

Article

Studies on the Aqueous Synthesis of Chalcones

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Abstract

In this study, an alternative methodology for the aqueous synthesis of chalcones is presented. This procedure is performed on a green basis at room temperature (25–40 °C) and using KOH. From this method, thirty-seven derivatives were obtained with yields of up to 98%. In addition, many compounds were recovered sufficiently pure by direct filtration and washing with water. The manuscript is accompanied by a study that demonstrates that the yield of the products and the reaction mechanism, which occurs on-water and in-water, are directly affected by the solubility and physical state of the starting materials.

Keywords: aqueous synthesis of chalcones; green synthesis of organic compounds; sustainable chemistry; flavonoids; Claisen–Schmidt condensation

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1. Introduction

Chalcones can be classified as flavonoids, a diverse group of secondary metabolites derived from plants that exhibit significant biological activities [1,2]. They function as intermediary metabolic products in the synthesis of various flavonoids, including flavanones, flavones, and flavanols, among others [3]. Additionally, these compounds are present in different plant tissues, where they fulfill critical functions, for example, pigmentation, attraction or repulsion of insects, antifeedants, allelochemicals, and UV light protectors [4,5].

Chalcones have an interesting pharmacological profile, which gives them a high probability of becoming therapeutic agents [6,7]. The α,β -unsaturated carbonyl system present in chalcones makes them electrophilic, so, like in nature, chalcones are important

intermediaries for the synthesis of more complex molecules [8–14]. Numerous reports illustrate the pharmacological properties of chalcones in the literature, including antioxidants [15,16], anti-inflammatory [17], antiallergic [18,19], anticancer [14,20,21], antimicrobial [22,23], and antidiabetic [24], to mention a few. This versatility confers upon the chalcone framework the privileged structure denomination and underscores the necessity for the continuous development of new synthetic methodologies for its production [25–29]. Some examples of chalcones with important biological properties are shown in Figure 1. Licochalcone A and morachalcone A are natural chalcones obtained from plants, while compounds **1Ae** and **1Ge** are synthetic products synthesized using the methodology outlined here. Compound **1Ae** exhibits important antiproliferative properties; for example, it is active against human A549 cells (lung cancer) [30], against human HCT116 cells (colon cancer), and against CAL51 cells (breast cancer) [31]. Compound **1Ge** exhibits anti-inflammatory activity [32].

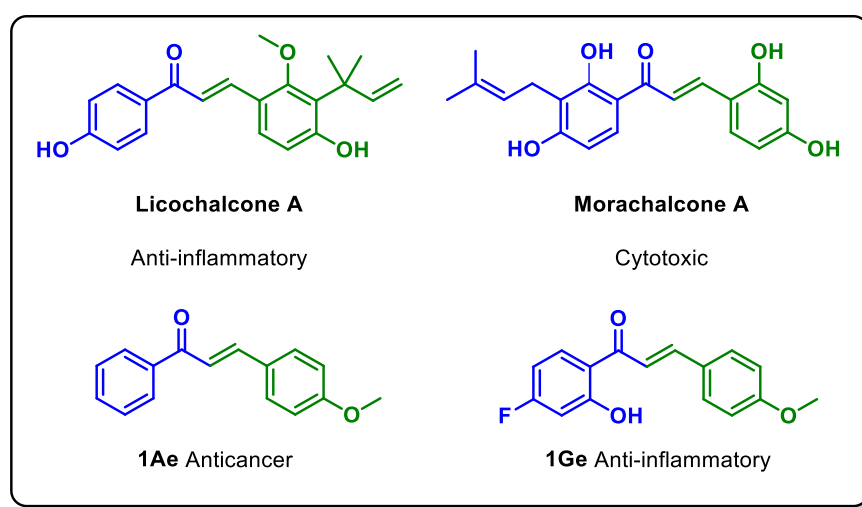


Figure 1. Chalcones with biological activity. Anti-inflammatory [7,32,33], cytotoxic [34], and anticancer [30,31].

Conventional methodologies employed for the synthesis of organic substances and active pharmaceutical ingredients (APIs) generate a substantial volume of waste and necessitate substantial energy consumption. A significant proportion of these methodologies are corrosive and hazardous [10,28,35]. This is not unexpected, as they were developed during a period that did not prioritize environmental considerations. Contemporary methods in organic synthesis are striving to adhere to the principles of sustainability and green chemistry, recognizing the imperative to safeguard our environment and natural resources. Consequently, traditional methodologies are being superseded by more sustainable alternatives. Among the greener alternatives available that have been explored for the synthesis of chalcones are solvent-free reactions, microwave-assisted synthesis [36], ultrasound-assisted synthesis, mechanochemical methods [37], and the use of environmentally benign catalysts [38–40]. These methodologies can often reduce reaction times, energy consumption, and waste generation while maintaining or improving product yields. Conversely, the methodology presented herein uses water as the dispersion medium, or solvent, operates at a temperature range of 25–40 °C, and does not necessitate specialized equipment, specific catalysts, or additives, solely requiring potassium hydroxide, a green base [41].

2. Materials and Methods

The melting points were determined using a Fisher–Jones apparatus (Thermo Fisher Scientific, Waltham, MA, USA) and are not corrected. ^1H -NMR, ^{13}C , and DEPTQ spectra were recorded at 25 °C on a Bruker Ascend™ 600 MHz (^1H NMR and 150 MHz DEPTQ, ^{13}C) (Bruker, Billerica, MA, USA). Chemical shifts are expressed as δ (ppm) values relative to TMS, an internal standard, and coupling constant (J) values are given in Hertz. The majority of spectra were recorded in CDCl_3 . Multiplicities are described as s (singlet), d (doublet), dd (doublet double), dt (triplet double), t (triplet), q (quartet), or m (multiplet). All reagents were obtained from Sigma-Aldrich (Sigma-Aldrich, Burlington, MA, USA). Mass spectra were recorded on a JEOL JMS-700 MStation at a voltage of 70 eV (JEOL Ltd, Akishima, Tokyo, Japan). FTIR spectra were recorded on a Thermo Scientific Nicolet iS 50 Fourier Transform Infrared Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). The chromatography solvents were of technical grade, and they were purified and distilled prior to use.

Synthetic Procedure. Into a glass vial of 5 mL, water (either bottled water or distilled water, 1 mL), the corresponding acetophenone (0.5 mmol), the corresponding benzaldehyde (0.5 mmol), and potassium hydroxide (1N solution, 1 mmol, 1 mL) were introduced. The vial cap was placed, and the mixture was stirred at a rate of 850 r.p.m. for 48 h at a temperature range of 25–40 °C. The progression of the reaction was monitored by TLC. The solid obtained was filtered, washed with water (either bottled water or distilled water, 2 $\times$ 1 mL) and allowed to dry overnight at room temperature. Finally, the solid was introduced into a desiccator for a period of two days.

(*E*)-1-phenyl-3-(phenyl)prop-2-en-1-one (1Aa). This compound was obtained pure enough after filtration to afford white crystals (91.6 mg, 88%), m.p. 56–58 °C (lit. 56–57 °C) [21]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 8.02 (d, 2H, J = 7.3 Hz), 7.81 (d, 1H, J = 15.7 Hz), 7.67–7.63 (m, 2H), 7.59 (t, 1H, J = 7.4 Hz), 7.53 (d, 1H, J = 15.7 Hz), 7.51 (t, 2H, J = 7.6 Hz), 7.44–7.40 (m, 3H). DEPTQ (150 MHz, CDCl_3), δ (ppm) 190.8, 145.0, 138.5, 135.1, 132.9, 130.7, 129.1, 128.8, 128.7, 128.6, 122.4.

(*E*)-3-(3-fluorophenyl)-1-phenylprop-2-en-1-one (1Ab). This compound was obtained pure enough after filtration to afford yellow crystals (91.5 mg, 81%), m.p. 47–49 °C (lit. 48 °C) [36]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 8.03 (d, 2H, J = 8.5 Hz), 7.91 (d, 2H, J = 15.9 Hz), 7.66 (d, 1H, J = 15.9 Hz), 7.66 (s, 1H), 7.60 (t, 1H, J = 7.3 Hz), 7.52 (t, 2H, J = 7.6 Hz), 7.42–7.37 (m, 1H), 7.21 (t, 1H, J = 7.6 Hz), 7.17–7.11 (m, 1H). DEPTQ (150 MHz, CDCl_3), δ (ppm): 190.4, 164.1, 143.4, 138.2, 137.4, 133.1, 130.7, 129.1, 128.9, 128.8, 124.7, 123.5, 117.6, 114.7.

(*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (1Ac). This compound was obtained pure enough after filtration to afford white crystals (99.4 mg, 88%), m.p. 81–83 °C (lit. 79 °C) [36]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 8.01 (d, 2H, J = 8.5 Hz), 7.77 (d, 1H, J = 15.7 Hz), 7.64 (dd, 2H, J = 8.6, 5.4 Hz), 7.59 (t, 1H, J = 7.4 Hz), 7.51 (t, 2H, J = 7.6 Hz), 7.45 (d, 1H, J = 15.7 Hz), 7.11 (t, 2H, J = 8.6 Hz). DEPTQ (150 MHz, CDCl_3), δ (ppm): 190.5, 165.1, 143.7, 138.3, 133.0, 131.4, 130.5, 129.1, 128.8, 122.1, 116.4.

