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Research Paper

Intramolecular Oxa-Michael Cyclization of 2'-Hydroxychalcones for the Synthesis of Flavanones: A Comparative Study

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Abstract
In this study, flavanones were synthesized using a two-step reaction process starting from 2'-hydroxyacetophenone and aldehydes. Claisen-Schmidt condensations were carried out on the starting materials to produce 2'-hydroxychalcones with mono-, di-, and tri-substituents on ring B. Subsequently, flavanones were produced via intramolecular oxa-Michael cyclization under three different reaction conditions: methanesulfonic acid in ethanol, sodium acetate in methanol, and piperidine in water. These approaches aimed to investigate the steric and electronic effects to achieve high yields in optimal reaction conditions for flavanone synthesis. Twelve 2'-hydroxychalcones (1a-1l) were successfully synthesized with yields ranging from 17% to 99%. The use of methanesulfonic acid in ethanol resulted in modest flavanone yields (11% for 2a, 13% for 2c). The synthesis of flavanones using sodium acetate was successful for seven 2'-hydroxychalcones (2a-2g), yielding products with varying yields (2-49%). Furthermore, piperidine was effective for three 2'-hydroxychalcones (1a, 1b, 1e), resulting in high flavanone yields (74-93%). These findings indicate that the three reaction conditions are only effective for certain 2'-hydroxychalcones.

Keywords
Claisen-Schmidt Condensation, Flavanones, 2'-hydroxychalcones, Oxa-Michael Cyclization

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1. INTRODUCTION

Flavanones are valuable precursor for the biosynthesis of flavonoids that have significant pharmacological properties (Geissman, 1962). The flavanone derivatives have diverse biological activities such as anti-oxidant (Hanáková et al., 2017), anti-inflammatory (Chen et al., 2017), anti-cancer (Wang et al., 2017), anti-bacterial (Pouget et al., 2002), and anti-virus (Shi et al., 2013). In addition to their therapeutic applications, flavanones are integral to the development of new bioactive compounds, thereby playing a pivotal role in the synthesis of novel pharmaceuticals and health-related products. Their adaptability in both medicinal and synthetic chemistry highlights their significance in drug discovery and development (Iwash, 2013).

These compounds are structurally characterized by the presence of two aromatic rings connected via a three-carbon unsaturated carbonyl bridge (Santos et al., 2017). Flavanones are isomeric structures of chalcones and constitute a class of natural products within the flavonoid family (Rosa et al., 2019). Flavonoid compounds are naturally found in various plant species like fig leaves (*Ficus carica* L.) (Kurniawan and Audita, 2021) and star anise (*Illicium verum* Hook. F) (Syukur et al., 2023). Preliminary characterization of flavonoid compounds can be simply performed using thin layer chromatography (TLC), which often exhibits a characteristic yellowish-red coloration (Kurniawan and Audita, 2021). The isomeric structures of chalcone and flavanone position serve chalcone as a precursor to flavanone in the synthesis and development of pharmacologically active compounds. This process involves conjugation with other heterocyclic moieties to facilitate potential drug discovery and enhance pharmaceutical applications (Kar Mahapatra et al., 2019; Raj et al., 2013; Sharma et al., 2013). Chalcones can be synthesized through various reaction procedures and strategies. Notably, the Claisen-Schmidt condensation is a prevalent method for preparing these compounds, involving the condensation of carbonyl derivatives in the presence of a base (Gomes et al., 2017).

The synthesis of flavanones has been carried out through the intramolecular oxa-Michael addition of 2'-hydroxychalcone under various conditions using acid (Keane et al., 1970), base (Nabaei-Bidhendi and Bannerjee, 1991), thermal (Macquarrie et al., 2002), photochemical (Iguchi et al., 2014), Cobalt (II) Schiff-base complexes (Maruyama et al., 1989), zeolite (Climent et al., 1995), and L-Proline (Chandrasekhar et al., 2005). Another method for conducting acid-catalyzed oxa-Michael

addition involves refluxing the chalcone in acetic acid within ethanol or another suitable solvent, in the presence of an acid catalyst such as H_3PO_4 (Sagrera and Seoane, 2005). However, the yields obtained from these reactions are frequently moderate and occasionally suboptimal (Kulkarni et al., 2012).

Furthermore, flavanones can also be synthesized from other precursors. For instance, the reaction of 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4H-1-benzopyran-4-ones with tributyl tin hydride and 2,2'-azobisisobutyronitrile results in a complex mixture (Dauzonne and Monneret, 1997). Additionally, the treatment of 3-bromo-1-phenyl prop-2-ynyl aryl ethers with mercury (II) trifluoroacetate is noteworthy, although the mechanism of this reaction remains unresolved, with uncertainty as to whether the transformations proceed via a sigma-tropic rearrangement or a simpler electrophilic cyclization (Subramanian and Balasubramanian, 1990). Furthermore, the oxidation of flavan-4-ols yields only a minimal amount of product (Bhatia et al., 1968). When 1-(2-hydroxyphenyl)-3-phenyl-propane-1,3-diones are treated with benzaldehydes, a separation process is required to remove benzoic acid, which forms as a side product (Joglekar and Samant, 1988).

Kulkarni et al. (2012) reported synthesis of flavanones through oxa-Michael addition of 2'-hydroxychalcones with mono-, di-, and tri-substituents on the B ring catalysed by methanesulfonic acid (10 mol%) under acetic acid and refluxed for 2 hours. This method resulted in a good yield of the flavonoid products. In 2001, Tanaka and Sugino reported synthesis of flavanone from 2'-hydroxychalcones with mono-substituent on the B ring in the presence of piperidine or amino acid in a water suspension at room temperature for 1 hour (Tanaka and Sugino, 2001). Zheng et al. (2013) reported synthesis of flavanones from cyclization of 2'-hydroxychalcones with mono-substituent on the B ring activated by amino acid and base at room temperature for 15 minutes to obtain the products with high yields (Jiang et al., 2011; Zheng et al., 2013). Moreover, Zheng et al. (2013) conveyed synthesis of flavanones and tetrahydroquinolones in the presence of piperidine (2.7 mol%) and KOH (18 mol%) through oxa-Michael addition of 2'-hydroxychalcones and 2'-aminochalcones at room temperature for 2 minutes. Sinyeue et al. (2022) synthesized pinocembrin analogues from 2'-hydroxychalcone derivatives catalysed by sodium acetate as a base in methanol under reflux for 24 hours to gain the products from low to good yields. However, the yields of these reactions are generally moderate and frequently result in a mixture of compounds. Separation of these compounds requires the use of substantial quantities of organic solvents.

In this study, we present the synthesis of flavanones using 2'-hydroxchalcones with mono-, di-, and tri-substituents on the B ring, with the aim of examining the steric and electronic influences during the cyclization process through intramolecular oxa-Michael addition. Furthermore, the investigation was conducted under three reaction conditions, methanesulfonic acid in ethanol, sodium acetate in methanol, and piperidine in water, to achieve a high yield and an effective methodology.

