mycelial plugs were prepared using a cork borer with a 5 mm diameter and placed 20 mm away from a well containing 80 µL of 5 µg $µL^{-1}$ of chalcones (or flavones) on fresh PDA plates. Eighty µL of propiconazole (5 µg $µL^{-1}$) and DMSO were used as the positive and negative controls, respectively. All plates were incubated at 30°C for four days. The percentage of inhibition was determined using the following equation [45].

$$\text{Percentage of inhibition} = (1-(R_1/R_2)) \times 100$$

R_1 was the radius of the fungal colony on the experimental plate. R_2 was the radius of the fungal colony on the negative control plate with DMSO. Student's *t*-test was used to determine statistically significant differences ($P<0.05$).

2.5 Molecular docking

Succinate dehydrogenase (SDH) [29], which was previously used in the research and development of antifungal drugs, was employed as a target enzyme in a molecular docking simulation [30, 31]. The three-dimensional structure of the target fungal protein (PDB ID: 2FBW) was downloaded from the RCSB Protein Data Bank [46], with a resolution of 2.06 Å. This macromolecule contained the

following components: The entire structural weight was 253.55 kDa, the atom count was 19,292, and there were four unique protein chains. All hydrogen atoms were added to the protein, and all water molecules were removed using the Discovery Studio Visualizer 2017 program [47]. The 3D structure of 2-bromoflavone (**40**) was generated and optimized by DFT calculation at the M062X/6-31G(d) level of theory using the Gaussian09 D.01 program [48]. The binding mode of the antifungal inhibitor in the binding pocket of succinate dehydrogenase (SDH) was performed using the Schrödinger software suite with default settings [49], and ligand docking was performed using an OPLS force field. In order to predict the binding affinity and preeminent docked structures, the combined ligand docking, and energy-grid scores were ranked using the E model and Glide scores. Docking was performed using the Extra Precision (XP) feature of the GLIDE 5.0 module implemented in Schrodinger LLC. The visualization and analysis of protein–ligand complexes were performed using the Discovery Studio Visualizer 2017 program.

3. Results and Discussion

3.1 Synthesis of flavokawains, chalcones and flavones

All the chalcones (Figure 2) were successfully prepared using the Claisen-Schmidt reaction between xanthoxyline (**1**) and various aromatic aldehydes [33]. Flavokawains A and B, as well as chalcones **2**-**4**, and **7**-**23**, were prepared by stirring the mixture in an ethanol medium at room temperature. To avoid using a protecting group, the neat mixtures were ground to produce chalcones with the hydroxyl group (flavokawain C and chalcones **5** and **6**). Most chalcones were obtained in moderate to high yields, while some were only produced in low quantities, including those with bromo (**15**-**17**) carboxyl (**19** and **20**) and *N*-methylpyrrole (**21**) groups.

In terms of flavones (Figure 2), almost all compounds were synthesized in reasonable yields using an oxidative cyclization reaction with I_2/DMSO [38]. However, only a modest yield of the carboxyl (**45**) and nitrogen-containing flavone (**46**) was obtained. Although the cause of this is still unknown, carboxyl and nitrogen might affect the reaction. The fungicidal activity of the synthesized chalcones and flavones against *R. solani* was evaluated and is described in the following section.

3.2 Antifungal activity of synthesized flavones

Initially, we first examined the antifungal activity of flavones (**24**-**48**) containing electron donating groups, electron withdrawing groups, and heterocycles, at a concentration of 100 µg using DMSO and propiconazole as negative and positive controls, respectively. Unfortunately, most synthesized compounds showed no fungicidal properties against *R. solani*, and only 2-bromoflavone (**40**) showed a small zone of inhibition against *R. solani* (data not shown). Then we increased the concentration to 400 µg and similar trends in the results were found. Most flavones showed no activity against *R. solani* (Table 1). Only 2-bromoflavone (**40**) displayed the percentage of growth inhibition against *R. solani* at 74.88±0.91%, while propiconazole, a positive control, displayed a significantly higher growth inhibition activity at 94.03±0.73% (Figure 3).

Results from the preliminary screening showed that most flavones had no effect on *R. solani*, possibly due to insufficient concentrations of the chemicals tested. Alternatively, *R. solani* is more resistant to flavones than other fungi previously tested [12, 20-25]. Numerous studies have found that the concentrations of tested fungicides are crucial for activity. Previously, antifungal activites of oleoylsalicylate derivatives [50], pyrimethanil grafted chitosan derivatives [51], thymol derivatives [52], ergosterol peroxide [53], benzothiazole-appended bis-triazole-

based derivatives [54], and piperazine containing chalcones [55] were tested against *R. solani* and the results were found to be highly dependent on concentrations.

Furthermore, when the types and positions of substituents on ring B were compared, only *o*-bromoflavone (**40**) was active, while flavones with other groups (Me, OH, OMe, F, Cl, NO_2, COOH, and heterocycles), at the *o*-, *m*-, or *p*- positions, were inactive. This finding indicated that the type of substituents used and where they were placed influenced the antifungal activity of the synthesized flavones. The types and locations of substituents in organic compounds generally determine their fungicidal properties. Excellent examples include aromatic geranyl sulfonamide compounds [56], nopal-derived 1,3,4-thiadiazole-thiourea compounds [57], coumarin oxime esters [58], nicotinamide derivatives [59], and piperazine-containing chalcones [55]. The fungicidal activity of these chemical classes against *R. solani* was determined by the types and positions of substituents on aromatic rings.