(*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (1Ad). This compound was obtained pure enough after filtration to afford yellow crystals (103.8 mg, 82%), m.p. 156–158 °C (lit. 157–159 °C) [42]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 8.28 (d, 2H, J = 8.8 Hz), 8.03 (d, 2H, J = 8.5 Hz), 7.82 (d, 1H, J = 15.8 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.64 (d, 1H, J = 15.7 Hz), 7.63 (t, 1H, J = 8.5 Hz), 7.54 (t, 2H, J = 7.7 Hz). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 189.6, 148.5, 141.5, 140.0, 133.3, 130.4, 128.9, 128.8, 125.7, 124.3, 124.2.

(*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (1Ae). This compound was obtained pure enough after filtration to afford white crystals (93 mg, 78%), m.p. 73–75 °C (lit. 77–78 °C) [21]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 8.01 (d, 2H, J = 8.5 Hz), 7.79 (d, 1H, J = 15.6 Hz), 7.61 (d, 2H, J = 8.6 Hz), 7.58 (t, 1H, J = 7.4 Hz), 7.51 (t, 2H, J = 7.6 Hz), 7.42 (d,

1H, $J = 15.6$ Hz), 6.95 (d, 2H, $J = 8.8$ Hz), 3.87 (s, 3H). DEPTQ (150 MHz, CDCl_3), δ (ppm): 190.8, 161.9, 144.9, 138.7, 132.7, 130.4, 128.7, 128.6, 127.9, 120.1, 114.6, 55.6.

(*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (**1Ba**). This compound was obtained pure enough after filtration to afford a yellow solid (104.4 mg, 86%), m.p. 99–101 °C (lit. 94–95 °C) [43]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.96 (d, 2H, $J = 8.5$ Hz), 7.81 (d, 1H, $J = 15.7$ Hz), 7.64 (dd, 2H, $J = 6.4, 3.5$ Hz), 7.48 (d, 2H, $J = 8.6$ Hz), 7.47 (d, 1H, $J = 15.5$ Hz), 7.45–7.40 (m, 3H). DEPTQ (150 MHz, CDCl_3), δ (ppm): 189.4, 145.5, 139.4, 136.7, 134.9, 130.9, 130.1, 129.2, 129.1, 128.7, 121.8.

(*E*)-1-(4-chlorophenyl)-3-(3-fluorophenyl)prop-2-en-1-one (**1Bb**). This compound was obtained pure enough after filtration to afford a white solid (105.6 mg, 81%), m.p. 99–101 °C (lit. m.p. not reported) [43]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.96 (d, 2H, $J = 8.6$ Hz), 7.76 (d, 1H, $J = 15.7$ Hz), 7.48 (d, 2H, $J = 8.7$ Hz), 7.46 (d, 1H, $J = 15.8$ Hz), 7.42–7.37 (m, 2H), 7.34 (dd, 1H, $J = 8.6, 2.4$ Hz), 7.15–7.09 (m, 1H). DEPTQ (150 MHz, CDCl_3), δ (ppm): 188.96, 164.07, 143.90, 139.64, 137.14, 136.43, 130.74, 130.07, 129.18, 124.73, 122.88, 117.76, 114.74.

(*E*)-1-(4-chlorophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**1Bc**). This compound was obtained pure enough after filtration to afford a white solid (104.3 mg, 80%), m.p. 120–122 °C (lit. 124–125 °C) [43]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.96 (d, 2H, $J = 8.5$ Hz), 7.78 (d, 1H, $J = 15.7$ Hz), 7.64 (dd, 2H, $J = 8.6, 5.4$ Hz), 7.48 (d, 2H, $J = 8.5$ Hz), 7.40 (d, 1H, $J = 15.7$ Hz), 7.12 (t, 2H, $J = 8.5$ Hz). DEPTQ (150 MHz, CDCl_3), δ (ppm): 189.1, 165.2, 144.1, 139.5, 136.6, 131.2, 130.6, 130.0, 129.1, 121.4, 116.4.

(*E*)-1-(4-chlorophenyl)-3-(4-nitrophenyl)prop-2-en-1-one (**1Bd**). This compound was obtained pure enough after filtration to afford yellow crystals (95 mg, 66%), m.p. 161–163 °C (lit. 164–166 °C) [42]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 8.28 (d, 2H, $J = 8.7$ Hz), 7.98 (d, 2H, $J = 8.5$ Hz), 7.83 (d, 1H, $J = 15.6$ Hz), 7.79 (d, 2H, $J = 8.8$ Hz), 7.59 (d, 1H, $J = 15.7$ Hz), 7.51 (d, 2H, $J = 8.5$ Hz). DEPTQ (150 MHz, CDCl_3), δ (ppm): 188.5, 148.9, 142.1, 141.0, 140.1, 136.0, 130.1, 129.3, 129.1, 125.4, 124.4.

(*E*)-1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1Be**). This compound was obtained pure enough after filtration to afford a white solid (107.7 mg, 79%), m.p. 120–122 °C (lit. 119–123 °C) [44]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.95 (d, 2H, $J = 8.6$ Hz), 7.78 (d, 1H, $J = 15.6$ Hz), 7.60 (d, 2H, $J = 8.8$ Hz), 7.47 (d, 2H, $J = 8.6$ Hz), 7.35 (d, 1H, $J = 15.5$ Hz), 6.94 (d, 2H, $J = 8.8$ Hz), 3.86 (s, 3H). DEPTQ (150 MHz, CDCl_3), δ (ppm): 189.3, 162.0, 145.3, 139.1, 137.0, 130.5, 130.0, 129.0, 127.6, 119.4, 114.6, 55.6.

(*E*)-1-(3-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1Ca**). This compound was purified by column chromatography (Hexane 10:AcOEt 1) to afford a white solid (85.2 mg, 76%), m.p. 134–136 °C (lit. 130–132 °C) [45]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.80 (d, 1H, $J = 15.7$ Hz), 7.66–7.62 (m, 2H), 7.58 (d, 1H, $J = 8.2$ Hz), 7.53 (s, 1H), 7.50 (d, 1H, $J = 15.7$ Hz), 7.43–7.40 (m, 3H), 7.38 (t, 1H, $J = 7.9$ Hz), 7.11 (ddd, 1H, $J = 8.1, 2.6, 0.87$ Hz). DEPTQ (150 MHz, CDCl_3), δ (ppm): 190.6, 156.4, 145.4, 139.9, 135.0, 130.8, 130.1, 129.1, 128.7, 122.2, 121.2, 120.4, 115.3.

(*E*)-3-(3-fluorophenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (**1Cb**). This compound was obtained pure enough after filtration to afford a white solid (94.5 mg, 78%), m.p. 120–122 °C (lit. 121–123 °C) [45]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.76 (d, 1H, $J = 15.7$ Hz), 7.58 (s, 1H), 7.57 (d, 1H, $J = 7.7$ Hz), 7.48 (d, 1H, $J = 15.7$ Hz), 7.41–7.35 (m, 3H), 7.33 (d, 1H, $J = 7.3$ Hz), 7.14–7.08 (m, 2H). DEPTQ (150 MHz, CDCl_3), δ (ppm): 190.4, 164.1, 156.6, 143.9, 139.5, 137.3, 130.7, 130.1, 124.7, 123.3, 121.2, 120.7, 117.7, 115.3, 114.8.

(*E*)-3-(4-fluorophenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (**1Cc**). This compound was purified by column chromatography (Hexane 10:AcOEt 1) to afford a white solid (100.5 mg, 83%), m.p. 123–125 °C (lit. 124–126 °C) [45]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 7.78 (d, 1H, $J = 15.7$ Hz), 7.63 (dd, 2H, $J = 8.8, 5.4$ Hz), 7.57 (d, 1H, $J = 7.6$ Hz), 7.54 (s, 1H), 7.42 (d, 1H, $J = 15.7$ Hz), 7.38 (t, 1H, $J = 7.8$ Hz), 7.14–7.08 (m, 3H). DEPTQ (150

MHz, CDCl₃), δ (ppm): 190.4, 165.2, 156.4, 144.1, 139.8, 131.3, 130.6 (2C), 130.1, 121.9, 121.2, 120.5, 116.4 2(C), 115.3.

(*E*)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (**1Cd**). This compound was purified by column chromatography (Hexane 8:AcOEt 1) to afford a yellow solid (103.7 mg, 77%), m.p. 176–178 °C (lit. 177–180 °C) [46]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.28 (d, 2H, *J* = 8.8 Hz), 7.81 (d, 1H, *J* = 15.8 Hz), 7.78 (d, 2H, *J* = 8.7 Hz), 7.59 (d, 1H, *J* = 15.7 Hz), 7.63–7.57 (m, 1H), 7.50 (s, 1H), 7.41 (t, 1H, *J* = 7.9 Hz), 7.11 (dd, 1H, *J* = 8.0, 2.5 Hz). DEPTQ (150 MHz, CDCl₃), δ (ppm): 189.4, 158.47, 148.68, 141.80, 140.71, 139.08, 130.27 (CH, C-6'), 129.10, 125.88, 124.40, 121.36, 120.75, 115.23.

(*E*)-1-(3-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1Ce**). This compound was purified by column chromatography (Hexane 10:AcOEt 1) to afford a yellow solid (101.7 mg, 80%), m.p. 141–143 °C (lit. 142–144 °C) [46]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.28 (d, 2H, *J* = 8.8 Hz), 7.81 (d, 1H, *J* = 15.8 Hz), 7.78 (d, 2H, *J* = 8.7 Hz), 7.59 (d, 1H, *J* = 15.7 Hz), 7.63–7.57 (m, 1H), 7.50 (s, 1H), 7.41 (t, 1H, *J* = 7.9 Hz), 7.11 (dd, 1H, *J* = 8.0, 2.5 Hz). DEPTQ (150 MHz, CDCl₃), δ (ppm): 190.7, 162.0, 156.5, 145.3, 140.1, 130.5, 130.0, 127.7, 121.0, 120.2, 120.0, 115.3, 114.6, 55.6.