2. EXPERIMENTAL SECTION

2.1 Chemicals

The chemicals used are 2'-hydroxyacetophenone (TCI), benzaldehyde derivatives (Sigma Aldrich), concentrated HCl (Sigma Aldrich), NaOH (Emsure), methane sulfonic acid (Sigma Aldr-ich), sodium acetate (Emsure), and piperidine (Sigma Aldrich). The solvents used are ethanol (Fulltime) and methanol (Emsure). Technical solvents such as acetone, n-hexane, ethyl acetate used for extraction and chromatography are purified by distillation. All reactions are viewed through Thin Layer Chromatography (TLC) with TLC aluminum sheets using silica gel 60 F254 and visualized by exposure to UV light at 254 nm. Manual column chromatography was carried out using silica gel (Silica 60–80 Mesh) produced by Sanpoint. The solvent used in characterization using NMR is $CDCl_3$ solvent.

2.2 Instrumentation

All reactions were monitored by thin-layer chromatography (TLC) on TLC aluminum sheets with silica gel 60 F254 and visualized by exposure to UV light at 254 nm; coloured compounds of chalcone derivatives were visible on daylight. ^{1}H and ^{13}C NMR spectra were obtained using Agilent Varian DD2 500 MHz spectrometers (Agilent, USA) (^{1}H) or 125 MHz (^{13}C), respectively. The deuterated solvent, $CDCl_3$, was purchased from Sigma-Aldrich. NMR measurements were reported in parts per million (ppm) relative and the chemical shifts are denoted as δ relative to $CDCl_3$ (^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.00 ppm). The coupling constants J are given in Hertz, and the splitting parameters or spin multiplicities for ^{1}H-NMR are given as *s* (singlet), *d* (doublet), *t* (triplet), and m (multiplet). The mass spectra (MS) of the products were recorded on a Waters LCT Premier XE ESI-TOF-MS system (Waters, USA). λ_{max} (nm) were checked using spectrophotometer UV-Vis Agilent Cary60 (Agilent, USA). The melting point (mp) was measured using a Fisher–Johns apparatus.

2.3 Methods

2.3.1 Synthesis of 2′-hydroxychalcones (1a–1l)

2′-hydroxyacetophenone (3 mmol, 1 eq.), and NaOH (9 mmol, 3 equiv.) was added to a two-neck round-bottom flask, and ethanol was added as a solvent as shown in Figure 1. The reaction mixture was stirred for 10 min, and aldehyde (3 mmol, 1 eq.) was added. Detailed amounts of each reactant are listed in Table 1. The synthesis was carried out in a round-bottom flask with a magnetic stirrer at room temperature for 24 h, which was monitored using TLC. To the reaction mixture, 10% HCl was added until the pH reached 5, and a chalcone precipitate was formed. The obtained precipitate was then vacuum-filtered (Vu Nguyen et al., 2024).

2.3.2 Spectra Data of Synthesized 2′-hydroxychalcones (1a–1l)

Compound 1a yellow solid 0.114 g (17%), mp 90 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.80 (1H, s), 7.93 (2H, d, J = 15.5 Hz), 7.93 (1H, dd, J = 8.0 and 1.6 Hz), 7.67 (1H,

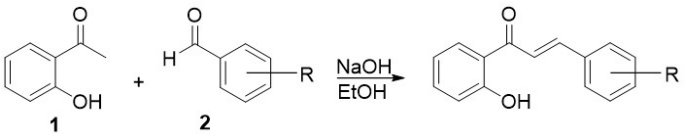


Figure 1. Claisen–Schmidt Reaction Scheme of 2′-hydroxychalcone Derivatives

d, J = 15.4 Hz), 7.67 (2H, m), 7.50 (1H, td, J = 7.5 and 1.5 Hz), 7.44 (3H, m), 7.03 (1H, dd, J = 8.4 and 1.2 Hz), 6.95 (1H, td, J = 7.6 and 7.4 Hz). δ_C 193.7; 163.5; 145.4; 136.4; 134.5; 130.9; 129.6; 129.0; 128.6; 120.0; 120.0; 118.8; 118.6. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 225.0916 for $C_{15}H_{13}O_2^+$, found 225.0903.

Compound 1b yellow solid 0.717 g (84%), mp 92 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.80 (1H, s), 8.20 (1H, d, J = 15.6 Hz), 7.92 (1H, d, J = 7.6 Hz), 7.75 (1H, d, J = 15.6 Hz), 7.49 (1H, t, J = 7.3 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 8.0 Hz), 7.03 (1H, d, J = 8.3 Hz), 7.00 (1H, d, J = 8.0 Hz), 6.94 (1H, t, J = 7.6 Hz), 3.91 (3H, s), 3.90 (3H, s). δ_C 194.1; 163.6; 153.2; 149.2; 140.4; 136.3; 129.7; 128.8; 124.2; 121.6; 120.1; 119.9; 118.8; 118.6; 114.6; 61.3; 55.9. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 285.1127 for $C_{17}H_{17}O_4^+$, found 285.1123.

Compound 1c yellow solid 0.608 g (65%), mp 130 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.82 (1H, s), 7.93 (1H, dd, J = 1.6 and 1.5 Hz), 7.85 (1H, d, J = 15.3 Hz), 7.53 (1H, d, J = 15.3 Hz), 7.03 (1H, d, J = 8.5 Hz), 6.75 (1H, t, J = 7.6 Hz), 6.89 (2H, s), 3.92 (6H, s), 3.91 (3H, s). δ_C 193.5; 163.6; 153.5; 145.6; 140.8; 136.3; 130.0; 129.6; 120.0; 119.2; 118.8; 118.6; 106.0; 61.0; 56.2. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 315.1232 for $C_{18}H_{19}O_5^+$, found 315.1222.

Compound 1d yellow solid 0.439 g (68%), mp 104 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.87 (1H, s), 7.91 (1H, dd, J = 1.5 and 7.9 Hz), 7.89 (1H, d, J = 15.5 Hz), 7.60 (1H, d, J = 15.5 Hz), 7.55 (2H, d, J = 7.8 Hz), 7.48 (1H, td, J = 1.5, 4.2, and 7.1 Hz), 7.24 (1H, d, J = 3.7 Hz), 7.01 (1H, dd, J = 1.1 and 8.4 Hz), 6.93 (1H, td, J = 1.2, 4.2, and 7.0 Hz), 2.39 (3H, s). δ_C 193.7; 163.5; 145.5; 141.6; 136.2; 131.8; 129.8; 129.6; 128.7; 120.0; 119.0; 118.8; 118.6; 21.5. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 239.1072 for $C_{16}H_{15}O_2^+$, found 239.1064.