Table 1. Antifungal activity of synthesized flavones at 400 µg against *R. solani*

Flavones	Growth Inhibition (%)*	Flavones	Growth Inhibition (%)*
24	-	**38**	-
25	-	**39**	-
26	-	**40**	74.88±0.91
27	-	**41**	-
28	-	**42**	-
29	-	**43**	-
30	-	**44**	-
31	-	**45**	-
32	-	**46**	-
33	-	**47**	-
34	-	**48**	-
35	-	DMSO	-
36	-	Propiconazole	94.03±0.73
37	-		

* Average percentage of growth inhibition at 400 µg; – inactive; ± represent the standard error of an average of three replicates

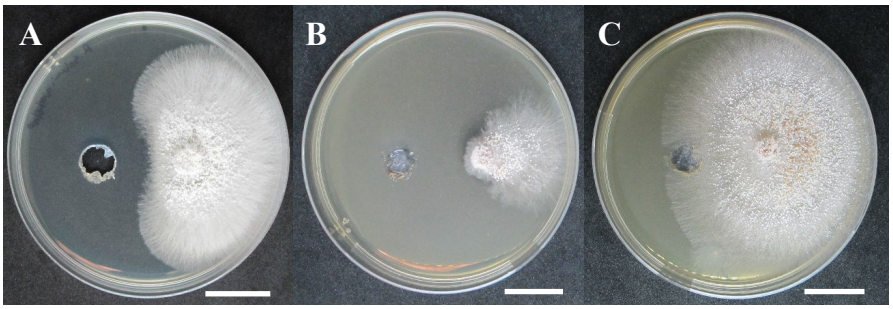

Figure 3. Antifungal activity of 400 µg of flavone **40** (A) and a positive control (propiconazole (B)) against *R. solani*. DMSO (C) was used as a negative control.

3.3 First-principles analysis

Although the mechanism of action of flavone against *R. solani* was not thoroughly investigated in this study, we did investigate the binding mode of flavone **40** on the enzyme succinate dehydrogenase (SDH). Molecular docking was performed using the Schrödinger software suite [49]. As illustrated in Figure 4, the pose between *o*-bromoflavone (**40**) and SDH reveals the interaction sites within the binding pocket to be comprised of Ile27, Trp32, Met36, Ile40, Tyr58, Trp172, Trp173, Pro169, and Ile218. From the molecular docking analysis, it can be noticed that the bromophenyl moiety (ring B) is a key molecular substructure of the compound (Figure 4), which forms Pi-Sigma interactions with Ile40 and Pi-Sulfur interactions with Met36, including Pi-Alkyl and Pi-Pi interactions with Pro169 and Trp173, respectively. Bromine also connects with Pro169 and Trp173 via a Pi-Alkyl interaction, while benzopyranone (rings A and C) interacts with Trp173 and Tyr58 via the Pi-Pi interaction. Altogether, it can be suggested that the substituent group should consist of a bromo group at the ortho position of ring B to exhibit the fungicidal activity of flavone inhibitors.

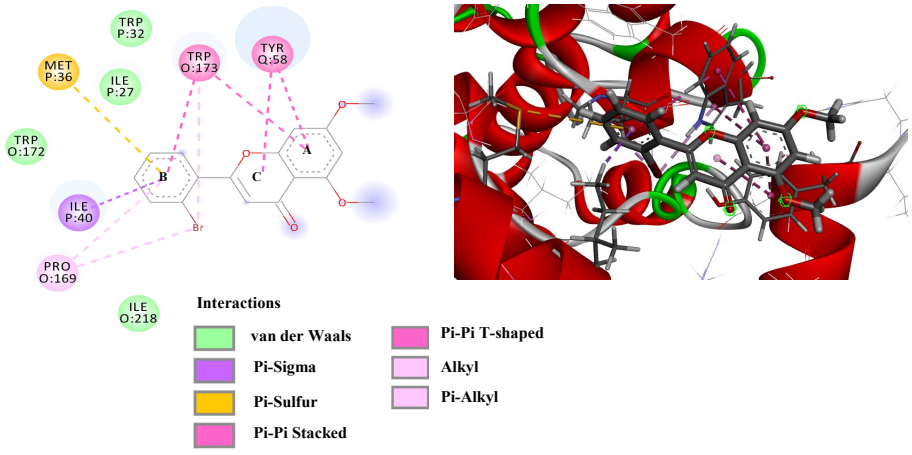

Figure 4. Representative ligand-protein interactions of *o*-bromoflavone (**40**) in the active site of succinate dehydrogenase enzyme

4. Conclusions

In summary, we successfully synthesized a variety of flavones from flavokawains A, B, and C and their chalcone analogues via an iodine-catalyzed oxidative cyclization reaction. All flavones were tested for antifungal properties against the plant pathogenic fungus, *Rhizoctonia solani*. At 400 µg, most of the chemicals did not affect the tested species. *o*-Bromoflavone (**40**) was the only flavone that could inhibit the growth of *R. solani*; however, the level of inhibition was still lower than that of propiconazole. This discovery demonstrated that the type and position of the substituent in flavones affects their anti-plant pathogenic fungal activity. The molecular docking study on the succinate dehydrogenase (SDH) enzyme revealed that the flavone fungicide bearing a bromo group in the ortho position of ring B could exhibit fungicidal activity. The information gained from this study will be used to develop anti-plant pathogenic fungal agents.

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