(*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (**1Cf**). This compound was purified by column chromatography (Hexane 10:AcOEt 1) to afford a yellow solid (92 mg, 68%), m.p. 158–160 °C (lit. m.p. not reported) [47]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 7.69 (d, 1H, *J* = 15.4 Hz), 7.54–7.52 (m, 1H), 7.49 (d, 1H, *J* = 15.5 Hz), 7.40 (t, 1H, *J* = 2.1 Hz), 7.34–7.28 (m, 2H), 7.19 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.01 (dd, 1H, *J* = 8.0, 2.6 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 3.9 (s, 3H). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 192.7, 159.1, 151.1, 149.4, 147.1, 141.1, 130.8, 128.2, 124.9, 121.1, 120.9, 120.1, 116.6, 115.8, 112.1, 56.5.

(*E*)-1-(4-nitrophenyl)prop-2-en-1-one (**1Da**). This compound was obtained pure enough after filtration to afford a yellow solid (117.8 mg, 93%), m.p. 148–150 °C (lit. 143–144 °C) [43]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.36 (d, 2H, *J* = 8.9 Hz), 8.16 (d, 2H, *J* = 8.9 Hz), 7.86 (d, 1H, *J* = 15.7 Hz), 7.70–7.64 (m, 2H), 7.49 (d, 1H, *J* = 15.7 Hz), 7.49–7.43 (m, 3H). DEPTQ (150 MHz, CDCl₃), δ (ppm): 189.2, 150.3, 147.0, 143.3, 134.5, 131.4, 129.6, 129.3, 128.9, 124.0, 121.6.

(*E*)-3-(4-fluorophenyl)-1-(4-nitrophenyl)prop-2-en-1-one (**1Dc**). This compound was obtained pure enough after filtration to afford a yellow solid (133 mg, 98%), m.p. 208–210 °C (lit. 210–212 °C) [48]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.35 (d, 2H, *J* = 8.9 Hz), 8.13 (d, 2H, *J* = 8.9 Hz), 7.83 (d, 1H, *J* = 15.6 Hz), 7.63 (d, 2H, *J* = 8.7 Hz), 7.36 (d, 1H, *J* = 15.6 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 3.88 (s, 3H). DEPTQ (150 MHz, CDCl₃), δ (ppm): 189.0, 165.5, 163.8, 150.3, 145.6, 143.2, 130.9, 129.5, 124.0, 121.2, 116.5.

(*E*)-3-(4-methoxyphenyl)-1-(4-nitrophenyl)prop-2-en-1-one (**1De**). This compound was obtained pure enough after filtration to afford a mustard yellow solid (110.5 mg, 78%), m.p. 182–183 °C (lit. 178–180 °C) [48]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.35 (d, 2H, *J* = 8.9 Hz), 8.13 (d, 2H, *J* = 8.9 Hz), 7.83 (d, 1H, *J* = 15.6 Hz), 7.63 (d, 2H, *J* = 8.7 Hz), 7.36 (d, 1H, *J* = 15.6 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 3.88 (s, 3H). DEPTQ (150 MHz, CDCl₃), δ (ppm): 189.2, 165.2, 150.2, 146.9, 143.7, 130.8, 129.4, 127.3, 124.0, 119.2, 114.8, 55.64.

(*E*)-1-(5-chloro-2-hydroxyphenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**1Ec**). This compound was obtained pure after filtration to afford a yellow solid (132.8 mg; 96%), m.p. 158–160 °C (lit. 158–160 °C) [49]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 12.65 (s, 1H), 7.90 (d, *J* = 15.4 Hz, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.71–7.64 (m, 3H), 7.48 (d, *J* = 15.4 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.14 (t, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 193.1, 165.0 (d, *J* = 253.4 Hz), 162.6, 145.7, 136.7, 131.3 (d, *J* = 8.9 Hz), 131.2 (d, *J* = 3.6 Hz), 129.3, 124.1, 121.1, 120.8, 119.7 (d, *J* = 3.1 Hz), 116.9 (d, *J* = 22.1 Hz).

(*E*)-1-(5-chloro-2-hydroxyphenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**1Eg**). This compound was purified by column chromatography (hexane: ethyl acetate, 95:5) to afford

a yellow solid (119.8 mg, 83%), m.p. 132–134 °C (lit. m.p. not reported) [50]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.78 (s, 1H), 8.18 (d, $J = 15.6$ Hz, 1H), 7.79 (d, $J = 2.6$ Hz, 1H), 7.61 (d, $J = 15.5$ Hz, 2H), 7.39–7.32 (m, 2H), 6.95 (t, $J = 7.5$ Hz, 1H), 6.90 (dd, $J = 8.6, 6.4$ Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 193.38, 162.05, 159.18, 142.19, 135.94, 132.61, 129.78, 128.93, 123.41, 123.37, 120.88, 120.81, 120.16, 120.04, 111.37, 55.67.

(*E*)-1-(5-chloro-2-hydroxyphenyl)-3-(3-methoxyphenyl)-prop-2-en-1-one (**1Eh**). This compound was purified by column chromatography (hexane: ethyl acetate, 95:5) to afford a yellow solid (94.7 mg, 67%), m.p. 96–98 °C (lit. m.p. not reported) [50]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.70 (s, 1H), 7.91 (d, $J = 15.4$ Hz, 1H), 7.87 (d, $J = 2.6$ Hz, 1H), 7.55 (d, $J = 15.4$ Hz, 1H), 7.45 (dd, $J = 8.9, 2.5$ Hz, 1H), 7.37 (t, $J = 7.9$ Hz, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.18 (t, $J = 2.1$ Hz, 1H), 7.02 (dd, $J = 5.6, 2.1$ Hz, 1H), 7.00 (d, $J = 8.9$ Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.8, 162.1, 160.0, 146.5, 136.2, 135.7, 130.1, 128.8, 123.6, 121.5, 120.6, 120.3, 119.7, 117.0, 113.8, 55.5.

(*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(3-fluorophenyl)-prop-2-en-1-one (**1Fb**). This compound was purified by column chromatography (hexane: ethyl acetate, 95:5) to afford a yellow solid (120.6 mg, 83%), m.p. 138–140 °C. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.5 (d, $J = 1.1$ Hz, 1H), 7.8 (d, $J = 15.5$ Hz, 1H), 7.8 (s, 1H), 7.5 (d, $J = 15.4$ Hz, 1H), 7.4 (t, $J = 1.5$ Hz, 1H), 7.4–7.3 (m, 1H), 7.3 (dt, $J = 9.5, 2.0$ Hz, 1H), 7.1 (tt, $J = 7.1, 1.6$ Hz, 1H), 6.9 (s, 1H), 2.3 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.1, 163.1 (d, $J = 247.3$ Hz), 162.1, 145.9, 144.4 (d, $J = 2.8$ Hz), 136.7 (d, $J = 7.7$ Hz), 130.7 (d, $J = 8.1$ Hz), 129.2, 124.8 (d, $J = 3.1$ Hz), 124.3, 120.9, 120.7, 118.9, 117.9 (d, $J = 21.5$ Hz), 114.8 (d, $J = 22.0$ Hz), 20.9. HRMS (FAB $^+$): m/z $[\text{M}+\text{H}]^+$ observed for $[\text{C}_{16}\text{H}_{12}\text{ClFO}_2]^+$: 291.0581, estimated: 291.0588. IR (cm^{-1}) 3414, 3061, 2965, 2922, 1646, 1580, 1487, 1450, 1359, 1223, 985, 849, 790, 747.

(*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(4-fluorophenyl)-prop-2-en-1-one (**1Fc**). This compound was obtained pure after filtration to afford a yellow solid (136.6 mg, 94%), m.p. 194–198 °C (lit. m.p. not reported) [51,52]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.6 (s, 1H), 7.9 (d, $J = 15.4$ Hz, 1H), 7.9 (s, 1H), 7.7 (dd, $J = 8.5, 5.5$ Hz, 3H), 7.5 (d, $J = 15.4$ Hz, 1H), 7.2 (t, $J = 8.5$ Hz, 2H), 6.9 (s, 1H), 2.4 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.7, 164.9 (d, $J = 253.2$ Hz), 162.5, 146.2, 145.1, 131.2 (d, $J = 8.9$ Hz), 129.6, 124.7, 121.1, 119.9 (d, $J = 2.1$ Hz), 119.5, 116.8 (d, $J = 22.1$ Hz), 21.3.

(*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**1Fe**). This compound was obtained pure after filtration to afford an orange solid (145.3 mg, 96%), m.p. 110–112 °C (lit. m.p. not reported) [53]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.8 (s, 1H), 7.9 (d, $J = 15.3$ Hz, 1H), 7.8 (s, 1H), 7.6 (d, $J = 8.6$ Hz, 1H), 7.4 (d, $J = 15.3$ Hz, 1H), 7.0 (d, $J = 8.8$ Hz, 1H), 6.9 (s, 1H), 3.9 (s, 1H), 2.4 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.8, 162.7, 162.5, 146.4, 145.7, 131.2, 129.6, 127.8, 124.6, 121.1, 119.6, 117.7, 115.1, 56.0, 21.3.