Compound 1e yellow solid 0.900 g (99%), mp 142 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.73 (1H, s), 7.90 (1H, dd, J = 8.15 Hz), 7.85 (1H, d, J = 15.5 Hz), 7.64 (1H, d, J = 15.4 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.52 (2H, d, J = 8.4 Hz). δ_C 193.4; 163.6; 144.0; 136.5; 133.5; 132.3; 129.9; 129.6; 125.2; 120.7; 119.9; 118.9; 118.7. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 303.0021 for $C_{15}H_{12}BrO_2^+$, found 303.0008.

Compound 1f yellow solid 0.760 g (98%), mp 140 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.74 (1H, s), 7.91 (1H, dd, J = 1.6 and 8.0 Hz), 7.86 (1H, d, J = 15.4 Hz), 7.63 (1H, d, J = 15.3 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.51 (1H, td, J = 1.5 and 7.7 Hz), 7.41 (2H, d, J = 8.5 Hz), 7.03 (1H, td, J = 1.2 and 8.4 Hz), 6.95 (1H, td, J = 7.2 and 7.5 Hz). δ_C 193.5; 163.6; 143.9; 136.9; 136.5; 133.1; 129.8; 129.6; 129.3; 120.6; 119.9; 118.9; 118.7. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 257.0369 for $C_{15}H_{12}ClO_2^+$, found 257.0376.

Compound 1g yellow solid 0.228 g (27%), mp 104 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 13.00 (1H, s), 8.01 (1H, dd, J = 8.0 and 1.7 Hz), 7.97 (1H, dd, J = 15.3 Hz), 7.60 (1H, d, J = 15.4 Hz), 7.56 (1H, dd, J = 1.5 and 8.4 Hz), 7.35 (1H, dd, J = 2.0 and 8.3 Hz), 7.11 (1H, d, J = 8.4 and 9.5 Hz), 7.03 (1H, d, J = 8.2 Hz), 7.00 (1H, dd, J = 8.2 Hz), 4.05 (1H, s), 4.02 (1H, s). δ_C 193.6; 163.5; 151.8; 149.3; 145.6; 136.1; 129.5; 127.6; 123.6; 120.1; 118.7; 118.6; 117.8; 111.2; 110.3; 56.0. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 285.1127 for $C_{17}H_{17}O_4^+$, found 285.1132.

Compound 1h yellow solid 0.607 g (64%), mp 126 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 13.07 (1H, s), 8.20 (1H, d, J = 15.5 Hz), 7.91 (1H, d, J = 8.1 Hz), 7.60 (1H, d, J = 15.5 Hz), 7.45 (1H, t, J = 8.4 Hz), 7.10 (1H, s), 7.00 (1H, d, J = 8.4 Hz), 6.91 (1H, t, J = 7.1 Hz), 6.51 (1H, s), 3.94 (1H, s), 3.91 (6H, s). δ_C 194.0; 163.5; 155.1; 153.0; 143.3; 140.9; 135.8; 129.5; 120.3; 118.6; 118.5; 117.8; 115.2; 111.8; 96.7; 56.6; 56.3; 56.0. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 315.1232 for $C_{18}H_{19}O_5^+$, found 315.1222.

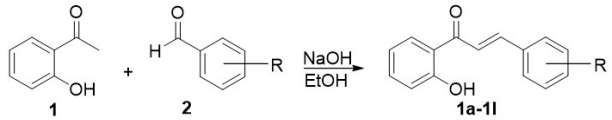
Compound 1i yellow solid 0.674 g (79%), mp 88 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.77 (1H, s), 7.85 (1H, d, J = 15.4 Hz), 7.60 (1H, dd, J = 1.6 and 8.2 Hz), 7.38 (1H, d, J = 15.4 Hz), 7.15 (1H, d, J = 15.5 Hz), 6.94 (1H, s), 6.69 (1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 15.5 Hz), 6.23 (1H, dd, J = 2.4 and 8.6 Hz), 6.17 (1H, s), 3.61 (1H, s), 3.54 (1H, s). δ_C 194.2; 163.5; 163.4; 160.7; 141.3; 135.8; 131.5; 129.5; 120.3; 118.6; 118.5; 118.1; 116.9; 105.6; 98.4; 55.6; 55.5. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 285.1127 for $C_{17}H_{17}O_4^+$, found 285.1120.

Compound 1j yellow solid 0.503 g (53%), mp 126 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 13.27 (1H, s), 8.39 (1H, d, J = 15.6 Hz), 8.02 (1H, d, J = 15.6 Hz), 7.90 (1H, dd, J = 1.6 and 8.0 Hz), 7.44 (1H, td, J = 1.6 and 7.8 Hz), 7.00 (1H, dd, J = 1.1 and 8.3 Hz), 6.91 (1H, td, J = 1.2 and 7.6 Hz), 6.14 (2H, s), 3.93 (6H, s), 3.87 (3H, s). δ_C 195.3; 163.6; 163.5; 162.0; 136.7; 135.5; 129.6; 120.6; 119.4; 118.4; 118.3; 106.5; 90.5; 55.9; 55.4. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 315.1232 for $C_{18}H_{19}O_5^+$, found 315.1230.

Compound 1k yellow solid 0.439 g (58%), mp 84 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 12.93 (1H, s), 7.91 (1H, dd, J = 1.6 and 8.1 Hz), 7.89 (1H, d, J = 15.4 Hz), 7.62 (2H, dd, J = 2.1 and 6.8 Hz), 7.53 (1H, d, J = 15.4 Hz), 7.48 (1H, td, J = 1.6, 7.1, and 8.3 Hz), 7.01 (1H, dd, J = 1.2 and 8.3 Hz), 6.94 (2H, d, J = 8.7 Hz), 6.93 (1H, td, J = 1.1 and 7.2 Hz), 3.85 (1H, s). δ_C 193.6; 163.5; 162.0; 145.3; 136.1; 130.5; 129.5; 127.3; 120.1; 118.7; 118.5; 117.6; 114.5; 55.4. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 255.1021 for $C_{16}H_{15}O_3^+$, found 255.1012.

Compound 1l violet solid 0.379 g (47%), mp 150 °C. ^{1}H-

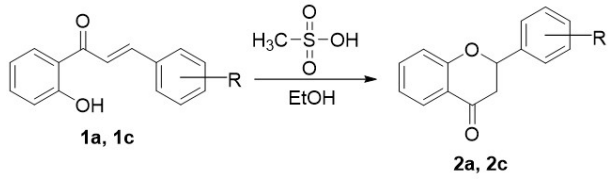
Table 1. Reaction Conditions for the Synthesis of 2'-hydroxychalcones



Compound	R	EtOH (mL)	Time (h)	Yield (%)*
1a	H	15	48	17
1b	2,3-diOMe	7.5	24	84
1c	3,4,5-triOMe	7.5	24	65
1d	4-Me	7.5	24	68
1e	4-Br	15	24	99
1f	4-Cl	15	24	98
1g	3,4-diOMe	7.5	24	27
1h	2,4,5-triOMe	7.5	24	64
1i	2,4-diOMe	7.5	24	79
1j	2,4,6-triOMe	7.5	24	53
1k	4-OMe	7.5	24	58
1l	4-N(Me)$_2$	7.5	48	74

*Isolated yields.