(*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(2-methoxyphenyl)-prop-2-en-1-one (**1Fg**). This compound was purified by column chromatography (hexane: ethyl acetate, 95:5) to afford a yellow solid (113.5 mg, 75%), m.p. 178–180 °C. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.8 (s, 1H), 8.2 (d, $J = 15.6$ Hz, 1H), 7.9 (s, 1H), 7.7 (ddd, $J = 15.5, 7.9, 1.6$ Hz, 2H), 7.4 (ddd, $J = 8.7, 7.4, 1.7$ Hz, 1H), 7.0 (t, $J = 8.2$ Hz, 1H), 7.0 (d, $J = 8.3$ Hz, 1H), 6.9 (s, 1H), 3.9 (s, 3H), 2.4 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 193.0, 162.0, 159.1, 145.3, 141.6, 132.4, 129.6, 129.3, 124.1, 123.5, 120.9, 120.5, 120.2, 119.2, 111.3, 55.7, 20.8. HRMS (FAB $^+$): m/z $[\text{M}+\text{H}]^+$ observed for $[\text{C}_{17}\text{H}_{15}\text{ClO}_3]^+$: observed: 303.0794, estimated: 303.0788. IR (cm^{-1}) 2920, 2848, 1627, 1599, 1566, 1489, 1463, 1364, 1241, 1189, 1167, 992, 792, 734.

(*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(2-fluorophenyl)-prop-2-en-1-one (**1Fi**). This compound was purified by column chromatography (hexane: ethyl acetate, 95:5) to afford a yellow solid (81.4 mg, 56%), m.p. 138–140 °C. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 12.6 (s, 1H), 8.0 (d, $J = 15.6$ Hz, 1H), 7.8 (s, 1H), 7.7 (ddt, $J = 15.6, 7.6, 1.4$ Hz, 2H), 7.4 (ddd, $J = 8.0, 5.0, 1.8$ Hz, 1H), 7.2 (td, $J = 7.5, 1.1$ Hz, 1H), 7.2 (ddd, $J = 10.9, 8.3, 1.1$ Hz,

1H), 6.9 (s, 1H), 2.4 (d, $J = 0.7$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.4, 162.8 (d, $J = 255.6$ Hz), 162.0, 145.8, 138.7 (d, $J = 2.2$ Hz), 132.5 (d, $J = 8.9$ Hz), 130.1 (d, $J = 2.8$ Hz), 129.3, 124.7 (d, $J = 3.5$ Hz), 124.3, 122.7 (d, $J = 11.2$ Hz), 122.3 (d, $J = 7.7$ Hz), 120.6, 118.9, 116.4 (d, $J = 22.1$ Hz), 20.9. HRMS (FAB⁺): m/z $[\text{M}+\text{H}]^+$ observed for $[\text{C}_{16}\text{H}_{12}\text{ClFO}_2]^+$: 291.0581, estimated: 291.0588. IR (cm^{-1}) 2982, 2955, 2857, 1644, 1610, 1567, 1487, 1457, 1364, 1269, 1191, 977, 746.

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1Ga**). This compound was obtained pure after filtration to afford a yellow solid (78.7 mg, 65%), m.p. 110–112 °C (lit. m.p. not reported) [54]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 13.2 (d, $J = 1.5$ Hz, 1H), 7.9 (dtd, $J = 15.1, 5.9, 3.0$ Hz, 1H), 7.7 (dd, $J = 6.6, 2.9$ Hz, 2H), 7.6 (d, $J = 15.5$ Hz, 1H), 7.4 (dd, $J = 4.8, 1.9$ Hz, 3H), 6.7 (dd, $J = 10.4, 2.5$ Hz, 1H), 6.7 (td, $J = 8.5, 2.6$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.6, 167.5 (d, $J = 257.0$ Hz), 166.2 (d, $J = 14.4$ Hz), 145.8, 134.5, 132.0 (d, $J = 11.9$ Hz), 131.1, 129.1, 128.7, 119.9, 117.1 (d, $J = 2.1$ Hz), 107.2 (d, $J = 2.1$ Hz), 105.2 (d, $J = 23.3$ Hz).

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(3-fluorophenyl)-prop-2-en-1-one (**1Gb**). This compound was obtained pure after filtration to afford a yellow solid (93.7 mg, 72%), m.p. 142–144 °C (lit. m.p. not reported) [55]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 13.1 (d, $J = 1.5$ Hz, 1H), 7.9 (dd, $J = 9.0, 6.3$ Hz, 1H), 7.9 (d, $J = 15.4$ Hz, 1H), 7.6 (d, $J = 15.4$ Hz, 1H), 7.4–7.4 (m, 2H), 7.4 (dq, $J = 9.7, 1.4$ Hz, 1H), 7.2–7.1 (m, 1H), 6.7 (dd, $J = 10.3, 2.5$ Hz, 1H), 6.7 (ddd, $J = 9.0, 8.0, 2.5$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.3, 167.6 (d, $J = 257.6$ Hz), 166.3 (d, $J = 14.3$ Hz), 163.1 (d, $J = 247.2$ Hz), 144.2 (d, $J = 2.7$ Hz), 136.7 (d, $J = 7.6$ Hz), 132.0 (d, $J = 11.8$ Hz), 130.7 (d, $J = 8.1$ Hz), 124.8 (d, $J = 2.9$ Hz), 121.2, 117.9 (d, $J = 21.4$ Hz), 117.0 (d, $J = 1.9$ Hz), 114.7 (d, $J = 22.0$ Hz), 107.3 (d, $J = 23.1$ Hz), 105.2 (d, $J = 23.6$ Hz).

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**1Ge**). This compound was obtained pure after filtration to afford a yellow solid (98 mg, 72%), m.p. 148–150 °C (lit. m.p. not reported) [55]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 13.3 (s, 1H), 7.9 (td, $J = 8.5, 2.6$ Hz, 1H), 7.9 (d, $J = 15.3$ Hz, 1H), 7.6 (d, $J = 8.7$ Hz, 2H), 7.4 (d, $J = 15.3$ Hz, 1H), 7.0 (d, $J = 8.7$ Hz, 2H), 6.7 (dd, $J = 7.8, 2.6$ Hz, 1H), 6.7 (td, $J = 8.5, 2.6$ Hz, 1H), 3.9 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.5, 167.3 (d, $J = 256.6$ Hz), 166.1 (d, $J = 14.2$ Hz), 162.1, 145.6, 131.8 (d, $J = 11.7$ Hz), 130.6, 127.2, 117.3, 117.2 (d, $J = 2.2$ Hz), 114.6, 107.0 (d, $J = 22.8$ Hz), 105.1 (d, $J = 23.4$ Hz), 55.5.

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(2-methoxyphenyl)-prop-2-en-1-one (**1Gg**). This compound was obtained pure after filtration to afford a yellow solid (117 mg, 86%), m.p. 138–140 °C. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 13.3 (d, $J = 1.4$ Hz, 1H), 8.2 (d, $J = 15.6$ Hz, 1H), 7.9 (dd, $J = 8.9, 6.4$ Hz, 1H), 7.7 (d, $J = 15.6$ Hz, 1H), 7.6 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.4 (ddd, $J = 8.3, 7.4, 1.7$ Hz, 1H), 7.0 (td, $J = 7.5, 1.0$ Hz, 1H), 7.0 (dd, $J = 8.3, 1.0$ Hz, 1H), 6.7 (dd, $J = 10.4, 2.5$ Hz, 1H), 6.7 (ddd, $J = 8.8, 8.0, 2.6$ Hz, 1H), 3.9 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 193.2, 167.3 (d, $J = 256.5$ Hz), 166.2 (d, $J = 14.3$ Hz), 159.1, 141.5, 132.3, 132.0 (d, $J = 12.0$ Hz), 129.8, 123.5, 120.8, 120.6, 117.3 (d, $J = 2.4$ Hz), 111.4, 107.0 (d, $J = 22.7$ Hz), 106.9, 105.1 (d, $J = 23.6$ Hz), 55.6. HRMS (FAB⁺): m/z $[\text{M}+\text{H}]^+$ observed for $[\text{C}_{16}\text{H}_{13}\text{FO}_3]^+$: 273.0929, estimated: 273.0927. IR (cm^{-1}) 3092, 3063, 1640, 1610, 1595, 1571, 1510, 1457, 1374, 1272, 1228, 1207, 1120, 971, 800, 753.

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(3-methoxyphenyl)-prop-2-en-1-one (**1Gh**). This compound was obtained pure after filtration to afford a yellow solid (115.7 mg, 85%), m.p. 128–130 °C (lit. m.p. not reported) [55]. ^1H NMR (600 MHz, CDCl_3), δ (ppm): 13.2 (d, $J = 1.3$ Hz, 1H), 7.9 (dd, $J = 9.0, 6.4$ Hz, 1H), 7.9 (d, $J = 15.4$ Hz, 1H), 7.5 (d, $J = 15.4$ Hz, 1H), 7.4 (t, $J = 7.9$ Hz, 1H), 7.3 (d, $J = 8.2$ Hz, 2H), 7.2 (t, $J = 2.4$ Hz, 1H), 7.0 (dd, $J = 8.3, 2.6$ Hz, 1H), 6.7 (dd, $J = 10.4, 2.6$ Hz, 1H), 6.7 (ddd, $J = 9.0, 8.0, 2.5$ Hz, 1H), 3.9 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3), δ (ppm): 192.6, 167.5 (d, $J = 257.0$ Hz), 166.2 (d, $J = 14.3$ Hz), 160.0, 145.7, 135.8, 132.0 (d, $J = 11.7$ Hz), 130.1, 121.3, 120.2, 117.1 (d, $J = 2.2$ Hz), 116.7, 113.8, 107.2 (d, $J = 22.7$ Hz), 105.2 (d, $J = 23.3$ Hz), 55.4.

(*E*)-1-(4-fluoro-2-hydroxyphenyl)-3-(2-fluorophenyl)-prop-2-en-1-one (**1Gi**). This compound was obtained pure after filtration to afford a solid (97.6 mg, 75%), m.p. 110–112 °C. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 13.1 (d, *J* = 1.4 Hz, 1H), 8.0 (d, *J* = 15.7 Hz, 1H), 7.9 (dd, *J* = 8.9, 6.4 Hz, 1H), 7.7 (d, *J* = 15.7 Hz, 1H), 7.6 (td, *J* = 7.6, 1.7 Hz, 1H), 7.4 (dddd, *J* = 8.7, 7.2, 5.1, 1.7 Hz, 1H), 7.2 (td, *J* = 7.6, 1.1 Hz, 1H), 7.2 (ddd, *J* = 11.0, 8.3, 1.2 Hz, 1H), 6.7 (dd, *J* = 10.4, 2.5 Hz, 1H), 6.7 (ddd, *J* = 8.8, 8.0, 2.6 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 192.7, 167.6 (d, *J* = 257.1 Hz), 166.3 (d, *J* = 14.4 Hz), 161.9 (d, *J* = 255.3 Hz), 138.6 (d, *J* = 1.7 Hz), 132.4 (d, *J* = 8.9 Hz), 132.1 (d, *J* = 11.8 Hz), 130.3 (d, *J* = 2.8 Hz), 124.7 (d, *J* = 3.6 Hz), 122.7 (d, *J* = 8.2 Hz), 122.6 (d, *J* = 11.3 Hz), 117.1 (d, *J* = 2.1 Hz), 116.5 (d, *J* = 22.1 Hz), 107.2 (d, *J* = 22.7 Hz), 105.2 (d, *J* = 23.6 Hz). HRMS (FAB+): *m/z* [M+H]⁺ observed for [C₁₅H₁₀F₂O₂]⁺: 261.0724, estimated: 261.0727. IR (cm^{−1}) 3079, 2967, 2935, 2855, 2837, 1636, 1599, 1562, 1510, 1465, 1372, 1249, 1200, 1122, 1027, 975, 805, 744.

(*E*)-1-(5-fluoro-2-hydroxyphenyl)-3-(4-fluorophenyl)-prop-2-en-1-one (**1Hc**). This compound was obtained pure after filtration to afford a yellow solid (123.6 mg, 95%), m.p. 184–186 °C (lit. m.p. not reported) [56]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 12.5 (s, 1H), 7.9 (d, *J* = 15.4 Hz, 1H), 7.7 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.6 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.5 (d, *J* = 15.4 Hz, 1H), 7.3 (ddd, *J* = 8.2, 3.2, 1.4 Hz, 2H), 7.1 (t, *J* = 8.6 Hz, 2H), 7.0 (dd, *J* = 9.1, 4.6 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 192.7 (d, *J* = 2.7 Hz), 164.5 (d, *J* = 253.2 Hz), 159.8, 154.9 (d, *J* = 238.4 Hz), 145.0, 130.8 (d, *J* = 8.5 Hz), 130.6 (d, *J* = 3.3 Hz), 124.0 (d, *J* = 23.4 Hz), 119.9 (d, *J* = 7.3 Hz), 119.4 (d, *J* = 6.0 Hz), 119.3 (d, *J* = 2.3 Hz), 116.4 (d, *J* = 22.0 Hz), 114.5 (d, *J* = 23.3 Hz).

(*E*)-1-(5-fluoro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**1He**). This compound was purified by column chromatography (hexane: ethyl acetate, 95:5) to afford a yellow solid of 115.7 mg, 85%, m.p. 126–128 °C (lit. m.p. not reported) [55]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 12.7 (s, 1H), 7.9 (d, *J* = 15.3 Hz, 1H), 7.6 (d, *J* = 8.8 Hz, 2H), 7.6 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.4 (d, *J* = 15.4 Hz, 1H), 7.2 (ddd, *J* = 9.1, 7.7, 3.1 Hz, 1H), 7.0 (ddd, *J* = 9.2, 7.5, 4.6 Hz, 1H), 7.0 (d, *J* = 8.7 Hz, 2H), 3.9 (s, 3H). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 192.8, 162.3, 159.7 (d, *J* = 1.4 Hz), 154.9 (d, *J* = 238.2 Hz), 146.3, 130.8, 127.1, 123.6 (d, *J* = 23.7 Hz), 119.8 (d, *J* = 7.2 Hz), 119.7 (d, *J* = 6.1 Hz), 117.0, 114.6, 114.5 (d, *J* = 23.5 Hz), 55.5.

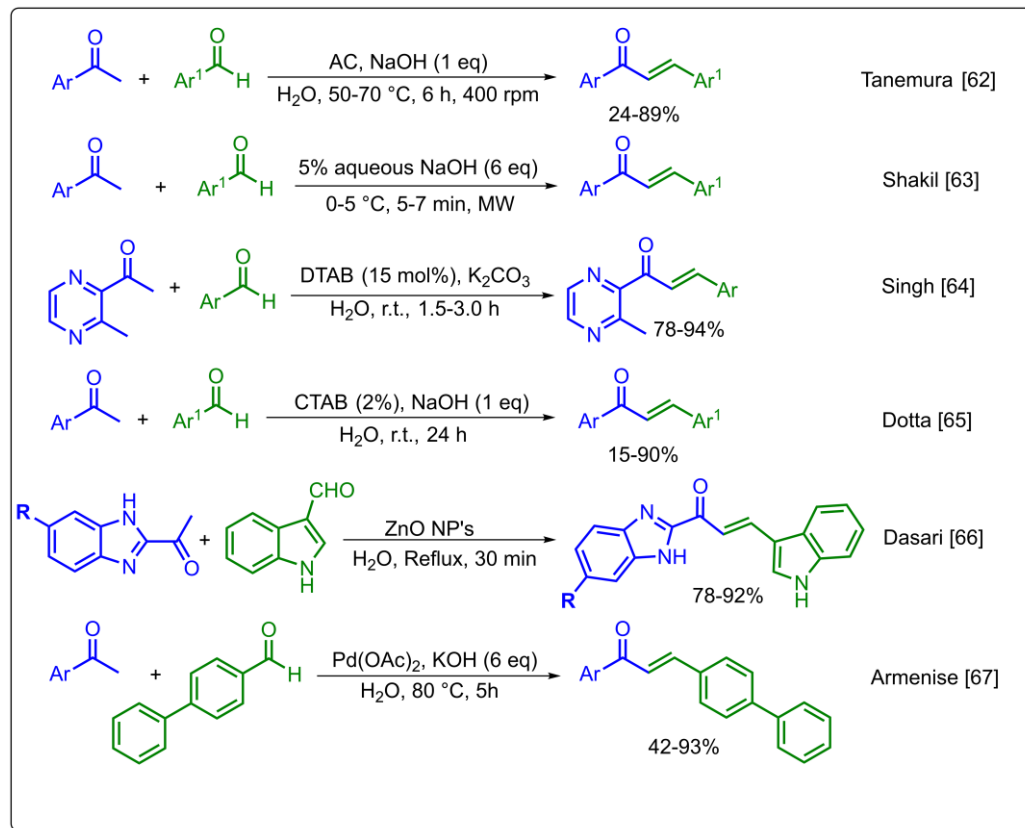
(*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (**1Ia**). This compound was obtained pure enough after filtration to afford a white solid (80.3 mg, 81%), m.p. 80 °C (lit. m.p. not reported) [57]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.28 (d, 2H, *J* = 8.8 Hz), 8.03 (d, 2H, *J* = 8.5 Hz), 7.82 (d, 1H, *J* = 15.8 Hz), 7.79 (d, 2H, *J* = 8.6 Hz), 7.64 (d, 1H, *J* = 15.7 Hz), 7.63 (t, 1H, *J* = 8.5 Hz), 7.54 (t, 2H, *J* = 7.7 Hz). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 178.2, 153.9, 146.6, 144.2, 135.0, 130.8, 129.1, 128.7, 121.4, 117.6, 112.7.

(*E*)-3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one (**1Ja**). This compound was obtained pure enough after filtration to afford a white solid (89.4 mg, 85%), m.p. 70–72 °C (lit. 70–72 °C) [58]. ¹H NMR (600 MHz, CDCl₃), δ (ppm): 8.74 (d, 1H, *J* = 4.7 Hz), 8.30 (d, 1H, *J* = 16.0 Hz), 8.18 (d, 1H, *J* = 7.8 Hz), 7.94 (d, 1H, *J* = 16.0 Hz), 7.86 (td, 1H, *J* = 7.7, 1.6 Hz), 7.76–7.70 (m, 2H), 7.50–7.44 (m, 1H), 7.43–7.37 (m, 3H). ¹³C NMR (150 MHz, CDCl₃), δ (ppm): 189.5, 154.2, 148.9, 144.8, 137.0, 135.2, 130.6, 128.9 (2C), 126.9, 123.0, 120.9.

3. Results and Discussion

It was previously theorized that a chemical reaction could not occur unless reagents were liquid or in solution [59,60]. This theory led to the extensive use of organic solvents and the limited or non-use of water in organic product manufacturing. Water is incapable of dissolving many organic compounds. However, it should be noted that many organic solvents are volatile and toxic, and they frequently constitute most of the waste produced during a reaction. Consequently, the employment of water or environmentally friendly solvents has emerged as the prevailing approach in the development of novel methodologies. Historically, the synthesis of chalcones has been predominantly carried out in

ethanolic media under basic conditions, whereas the use of water as a reaction medium has been much less explored [61]. A comprehensive review of the extant literature revealed six distinct water-promoted methodologies for synthesizing chalcones, all of which operate under the Claisen–Schmidt reaction conditions, employing aromatic ketones and aromatic aldehydes as starting materials (Scheme 1).