Table 2. Intramolecular oxa-Michael Cyclization of 2'-hydroxychalcones with Methanesulfonic Acid



Compound	R	Solvent	Temperature (°C)	Time (h)	Yield (%)*
1a	H	EtOH	80	2	**2a** (11)
1c	2,3-diOMe	EtOH	80	2	**2c** (13)

*Isolated yields.

NMR (500 MHz, $CDCl_3$): δ_H 13.18 (1H, s), 7.92 (1H, d, J = 15.1 Hz), 7.92 (1H, d, J = 1.55 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.46 (1H, dd, J = 15.2 Hz), 7.46 (1H, t, J = 1.4 Hz), 7.00 (1H, dd, J = 1.1 and 8.3 Hz), 6.92 (1H, td, J = 1.1 and 4.0 Hz), 6.70 (2H, d, J = 10.2 Hz), 3.06 (6H, s). δ_C 193.5; 163.5; 146.5; 135.6; 130.8; 129.3; 122.4; 120.4; 118.5; 118.5; 114.3; 111.8; 40.1. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 268.1338 for $C_{17}H_{18}NO_2^+$, found 268.1339.

2.3.3 Synthesis of Flavanones from 2'-hydroxychalcones (2a-2f)

- Synthesis of Flavanones using Methanesulfonic Acid

2′-hydroxychalcone derivatives (1 mmol) (1) and methanesulfonic acid (15% mmol), and a magnetic stirrer were added to a two-neck flask in a reflux system at 80 °C for 2 hours with ethanol. The reaction scheme is shown in Figure 2. The reaction was monitored by TLC, and the reaction mixture was dissolved in water (50% solvent volume) and extracted using ethyl acetate. The product (2) was evaporated and purified by radial chromatography (Kshatriya and Nazeruddin, 2014).

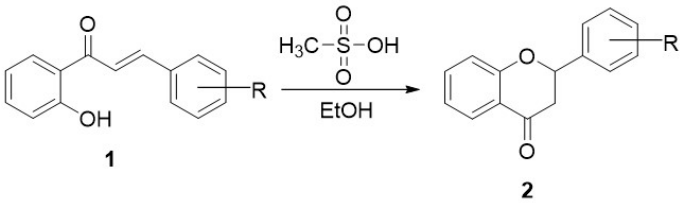
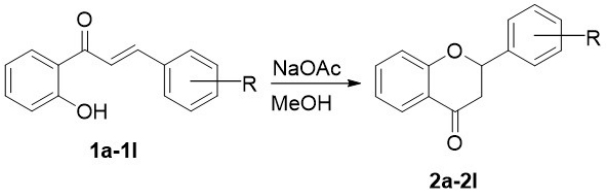


Figure 2. Reaction Scheme of Cyclization Synthesis with Methane Sulfonic Acid

- Synthesis of Flavanones using Sodium Acetate

2′-hydroxychalcones (1 mmol) (1) in ethanol (10 mL) was then added to sodium acetate and two drops of water. The mixture was heated at 60 °C for 48 hours, and water was added

Table 3. Intramolecular Oxa-Michael Cyclization of 2′-hydroxychalcones (2a–2l) with Sodium Acetate



Compound	R	Base (Equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)*
1a	H	CH_3COONa (10)	MeOH	60	48	2a (42)
1b	2,3-diOMe	CH_3COONa (10)	MeOH	60	48	2b (49)
1c	3,4,5-triOMe	CH_3COONa (10)	MeOH	60	48	2c (23)
1d	4-OMe	CH_3COONa (10)	MeOH	60	48	2d (46)
1e	4-Br	CH_3COONa (10)	MeOH	60	48	2e (36)
1f	4-Cl	CH_3COONa (10)	MeOH	60	48	2f (2)
1g	3,4-diOMe	CH_3COONa (10)	MeOH	60	48	2g (18)
1h	2,4,5-triOMe	CH_3COONa (10)	MeOH	60	48	NR
1i	2,4-diOMe	CH_3COONa (10)	MeOH	60	48	NR
1j	2,4,6-triOMe	CH_3COONa (10)	MeOH	60	48	NR
1k	4-OMe	CH_3COONa (10)	MeOH	60	48	NR
1l	4-NMe_2	CH_3COONa (10)	MeOH	60	48	NR

*Isolated yields. NR = no reaction.

and extracted with ethyl acetate. Sodium sulphate (Na_2SO_4) was added to the organic phase, followed by filtration and evaporation under reduced pressure. The product was purified by radial chromatography using an eluent mixture of *n*-hexane and ethyl acetate, applying a gradient composition from 19:1 to 9:1, yielding compound (2) as a white gel. The reaction scheme is illustrated in Figure 3 (Sinyeue et al., 2022).

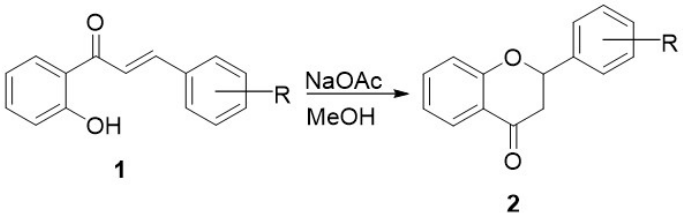


Figure 3. Reaction Scheme of Cyclization Synthesis with Sodium Acetate

- Synthesis of Flavanones using Piperidine

2′-hydroxychalcones (1 mmol) (1), piperidine, water, and a magnetic stirrer were added to a 10 mL flask and stirred at room temperature for 24 hours as presented at Figure 4. The precipitates were observed in the reaction mixture and vacuum filtered to produce a white powder. The white powder was dried in desiccator to yield the cyclization product (2) (Tanaka and Sugino, 2001).

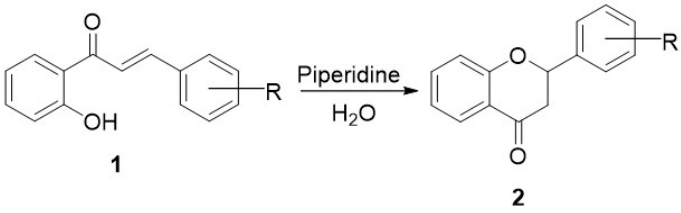


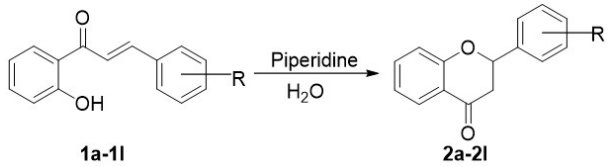
Figure 4. Reaction Scheme of Cyclization Synthesis with Piperidine

2.3.4 Spectra Data of Synthesized Flavanones (2a-2g)

Compound 2a white solid, mp 75 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.94 (1H, dd, *J*=1.8 and 8.1), 7.53–7.38 (6H, m), 7.06 (2H, m), 5.49 (1H, dd, *J*=2.9 and 13.4 Hz), 3.10 (1H, dd, *J*=13.5 and 16.9 Hz), 2.90 (1H, dd, *J*=2.8 and 16.8 Hz). δ_C 192.0; 161.5; 138.7; 136.2; 128.8; 128.8; 126.1; 121.6; 120.9; 118.1; 79.6; 44.6. HR-ESI-TOF-MS $[M+H]^+$ *m/z* calculated 225.0916 for $C_{15}H_{13}O_2^+$, found 225.0911.

Compound 2b white solid, mp 99 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.95 (1H, dd, *J*=1.7 and 7.8), 7.50 (1H, td, *J*=1.7 and 7.6 Hz), 7.20 (1H, dd, *J*=1.5 and 7.8 Hz), 7.15 (1H, t, *J*=8 Hz), 7.05 (2H, td, *J*=1.0 and 9.0 Hz), 6.95 (1H, dd, *J*=1.6 and 8 Hz), 5.83 (1H, dd, *J*=2.8 and 13.7 Hz), 3.89 (3H, s), 3.88 (3H, s), 3.04 (1H, dd, *J*=13.6 and 16.9 Hz), 2.88 (1H, dd, *J*=2.8 and 16.9 Hz). δ_C 192.3; 161.8; 152.6; 146.1; 136.0; 132.6; 127.1; 124.4; 121.5; 121.0; 118.4; 118.1; 112.6; 74.8; 61.0; 55.8; 44.0. HR-ESI-TOF-MS $[M+Na]^+$ *m/z* calculated 307.0946 for $C_{17}H_{16}O_4^+$, found 307.0945.

Table 4. Intramolecular Oxa-Michael Cyclization of 2′-hydroxychalcones (1a–1l) with Piperidine



1a-1l 2a-2l

Compound	R	Base (Equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1a	H	Piperidine (5.06)	H_2O	rt	24	2a (74)
1b	2,3-diOMe	Piperidine (5.06)	H_2O	rt	24	2b (93)
1c	3,4,5-triOMe	Piperidine (5.06)	H_2O	rt	24	NR
1d	4-Me	Piperidine (5.06)	H_2O	rt	24	NR
1e	4-Br	Piperidine (5.06)	H_2O	rt	24	2e (74)
1f	4-Cl	Piperidine (5.06)	H_2O	rt	24	2f (2)
1g	3,4-diOMe	Piperidine (5.06)	H_2O	rt	24	NR
1h	2,4,5-triOMe	Piperidine (5.06)	H_2O	rt	24	NR
1i	2,4-diOMe	Piperidine (5.06)	H_2O	rt	24	NR
1j	2,4,6-triOMe	Piperidine (5.06)	H_2O	rt	24	NR
1k	4-OMe	Piperidine (5.06)	H_2O	rt	24	NR
1l	4-$N(Me)_2$	Piperidine (5.06)	H_2O	rt	24	NR
1d	4-Me	Piperidine (5.06)	H_2O	80	24	2d (13)
1g	3,4-diOMe	Piperidine (5.06)	H_2O	80	24	NR
1h	2,4,5-triOMe	Piperidine (5.06)	H_2O	80	24	NR
1i	2,4-diOMe	Piperidine (5.06)	H_2O	80	24	NR
1j	2,4,6-triOMe	Piperidine (5.06)	H_2O	80	24	NR
1k	4-OMe	Piperidine (5.06)	H_2O	80	24	NR
1l	4-$N(Me)_2$	Piperidine (5.06)	H_2O	80	24	NR
1g	3,4-diOMe	Piperidine (10)	H_2O	80	24	NR
1h	2,4,5-triOMe	Piperidine (10)	H_2O	80	24	NR
1i	2,4-diOMe	Piperidine (10)	H_2O	80	24	NR
1j	2,4,6-triOMe	Piperidine (10)	H_2O	80	24	NR
1k	4-OMe	Piperidine (10)	H_2O	80	24	NR
1l	4-$N(Me)_2$	Piperidine (10)	H_2O	80	24	NR

*Isolated yields. NR = no reaction.

Compound 2c white solid, mp 128 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.94 (1H, dd, J=1.8 and 8.2), 7.52 (1H, t, J=1.2 Hz), 6.70 (2H, d, J=0.2 Hz), 5.41 (1H, dd, J=2.9 and 13.4 Hz), 3.10 (1H, dd, J=13.4 and 16.8 Hz), 2.89 (1H, dd, J=2.8 and 16.8 Hz). δ_C 191.9; 161.4; 153.5; 138.3; 136.2; 134.3; 127.0; 121.7; 120.9; 118.1; 103.3; 79.8; 60.8; 56.3; 56.2; 44.8; 29.7. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 315.1232 for $C_{18}H_{19}O_5^+$, found 315.1223.

Compound 2d white solid, mp 98 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.92 (1H, dd, J=1.7 and 8.1), 7.48 (1H, td, J=1.8 and 9.2 Hz), 7.36 (2H, d, J=8.1 Hz), 7.23 (2H, d, J=7.8 Hz), 7.03 (2H, m), 5.42 (1H, dd, J=2.8 and 13.3 Hz), 3.07 (1H, dd, J=13.3 and 16.8 Hz), 2.85 (1H, dd, J=2.8 and 16.8 Hz), 2.37 (3H, s). δ_C 192.3; 161.8; 152.6; 146.1; 136.0; 132.6; 127.1; 124.4; 121.5; 121.0; 118.4; 118.1; 112.6; 74.8; 61.0; 55.8; 44.0. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 239.1072 for $C_{16}H_{15}O_2^+$, found 239.1060.

Compound 2e white solid, mp 120 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.93 (1H, dd, J = 1.8 and 7.8 Hz), 7.58–7.55 (2H, m), 7.52 (1H, td, J = 1.8 and 7.8 Hz), 7.36 (2H, dt, J = 3.6 and 8.7 Hz), 7.08–7.04 (2H, m), 5.45 (1H, dd, J = 6.0 and 13.1 Hz), 3.04 (1H, dd, J = 13.1 and 16.8 Hz), 2.88 (1H, dd, J = 3.0 and 16.8 Hz). δ_C 191.4, 161.2, 137.8, 136.3, 132.0, 127.8, 127.1, 122.7, 121.8, 120.9, 118.1, 78.8, 44.5. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 303.0021 for $C_{15}H_{12}BrO_2^+$, found 303.0023.

Compound 2f white solid, mp 135 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.93 (1H, dd, J = 1.7 and 7.9 Hz), 7.52 (1H, td, J = 1.8 and 7.8 Hz), 7.44–7.40 (4H, m), 7.06 (2H, dd, J = 7.5 and 12.6 Hz), 5.47 (1H, dd, J = 2.9 and 13.2 Hz), 3.04 (1H, dd, J = 13.3 and 16.8 Hz), 2.88 (1H, dd, J = 2.9 and 16.8 Hz). δ_C 191.5, 1651.3, 137.2, 136.4, 136.3, 134.5, 130.6, 129.0, 128.5, 127.5, 127.1, 121.8, 120.8, 118.1, 78.8, 44.6. HR-ESI-TOF-MS $[M+Na]^+$ m/z calculated 281.0345 for $C_{15}H_{11}ClNaO_2^+$, found 281.0344.