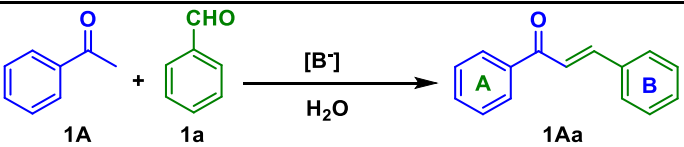
Scheme 1. Water-promoted methodologies for the synthesis of chalcones [62–67].

In these methodologies, a variety of catalysts are employed, including, but not limited to, activated charcoal (AC); metallic salts such as ZnO and $\text{Pd}(\text{OAc})_2$; and the utilization of quaternary ammonium surfactants such as dodecyltrimethylammonium bromide (DTAB) and cetyltrimethylammonium bromide (CTAB). The temperature range of the reactions extends from 0 °C to reflux, and the use of strong bases such as NaOH, KOH, and K_2CO_3 is employed. Under these conditions, reaction time is reduced, though the most optimal result was obtained when MW energy was used, since time is reduced to minutes. In comparison, the methodology presented herein operates at a temperature range of 25–40 °C and is more straightforward, as it does not necessitate specialized equipment, specific catalysts, or additives, solely requiring potassium hydroxide, a strong, green base [41]. Unfortunately, under the conditions described the reaction time for this methodology increases to 2 days, which is the longest of those described in Scheme 1.

Acetophenone **1A** and salicylaldehyde **1a** were the starting materials utilized during the screening of the reaction. Initially, potassium hydroxide (1 eq) and water (bottled or distilled, 2 mL) were tested to promote the reaction (Table 1, entry 1), which was performed at a temperature range of 25–40 °C. As this reaction occurs independently of a surfactant agent, vigorous stirring was required to promote the formation of organic droplets; consequently, the stirring rate was set at 850 rpm. Fortunately, after 4 days, a solid precipitate was obtained from the reaction. Subsequent analysis of the solid by ^1H -NMR spectroscopy allowed its identification as the chalcone **1Aa**. The experiment was repeated

(entry 2), but now using 1 mL of water, and chalcone **1Aa** was obtained in an excellent yield (88%). In comparison, when the volume of water was reduced to 1 mL, stirring and filtering were more difficult, and a slurry was formed in the vial; therefore, 2 mL of water was established for the reaction.

Table 1. Screening for the aqueous synthesis of chalcones.

				
Entry	Base	Base (eq)	Time (d)	Yield (%)
1	KOH	1	4	ND
2 ¹	KOH	1	4	88
3	Na ₂ CO ₃	2	7	0
4	K ₂ CO ₃	2	7	0
5	KOH	2	2	88
6	KOH	3	2	88
7	NaOH	2	2	88
8	KOH/piperidine	2/0.1 M	2	85
9 ²	KOH	2	1	-

Reactions were performed at a 0.5 mmol scale with 2 mL of water. Stirring was adjusted to 850 r.p.m. and temperature to 25–40 °C. ¹ 1 mL of water, ² reactions performed at 60 °C. ND, Not Determined.

Subsequent to demonstrating the capacity to obtain a chalcone under these conditions, the impact of varying bases was examined. However, after a seven-day reaction period in the presence of weaker bases, such as Na₂CO₃ or K₂CO₃, no product formation was observed (entries 3 and 4). In an effort to reduce the reaction time, the effects of varying quantities of strong base were examined. Notably, the use of 2 eq of KOH resulted in a significant reduction in the reaction time to 2 days (entry 5). A similar outcome was observed when NaOH was employed in equal proportion (entry 7). In addition, the effect of 3 eq. of KOH (entry 6) and KOH in the presence of piperidine (0.1 mol, entry 8) were tested; however, the reaction time remained unaltered (2 d). To determine whether a higher reaction temperature could enhance the reaction rate, an additional experiment was performed. In a previous report, the reaction was carried out in water at 70 °C in the presence of NaOH, affording the desired chalcone in 30% yield [68]. Accordingly, in the present study, the reaction was evaluated at 60 °C (entry 9); unfortunately, TLC analysis revealed the formation of multiple products, which precluded a conclusive evaluation of the reaction outcome. Therefore, the optimized reaction conditions were those described in entry 5.

A ¹H NMR study was conducted to verify the conversion time of starting materials to product under the best conditions (Figure 2). Initially, the aldol:chalcone ratio was determined to be 8:33 (1 h). At the 4 h mark, the aldol concentration peaked at 39% while the chalcone concentration continued to rise, reaching 30%. At 6 h, the aldol concentration (26%) was half the chalcone concentration (51%), indicating the rapid conversion of aldol to chalcone and its enhanced stability. At 24 h, the reaction was still in progress, with a vast concentration of chalcone (85%) and the continued presence of aldol (9%). However, at 48 h, the aldol was undetectable, and the chalcone had reached a concentration of 100%. This experimental data enabled the determination of the reaction time to be 48 h (2 d).

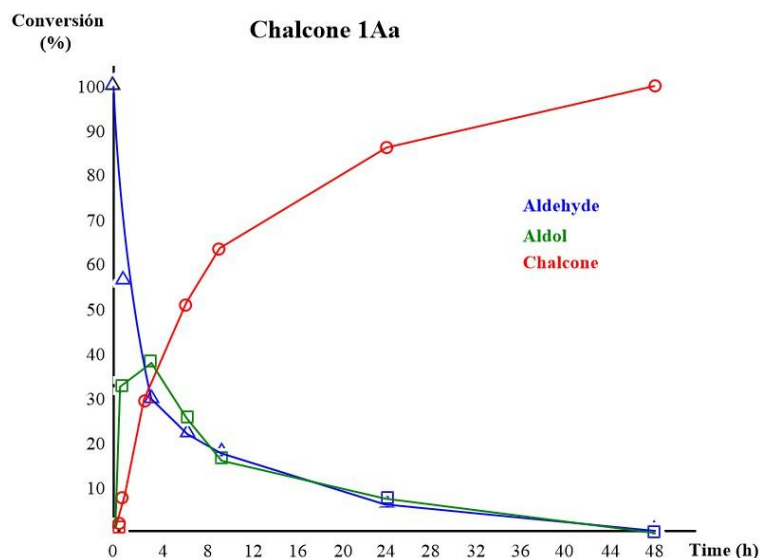


Figure 2. ^1H NMR study of the conversion time for chalcone **1Aa**.

Following the establishment of the reaction conditions (see Table 1, entry 5), the scope was investigated, and a total of nine distinct series of chalcones (**1Aa–1Ja**) were prepared (see Table 2). During the experimental phase, it was observed that the yield and the compound's acquisition were less influenced by the electronic effects of substituents on aromatic rings compared to their physical state and hydrophilicity/lipophilicity. Fortunately, it was found that most products were synthesized in good to excellent yields (66–98%) and in a pure state through simple filtration and water washing, though; column chromatography was also used to purify several of the chalcones. Compound **1Dd** (entry 19, 40% conversion) decomposes in the column, and we were unable to obtain it. In addition, this methodology can be extended to the preparation of heterochalcones (**1Ia**, **1Ja**). Notably, the reaction was successfully scaled up to 50 mmol with chalcone **1Aa**, resulting in 87% yield (entry 39). It is noteworthy that certain 2'-OH-chalcones in series **1F**, **1G**, and **1H** exhibit a propensity to cyclize, resulting in the formation of flavanones. However, the present study focuses exclusively on the introduction of stable chalcones [12].

Table 2. Scope for the aqueous synthesis of chalcones.

Entry	Ar	R	Chalcone Yield (%)
1	1A Ph	1a H	1Aa (88)
2		1b 3-F	1Ab (81)
3		1c 4-F	1Ac (88)
4		1d 4-NO ₂	1Ad (82)
5		1e 4-OMe	1Ae (78)
6	1B 4'-Cl-Ph	1a H	1Ba (86)
7		1b 3-F	1Bb (81)
8		1c 4-F	1Bc (80)
9		1d 4-NO ₂	1Bd (66)
10		1e 4-OMe	1Be (79)
11	1C 3'-OH-Ph	1a H	1Ca (76)

12		1b 3-F	1Cb (78)
13		1c 4-F	1Cc (83)
14		1d 4-NO ₂	1Cd (77)
15		1e 4-OMe	1Ce (80)
16		1f 3-OMe,4-OH	1Cf (68)
17		1a H	1Da (93)
18	1D 4'-NO ₂ -Ph	1c 4-F	1Dc (98)
19		1d 4-NO ₂	1Dd (-)
20		1e 4-OMe	1De (78)
21		1c 4-F	1Ec (96)
22	1E 2'-OH-5'-Cl-Ph	1g 2-OMe	1Eg (83)
23		1h 3-OMe	1Eh (67)
24		1b 3-F	1Fb (83)
25	1F 2'-OH-4'-Me-5'-Cl-Ph	1c 4-F	1Fc (94)
26		1e 4-OMe	1Fe (96)
27		1g 2-OMe	1Fg (75)
28		1i 2-F	1Fi (56)
29		1a H	1Ga (65)
30		1b 3-F	1Gb (72)
31	1G 2'-OH-4'-F-Ph	1e 4-OMe	1Ge (72)
32		1g 2-OMe	1Gg (86)
33		1h 3-OMe	1Gh (85)
34		1i 2-F	1Gi (75)
35	1H 2'-OH-5'-F-Ph	1c 4-F	1Hc (95)
36		1e 4-OMe	1He (85)
37	1I Furane	1a H	1Ia (81)
38	1J Pyridine	1a H	1Ja (85)
39 ¹	1A	1a H	1Aa (87)

Reactions were performed at a 0.5 mmol scale with 2 mL of water. Stirring was adjusted to 850 rpm, temperature to 25–40 °C. Time of 2 d. ¹ 50 mmol scale reaction.