Compound 2g white solid, mp 123 °C. ^{1}H-NMR (500

MHz, $CDCl_3$): δ_H 7.93 (1H, dd, J = 1.8 and 8.0 Hz), 7.51 (1H, td, J = 1.8 and 7.6 Hz), 7.02 (4H, m), 6.91 (1H, d, J = 8 Hz), 5.43 (1H, dd, J = 2.8 and 13.4 Hz), 3.90 (6H, d, J = 9.9 Hz), 3.12 (1H, dd, J = 13.3 and 16.8 Hz), 2.88 (1H, dd, J = 2.8 and 16.9 Hz). δ_C 192.1, 161.5, 149.4, 149.2, 136.2, 131.1, 127.0, 121.6, 120.9, 118.8, 118.1, 111.0, 109.3, 79.5, 77.2, 77.0, 76.7, 55.9, 55.9, 44.6. HR-ESI-TOF-MS $[M+H]^+$ m/z calculated 307.0946 for $C_{17}H_{17}NaO_4^+$, found 307.0934.

3. RESULTS AND DISCUSSION

3.1 Synthesis of 2'-hydoxychalcones

Twelve compounds (1a-1l) were obtained for the synthesis of chalcone derivatives using an equimolar mixture (1 mmol) of 2'-hydroxyacetophenone (1) and various aldehydes (2). The reactions were performed in ethanol at room temperature in the presence of NaOH (Table 1).

The confirmations of 2'-hydroxychalcones were shown by the ^{1}H-NMR spectra of the α, β-unsaturated ketone displayed olefinic proton signals at δ_H 7.85–8.39 and 7.60–8.02 ppm, with coupling constants of approximately 15 Hz, corresponding to C_α-H and C_β-H, respectively. The high coupling constant suggests a trans configuration of the protons. Additionally, the presence of hydrogen bonding shifts the bonded proton further downfield, resulting in a singlet at δ_H 12.73–13.07 ppm, belonging to the *O*-hydroxy group, where intramolecular hydrogen bonds with the carbonyl oxygen.

The yields of chalcone synthesis vary depending on the substituents used on ring B, whether electron-donating groups (EDG) or electron-withdrawing groups (EWG), and the position of the substituent. In this study, several different substituents were used on ring B to produce various % yields ranging from 17–99%. Table 1 presents the data in the form of reaction product results with various types of substituents on ring B with different solvent volumes and reaction times for each chalcone derivative.

A key factor in aldol condensation in our study was the electrophilicity of the carbonyl carbon on the aldehydes. The variation of substituents on aldehydes shows their electronic and steric effects on the reactivity of the aldehydes. Here, we show that halogen substituents at the *para* positions gave very high yields (~ 99%), that is, compounds 1e and 1f, which are −Br and −Cl substituents. The presence of EWG, such as −Br and −Cl, enhances the electrophilicity of the carbonyl carbon in the aldehyde, making it more susceptible to nucleophilic attack by the enolate formed from 2′-hydroxyacetophenone. This increased reactivity generally leads to a higher yield of chalcone products.

The other chalcone derivatives in this study were aldehydes with a methoxy group ($-OCH_3$) substitution. It produced a better yield than the reaction without substitution on ring B. This reaction produced ranging from 27–84% yield. The $-OCH_3$ substituent provides increased electron density to the ring B and the polarization of the carbonyl group during nucleophilic attack by Donaire-Arias et al. (2023).

The highest yield with a methoxy substituent was observed for compound 1b, which possessed two methoxy groups at positions 2′ and 3′. The worked-up step of this reaction readily formed precipitates after the addition of 10% HCl. The methoxy group at the *ortho* position, due to its resonance effect, enhances the reactivity of the carbonyl through resonance, increasing its electrophilicity, promoting enolate attack, and allowing the reaction to proceed. On the other hand, the 1g product showed the lowest yield of chalcone derivatives with methoxy substitution at the 3′ position. The work-up step of this reaction did not produce a precipitate after the addition of 10% HCl. This step was followed by liquid-liquid extraction using ethyl acetate. In addition, this reaction requires a recrystallization purification process to remove impurities. The presence of impurities suggests that there is a side reaction of trace that causes a low yield.

The lowest yield of the synthesized compound was observed for compound 1a, with no substituent on the B ring. This reaction required more solvent than the rest (15 mL ethanol) for 48 hours. The reaction also showed the presence of impurities, which were considered to reduce the yield of the product. The reaction of 2′-hydroxyacetophenone with benzaldehyde, which does not have a substituent, is less active. The resonance of benzaldehyde itself makes the carbonyl carbon less electrophile, and unlike the other benzaldehydes with substituents, there is no EWG to increase electrophilicity. As a result, the reaction takes a longer time and yields a lower yield.

3.2 Synthesis of Flavanones

The intramolecular oxa-Michael addition of 2′-hydroxychalcones to form flavanones was conducted under three different conditions. The first method involved acidic conditions using methanesulfonic acid in ethanol, whereas the second and third methods involved basic conditions using sodium acetate in methanol and piperidine in water. Twelve 2′-hydroxychalcones (1a–1l) prepared from the previous reactions were further studied to produce flavanones (2a–2l) under three reaction conditions. The best method was indicated by the high yield obtained from the cyclization process.

The intramolecular oxa-Michael addition of 2′-hydroxychalcones was confirmed by the ^{1}H-NMR spectra of the cyclization skeleton, which showed three new proton signals at approximately 3–5 ppm and the disappearance of olefin hydrogen at approximately 7–8 ppm. The formation of the pyran ring was confirmed by the value of the coupling constant of the new proton signals at approximately 3–5 Hz that suggests the presence of axial-equatorial coupling, 12 Hz, which indicates axial-axial coupling and 12–17 Hz for geminal coupling. This was also confirmed by the loss of the OH group signal on ring A at 12 ppm.

Intramolecular oxa-Michael addition with methanesulfonic acid under acidic conditions was performed on chalcones 1a and 1c. These cyclized products were obtained in 11% yield from 1a to produce 2a and 13% from 1c to 2c as presented in Table 2. This method was conducted based on the experi-

mental procedures by Kshatriya and Nazeruddin (2014). This acid was chosen because it is less corrosive and toxic than other mineral acids (Kulkarni, 2015). However, this method cannot be considered effective due to its low yield. The acid was expected to activate these reactions by protonating the carbonyl (Kulkarni, 2015).

A series of oxa-Michael addition reactions of 2′-hydroxychalcone derivatives were carried out under sodium acetate in methanol at 60 °C for 48 hours. This process was perfomed on twelve chalcone derivatives (1a–1k). This method showed an improvement over the previous method using metahane sulfonic acid by obtaining compounds 2a and 2c in 42% and 23% yields, respectively. Compound 2b was obtained in 49% yield with two methoxy groups at positions 2 and 3 on the B ring. Despite the improvement in yield, the method continues to produce a low yield and does not react with other substituents. Consequently, we have developed an alternative method to achieve better yields. Table 3 presents the results of the cyclization of 2′-hydroxychalcone to form flavanones in various derivatives of 2′-hydroxychalcone compounds.

The next method of Intramolecular oxa-Michael addition of 2′-hydroxychalcone derivatives was carried out using five equivalents of piperidine base in water as the solvent. This reaction is relatively straightforward because the products precipitate and are filtered. This method was reported as a good synthesis method because it minimize waste, simpler operation, and easier product work-up (Tanaka and Sugino, 2001). This method was carried out on all chalcone derivatives. The reaction at room temperature generated four compounds: 2a (74%), 2b (93%), 2e (74%), and 2f (2%). This method was optimized by increasing the temperature to 80 °C. One product was obtained (2d) in 13% yield. However, there was a purification step for compound 2d because the starting material still remained up to 24 hours. This results in a relatively low yield. There are six chalcones (1g–1j) that have not been able to produce cyclization products even when the reactions were carried out in 80 °C and higher equivalents of piperidine (10 eq.).

The yields summarized in Table 4 indicate that steric factors play a more important role than electronic effects. This is shown by the different results of similar substituents on ring B. For example, compound 2b has the highest yield at 93%, whereas other substrates that also contain methoxy groups failed to give a decent yield (2c, yield: 23%) or even cyclization products (2g–2k). Another high yield was also obtained from 2e, which contained bromide and gave a yield of 74%. This shows that the electronic properties of either methoxy (EDG) or halide (EWG) groups do not have a significant effect.

Steric factors may result in differences in the reactivity. The reaction depends on how easily nucleophilic phenolate can attack the alkene. The attack may be hindered in the presence of bulky methoxy groups. This might explain the presence of 2g–2k, which have multiple methoxy groups. The hindrance of the nucleophilic attack might have resulted from the rotation of the phenyl group. The greater the number of methoxy groups attached, the greater is the hindrance.

We demonstrate that 2′-hydroxychalcone bearing mono-, di-, and tri-substituents on the B-ring can be cyclized using sodium acetate. From the three methods employed, this method is the most compatible with many substituents. However, both the methanesulfonic acid and sodium acetate methods resulted in suboptimal yields and required additional purification steps. In contrast, cyclization with piperidine proved highly efficient, producing compounds 2a, 2b, and 2e in high yields without the need for further purification. Optimizing the use of piperidine in the synthesis of 2′-hydroxychalcone derivatives offers a promising direction for future research. Systematic exploration of derivatives with various functional groups is essential to define the effectivity toward a more comprehensive range of substrates.

4. CONCLUSIONS

Twelve synthesized 2'-hydroxychalcones (1a-1l) were successfully obtained via Claisen-Schmidt condensation, with yields ranging from 17% to 99%. Utilizing methanesulfonic acid in ethanol, two flavanones (2a, 2c) were produced with low yields of 11% and 13%, respectively. Employing sodium acetate in methanol, seven flavanones (2a-2g) were successfully synthesized, with yields ranging from low to moderate (2-49%). Additionally, four flavanones were obtained using piperidine in water at room temperature, with yields of 74% for 2a and 2e, 93% for 2b, and 2% for 2f. Consequently, piperidine in water demonstrated mild conditions for activating intramolecular oxa-Michael cyclization of 2'-hydroxychalcones for flavanone synthesis, although this method was effective in achieving high yields for only three chalcones (1a, 1b, and 1e) among the twelve chalcones. In summary, we can show that the synthesis of flavanone can be carried out effectively with piperidine and water as solvent as one alternative in flavanone synthesis in mild condition. Further development of this method is necessary to optimize conditions and ensure applicability for flavanone synthesis with 2'-hydroxychalcones possessing diverse functional groups in aqueous suspension.

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REFERENCES

Bhatia, V. K., H. G. Krishnamurty, R. Madhay, and T. R. Seshadri (1968). Oxidation of Flavan Derivatives. *Tetrahedron Letters*, **9**(35); 3859–3862

Chandrasekhar, S., K. Vijeender, and K. V. Reddy (2005). New Synthesis of Flavanones Catalyzed by L-Proline. *Tetrahedron Letters*, **46**(41); 6991–6993

Chen, P., Y. Cao, B. Bao, L. Zhang, and A. Ding (2017). Antioxidant Capacity of *Typha angustifolia* Extracts and Two Active Flavonoids. *Pharmaceutical Biology*, **55**(1); 1283–1288

Climent, M. J., A. Corma, S. Iborra, and J. Primo (1995). Base Catalysis for Fine Chemicals Production: Claisen-Schmidt Condensation on Zeolites and Hydrotalcites for the Production of Chalcones and Flavanones of Pharmaceutical Interest. *Journal of Catalysis*, **151**(1); 60–66

Dauzonne, D. and C. Monneret (1997). A New Synthesis of Flavanones. *Synthesis*, **1997**(11); 1305–1308

Donaire-Arias, A., M. L. Poulsen, J. Ramón-Costa, A. M. Montagut, R. Estrada-Tejedor, and J. I. Borrell (2023). Synthesis of Chalcones: An Improved High-Yield and Substituent-Independent Protocol for an Old Structure. *Molecules*, **28**(22); 7576

Geissman, T. A. (1962). *The Chemistry of Flavonoid Compounds*. Pergamon Press

Gomes, M., E. Muratov, M. Pereira, J. Peixoto, L. Rosseto, P. Cravo, C. Andrade, and B. Neves (2017). Chalcone Derivatives: Promising Starting Points for Drug Design. *Molecules*, **22**(8); 1210

Hanáková, Z., J. Hošek, Z. Kutil, V. Temml, P. Landa, T. Vaněk, D. Schuster, S. Dall'Acqua, J. Cvačka, O. Polanský, and K. Šmejkal (2017). Anti-Inflammatory Activity of Natural Geranylated Flavonoids: Cyclooxygenase and Lipoxygenase Inhibitory Properties and Proteomic Analysis. *Journal of Natural Products*, **80**(4); 999–1006

Iguchi, D., R. Erra-Balsells, and S. M. Bonesi (2014). Expeditious Photochemical Reaction Toward the Preparation of Substituted Chroman-4-ones. *Tetrahedron Letters*, **55**(33); 4653–4656

Iwash, T. (2013). Flavonoid Properties of Five Families Newly Incorporated into the Order Caryophyllales (Review). *Bull Natl Mus Nat Sci*, **39**; 25–51

Jiang, H., X. Zheng, Z. Yin, and J. Xie (2011). An Efficient Catalytic Synthesis of Flavanones Under Green Conditions. *Journal of Chemical Research*, **35**(4); 220–221