In this study, starting materials (**SM**) in both solid and liquid states were utilized (see Tables 2 and 3). While liquid starting materials were all water-insoluble (Lipophilic, **L**), among the solid materials, hydroxy ketones (**1C**, **1E**, **1H**) were water-soluble (Hydrophilic Solid, **HS**), while nitro ketone (**1D**) and nitro aldehyde (**1d**) were water-insoluble (Lipophilic Solid, **LS**). As previously mentioned, the physical state of reactants and their water solubility are significant factors because they affect the composition of the reaction system, the mechanism, the yield, and the reaction possibility itself.

Table 3. W/SM-SM reaction systems.

Ketone		Aldehyde		System
Liquid (L)	1A, 1B, 1G, 1I	L	1a–1c, 1e, 1g, 1h	W/L-L (Water/Lipophilic liquid–Lipophilic liquid)
		LS	1d	W/L-LS (Water/Lipophilic liquid–Lipophilic Solid)
Lipophilic Solid (LS)	1D	L	1a–1c, 1e, 1g, 1h	W/L-LS
		LS	1d	W/LS-LS (Water/Lipophilic Solid–Lipophilic Solid)
Hydrophilic Solid	1C, 1E–1H	L	1a–1c, 1e, 1g, 1h	W/L-HS (Water/Lipophilic liquid–Hydrophilic Solid)

(HS)	LS	1d	W/HS-LS (Water/Hydrophilic Solid–Lipophilic Solid)
	HS	1f	W/HS-HS (Water/Hydrophilic Solid–Hydrophilic Solid)

In accordance with these considerations, six distinct water/starting material–starting material (**W/SM-SM**) reaction systems can be delineated (Table 3). These include the following: water/lipophilic liquid–lipophilic liquid (**W/L-L**), water/lipophilic liquid–lipophilic solid (**W/L-LS**), water/lipophilic liquid–hydrophilic solid (**W/L-HS**), water/hydrophilic solid–lipophilic solid (**W/HS-LS**), water/lipophilic solid–lipophilic solid (**W/LS-LS**), and water/hydrophilic solid–hydrophilic solid (**W/HS-HS**). As previously stated, most products were obtained in good yields, indicating that water can facilitate reactions, irrespective of the hydrophilicity/lipophilicity or physical state of **SM**. However, in instances where both **SMs** are solid and lipophilic, a water/solid system (**W/LS-LS**) is formed, resulting in a suspension. Among the six systems that have been described, this last one presents the most significant challenges to the progression of the reaction. In theory, this reaction should not occur; however, product **1Dd** was detected by ¹H-NMR in low conversion (10%, entry 19). Unfortunately, the product **1Dd** could not be obtained.

According to the system formed, different mechanisms can be proposed (Table 3, Figure 3, and Supplementary Material). In the **W/L-L** system, both **SM** (aldehyde and ketone) are liquid and lipophilic. They follow the classical on-water mechanism (Figure 3a). The proximity of the **SM** molecules to each other enables their susceptibility to the pressure exerted by the water on them, thereby facilitating the reaction process. In the interphase, hydroxyl groups assist in enolate and chalcone formation by deprotonating the α -protons from the ketone and the aldol, respectively [59,69]. The resulting chalcone product, due to its solid and water-insoluble nature, precipitates upon formation. During the experimental phase, it was observed that when an **LS** was mixed with a lipophilic liquid **L**, both reactants were incorporated into a lipophilic droplet, and a **W/L-LS** system was formed. This system exhibited a mechanism analogous to that of **W/L-L** (Figure 3a). In the case of the **W/L-HS** system, since the ketone is hydrophilic, the hydroxyl deprotonation and enolate formation take place in the water (Figure 3b). Subsequently, the reaction progresses to the interphase, where the process culminates in the formation of the chalcone. Hydroxyl groups facilitate the hydrogen removal from the aldol in the interphase, where both **SMs** are present. Therefore, this could be regarded as a variation in the on-water mechanism described for the **W/L-L** system.

Aqueous reactions were observed to proceed even when both reactants are solids. In the **W/LS-HS** system, where one reactant is hydrophilic and the other is lipophilic, no problems were observed, even though the lipophilic solid was dispersed and forming a heterogeneous solid–liquid suspension (Figure 3c). The mechanism in this case could elapse in-water, by micro-solubilization of the lipophilic reactant [70], or in the solid–liquid interphase. For the **W/LS-LS** system, the mechanism could elapse in the same way. Finally, the **W/HS-HS** system reaction proceeds in water, showing the possibility of carrying out the Claisen–Schmidt condensation in this solvent, despite the excess of water that, in theory, should avoid the reaction from advancing (Figure 3d) [70].

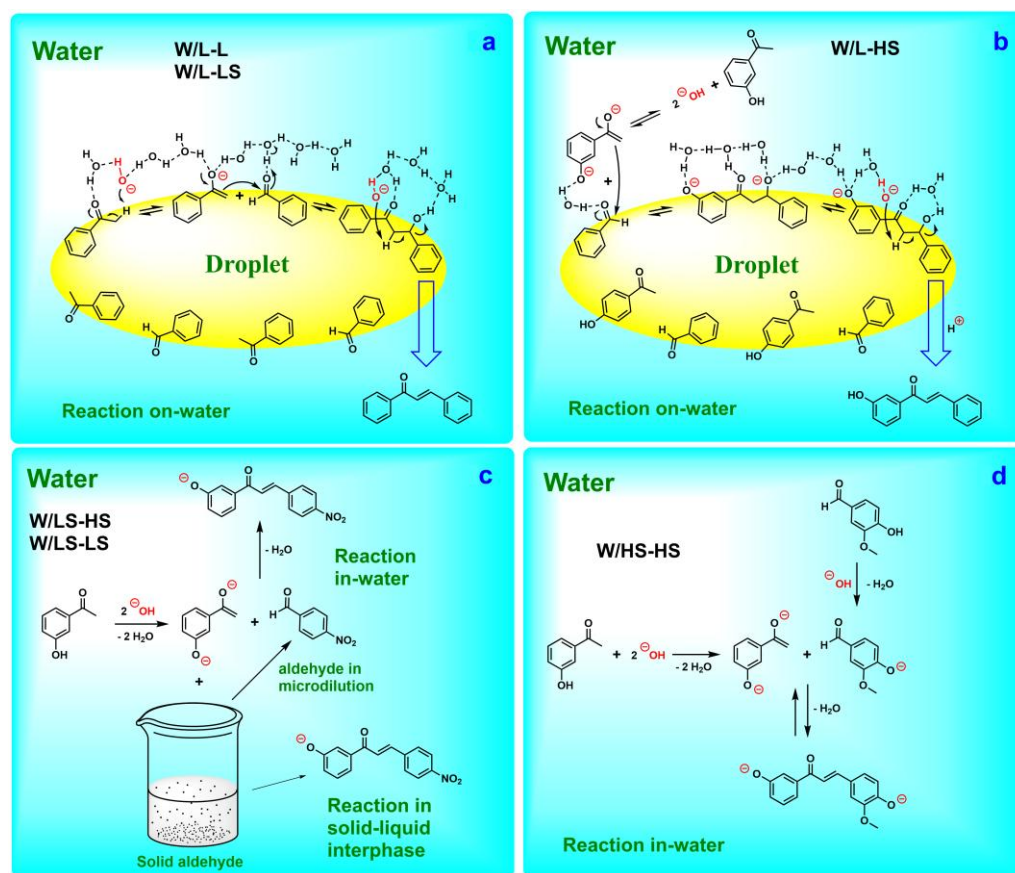


Figure 3. Mechanism proposal. (a) Reaction on-water for W/L-L and W/L-LS systems; (b) Reaction on-water for W/L-HS system; (c) Reaction in-water for W/LS-HS and W/LS-LS systems; (d) Reaction in-water for W/HS-HS system.

4. Conclusions

The Claisen–Schmidt condensation can be performed in aqueous media, under basic conditions. Under the conditions outlined in this study, a substantial number of compounds can be prepared with yields ranging from 56% to 98%, independent of the electronic nature of the substituents present in the starting materials. The yield and the mechanism by which the reaction proceeds (on-water, in-water) were found to be predominantly influenced by the hydrophilicity/lipophilicity of the starting materials and their physical state. Consequently, this methodology is not applicable when both starting materials are solids and water-insoluble (LSs). The results obtained herein demonstrate that water can and should replace volatile and contaminant organic solvents for the preparation of a large quantity of chalcones. Unfortunately, this methodology has some drawbacks compared to the reported ones: the reaction time is quite long, which could result in significant energy expenditure, and a chromatography column was required to purify certain compounds.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/reactions7030046/s1>, File S1.

Author Contributions: For Q.T.S.: data curation, investigation, methodology, writing—original-draft. D.G.M.Y.: data curation, investigation, methodology. L.F.R.d.l.F.: data curation, formal analysis, supervision, validation. R.M.: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation. J.R.J.P.: data curation, formal analysis, supervision, validation. M.V.X.: conceptualization, data curation, formal analysis, investigation, methodology,

supervision, validation. E.M.R.R.: data curation, formal analysis, investigation, validation. O.H.A.: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, resources. R.T.S.: data curation, formal analysis, investigation. R.M.-P.: data curation, formal analysis, investigation. O.S.S.: data curation, formal analysis, investigation. C.A.S.: conceptualization, data curation, funding acquisition, project administration, resources, supervision, validation, writing—reviewing and editing, investigation, writing—original draft. Author Luis Fernando Roa de la Fuente passed away prior to the publication of this manuscript. All authors have read and agreed to the published version of the manuscript.