Joglekar, S. J. and S. D. Samant (1988). Abnormal Base Catalysed Reaction of Formaldehyde and Benzaldehydes with 1-(2-hydroxyphenyl)-3-phenyl-1, 3-propanedione. *Tetrahedron Letters*, **29**(2); 241–244

Kar Mahapatra, D., V. Asati, and S. K. Bharti (2019). An Updated Patent Review of Therapeutic Applications of Chalcone Derivatives (2014-Present). *Expert Opinion on Therapeutic Patents*, **29**(5); 385–406

Keane, D. D., K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons, and P. C. Teague (1970). Configuration and Conformation of 3-arylideneflavanones. *The Journal of Organic Chemistry*, **35**(7); 2286–2290

Kshatriya, R. B. and G. M. Nazeruddin (2014). Synthesis of Flavanones Using Methane Sulphonic Acid as a Green Catalyst and Comparision Under Different Conditions. *Oriental Journal of Chemistry*, **30**(2); 857–862

Kulkarni, P. (2015). Methane Sulphonic Acid Is Green Catalyst in Organic Synthesis. *Oriental Journal of Chemistry*, **31**(1); 447–451

Kulkarni, P., P. Wagh, and P. Zubaidha (2012). An Improved and Eco-Friendly Method for the Synthesis of Flavanone by the Cyclization of 2'-Hydroxy Chalcone Using Methane Sulphonic Acid as Catalyst. *Chemistry Journal*, **2**(3); 106–101

Kurniawan, M. F. and M. Audita (2021). Formulation, Evaluation of Physical Properties, Anti-Cholesterol Activity From *Ficus carica* L. Leaves Extract Tablet. *Science and Technology Indonesia*, **6**(4); 285–295

Macquarrie, D. J., R. Nazih, and S. Sebti (2002). KF/Natural Phosphate As an Efficient Catalyst for Synthesis of 2'-hydroxychalcones and Flavanones. *Green Chemistry*, **4**(1); 56–59

Maruyama, K., K. Tamanaka, A. Nishinaga, A. Inada, and T. Nakanishi (1989). Conversion of 2'-hydroxychalcones to Flavanones Catalyzed by Cobalt Schiff Base Complex. *Tetrahedron Letters*, **30**(31); 4145–4148

Nabaei-Bidhendi, G. and N. R. Bannerjee (1991). ChemInform Abstract: Convenient Synthesis of Polyhydroxy Flavonoids. *ChemInform*, **22**(29); 172

Pouget, C., C. Fagnere, J.-P. Basly, G. Habrioux, and A.-J. Chulia (2002). New Aromatase Inhibitors Synthesis and Inhibitory Activity of Pyridinyl-Substituted Flavanone Derivatives. *Bioorganic & Medicinal Chemistry Letters*, **12**(7); 1059–1061

Raj, C. G. D., B. K. Sarojini, S. Hegde, S. Sreenivasa, Y. S. Ravikumar, V. Bhanuprakash, Y. Revanaiah, and R. Ragavendra (2013). In Vitro Biological Activities of New Heterocyclic Chalcone Derivatives. *Medicinal Chemistry Research*, **22**(5); 2079–2087

Rosa, G. P., A. M. L. Seca, M. d. C. Barreto, A. M. S. Silva, and D. C. G. A. Pinto (2019). Chalcones and Flavanones Bearing Hydroxyl and/or Methoxyl Groups: Synthesis and Biological Assessments. *Applied Sciences*, **9**(14); 2846

Sagrera, G. J. and G. A. Seoane (2005). Microwave Accelerated Solvent-Free Synthesis of Flavanones. *Journal of the Brazilian Chemical Society*, **16**(4); 851–856

Santos, E. L., B. H. L. N. S. Maia, A. P. Ferriani, and S. D. Teixeira (2017). Flavonoids: Classification, Biosynthesis and Chemical Ecology. In *Flavonoids - From Biosynthesis to Human Health*. InTech

Sharma, P., S. Kumar, F. Ali, S. Anthal, V. K. Gupta, I. A. Khan, S. Singh, P. L. Sangwan, K. A. Suri, B. D. Gupta, D. K. Gupta, P. Dutt, R. A. Vishwakarma, and N. K. Satti (2013). Synthesis and Biologic Activities of Some Novel Heterocyclic Chalcone Derivatives. *Medicinal Chemistry Research*, **22**(8); 3969–3983

Shi, L.-P., K.-M. Jiang, J.-J. Jiang, Y. Jin, Y.-H. Tao, K. Li, X.-H. Wang, and J. Lin (2013). Synthesis and Antimicrobial Activity of Polyhalobenzonitrile Quinazolin-4(3H)-one Derivatives. *Bioorganic & Medicinal Chemistry Letters*, **23**(21); 5958–5963

Sinyeue, C., M. Matsui, M. Oelgemöller, F. Bregier, V. Chaleix, V. Sol, and N. Lebouvier (2022). Synthesis and Investigation of Flavanone Derivatives as Potential New Anti-

Inflammatory Agents. *Molecules*, **27**(6); 1781

Subramanian, R. S. and K. K. Balasubramanian (1990). Mercury(II)trifluoroacetate-mediated Transformation of 3-bromo-1-phenylprop-2-ynyl aryl ethers; A Novel Synthesis of Flavanones. *Journal of the Chemical Society, Chemical Communications*, **21**; 1469

Syukur, M., M. S. Prahasiwi, N. Nurkhasanah, S. Yuliani, Y. Purwaningsih, and E. Indriyanti (2023). Profiling of Active Compounds of Extract Ethanol, n-Hexane, Ethyl Acetate and Fraction Ethanol of Star Anise (*Illicium verum* Hook. f.) and Determination of Total Flavonoids, Total Phenolics and Their Potential as Antioxidants. *Science and Technology Indonesia*, **8**(2); 219–226

Tanaka, K. and T. Sugino (2001). Efficient Conversion of 2'-hydroxychalcones into Flavanones and Flavanols in a Water Suspension Medium. *Green Chemistry*, **3**(3); 133–134

Vu Nguyen, D., C. Muanprasat, S. Kaewin, K. Hengphasatporn, Y. Shigeta, T. Rungrotmongkol, and W. Chavasiri (2024). Synthesis and Biological Evaluation of 2'-hydroxychalcone Derivatives as AMPK Activators. *Bioorganic Chemistry*, **143**; 107048

Wang, G., J.-J. Wang, R. Guan, L. Du, J. Gao, and X.-L. Fu (2017). Strategies to Target Glucose Metabolism in Tumor Microenvironment on Cancer by Flavonoids. *Nutrition and Cancer*, **69**(4); 534–554

Zheng, X., H. Jiang, J. Xie, Z. Yin, and H. Zhang (2013). Highly Efficient and Green Synthesis of Flavanones and Tetrahydroquinolones. *Synthetic Communications*, **43**(7); 1023–1029