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References

1. Miranda, C.L.; Maier, C.S.; Stevens, J.F. Flavonoids. In *eLS*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2012. <https://doi.org/10.1002/9780470015902.a0003068.pub2>.
2. Rosa, G.P.; Seca, A.M.; Barreto, M.D.; Silva, A.M.; Pinto, D.C. Chalcones and Flavanones Bearing Hydroxyl and/or Methoxyl Groups: Synthesis and Biological Assessments. *Appl. Sci.* **2019**, *9*, 2846. <https://doi.org/10.3390/app9142846>.
3. Ninomiya, M.; Koketsu, M. Minor Flavonoids (Chalcones, Flavanones, Dihydrochalcones, and Aurones). In *Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes*; Ramawat, K.G., Mérillon, J.-M., Eds.; Springer: Berlin/Heidelberg, Germany, 2013; pp. 1867–1900. https://doi.org/10.1007/978-3-642-22144-6_62.
4. Elkanzi, N.A.A.; Hrichi, H.; Alolayan, R.A.; Derafa, W.; Zahou, F.M.; Bakr, R.B. Synthesis of Chalcones Derivatives and Their Biological Activities: A Review. *ACS Omega* **2022**, *7*, 27769–27786. <https://doi.org/10.1021/acsomega.2c01779>.
5. Albuquerque, H.; Santos, C.; Cavaleiro, J.; Silva, A. Chalcones as Versatile Synthons for the Synthesis of 5- and 6-Membered Nitrogen Heterocycles. *Curr. Org. Chem.* **2014**, *18*, 2750–2775. <https://doi.org/10.2174/1385272819666141013224253>.
6. Salehi, B.; Quispe, C.; Chamkhi, I.; El Omari, N.; Balahbib, A.; Sharifi-Rad, J.; Bouyahya, A.; Akram, M.; Iqbal, M.; Docea, A.O.; et al. Pharmacological Properties of Chalcones: A Review of Preclinical Including Molecular Mechanisms and Clinical Evidence. *Front. Pharmacol.* **2021**, *11*, 592654. <https://doi.org/10.3389/fphar.2020.592654>.
7. Mezgebe, K.; Melaku, Y.; Mulugeta, E. Synthesis and Pharmacological Activities of Chalcone and Its Derivatives Bearing N-Heterocyclic Scaffolds: A Review. *ACS Omega* **2023**, *8*, 19194–19211. <https://doi.org/10.1021/acsomega.3c01035>.
8. Aoki, N.; Muko, M.; Ohta, E.; Ohta, S. C-Geranylated Chalcones from the Stems of Angelica Keiskei with Superoxide-Scavenging Activity. *J. Nat. Prod.* **2008**, *71*, 1308–1310. <https://doi.org/10.1021/np800187f>.
9. Nasir Abbas Bukhari, S.; Jasamai, M.; Jantan, I.; Ahmad, W. Review of Methods and Various Catalysts Used for Chalcone Synthesis. *Mini-Rev. Org. Chem.* **2013**, *10*, 73–83. <https://doi.org/10.2174/1570193X11310010006>.
10. Donaire-Arias, A.; Poulsen, M.L.; Ramón-Costa, J.; Montagut, A.M.; Estrada-Tejedor, R.; Borrell, J.I. Synthesis of Chalcones: An Improved High-Yield and Substituent-Independent Protocol for an Old Structure. *Molecules* **2023**, *28*, 7576. <https://doi.org/10.3390/molecules28227576>.
11. Radwan, M.A.A.; Alshubramy, M.A.; Abdel-Motaal, M.; Hemdan, B.A.; El-Kady, D.S. Synthesis, Molecular Docking and Antimicrobial Activity of New Fused Pyrimidine and Pyridine Derivatives. *Bioorganic Chem.* **2020**, *96*, 103516. <https://doi.org/10.1016/j.bioorg.2019.103516>.
12. Torres-Sauret, Q.; Vilchis-Reyes, M.A.; Martínez, R.; Romero-Ceronio, N.; Alarcon-Matus, E.; Hernández-Abreu, O.; Vázquez Cancino, R.; Alvarado Sánchez, C. Crossing Borders: On-Water Synthesis of Flavanones. *ChemistrySelect* **2022**, *7*, e202202567. <https://doi.org/10.1002/slct.202202567>.

13. El-Aziz El-Hashash, M.A.; Gomha, S.M.; El-Arab, E.E. Utility of Pyrazolylchalcone Synthons to Synthesize Azolopyrimidines under Grindstone Technology. *Chem. Pharm. Bull.* **2017**, *65*, 90–96. <https://doi.org/10.1248/cpb.c16-00759>.
14. Gomha, S.M.; Abdallah, M.A.; Abbas, I.M.; Kazem, M.S.H. Synthesis, Cytotoxicity Evaluation, Molecular Docking and Utility of Novel Chalcones as Precursors for Heterocycles Incorporating Pyrazole Moiety. *Med. Chem. Shariqah United Arab Emir.* **2018**, *14*, 344–355. <https://doi.org/10.2174/1573406413666171020114105>.
15. Janković, T.; Turković, N.; Kotur-Stevuljević, J.; Vujić, Z.; Ivković, B. Differences in Antioxidant Potential of Chalcones in Human Serum: In Vitro Study. *Chem. Biol. Interact.* **2020**, *324*, 109084. <https://doi.org/10.1016/j.cbi.2020.109084>.
16. Bale, A.T.; Salar, U.; Khan, K.M.; Chigurupati, S.; Fasina, T.; Ali, F.; Ali, M.; Nanda, S.S.; Taha, M.; Perveen, S. Chalcones and Bis-Chalcones Analogs as DPPH and ABTS Radical Scavengers. *Lett. Drug Des. Discov.* **2020**, *18*, 249–257. <https://doi.org/10.2174/1570180817999201001155032>.
17. Mahapatra, D.K.; Bharti, S.K.; Asati, V. Chalcone Scaffolds as Anti-Infective Agents: Structural and Molecular Target Perspectives. *Eur. J. Med. Chem.* **2015**, *101*, 496–524. <https://doi.org/10.1016/j.ejmech.2015.06.052>.
18. Yamamoto, T.; Yoshimura, M.; Yamaguchi, F.; Kouchi, T.; Tsuji, R.; Saito, M.; Obata, A.; Kikuchi, M. Anti-Allergic Activity of Naringenin Chalcone from a Tomato Skin Extract. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1706–1711. <https://doi.org/10.1271/bbb.68.1706>.
19. Iwamura, C.; Shinoda, K.; Yoshimura, M.; Watanabe, Y.; Obata, A.; Nakayama, T. Naringenin Chalcone Suppresses Allergic Asthma by Inhibiting the Type-2 Function of CD4 T Cells. *Allergol. Int.* **2010**, *59*, 67–73. <https://doi.org/10.2332/allergolint.09-OA-0118>.
20. Ouyang, Y.; Li, J.; Chen, X.; Fu, X.; Sun, S.; Wu, Q. Chalcone Derivatives: Role in Anticancer Therapy. *Biomolecules* **2021**, *11*, 894. <https://doi.org/10.3390/biom11060894>.
21. Syam, S.; Abdelwahab, S.I.; Al-Mamary, M.A.; Mohan, S. Synthesis of Chalcones with Anticancer Activities. *Molecules* **2012**, *17*, 6179–6195. <https://doi.org/10.3390/molecules17066179>.
22. Okolo, E.N.; Ugwu, D.I.; Ezema, B.E.; Ndefo, J.C.; Eze, F.U.; Ezema, C.G.; Ezugwu, J.A.; Ujam, O.T. New Chalcone Derivatives as Potential Antimicrobial and Antioxidant Agent. *Sci. Rep.* **2021**, *11*, 21781. <https://doi.org/10.1038/s41598-021-01292-5>.
23. Henry, E.J.; Bird, S.J.; Gowland, P.; Collins, M.; Cassella, J.P. Ferrocenyl Chalcone Derivatives as Possible Antimicrobial Agents. *J. Antibiot.* **2020**, *73*, 299–308. <https://doi.org/10.1038/s41429-020-0280-y>.
24. Gomha, S.M.; Riyadh, S.M.; Abdalla, M.M. Solvent-Drop Grinding Method: Efficient Synthesis, DPPH Radical Scavenging and Anti-Diabetic Activities of Chalcones, Bis-Chalcones, Azolines, and Bis-Azolines. *Curr. Org. Synth.* **2015**, *12*, 220–228. <https://doi.org/10.2174/1570179412666150122230447>.
25. Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem. Rev.* **2017**, *117*, 7762–7810. <https://doi.org/10.1021/acs.chemrev.7b00020>.
26. Farooq, S.; Ngaini, Z. Recent Synthetic Methodologies for Chalcone Synthesis (2013–2018). *Curr. Organocatal.* **2019**, *6*, 184–192. <https://doi.org/10.2174/2213337206666190306155140>.
27. Rammohan, A.; Reddy, J.S.; Sravya, G.; Rao, C.N.; Zyryanov, G.V. Chalcone Synthesis, Properties and Medicinal Applications: A Review. *Environ. Chem. Lett.* **2020**, *18*, 433–458. <https://doi.org/10.1007/s10311-019-00959-w>.
28. Doraghi, F.; Kaloei, Y.M.; Ghasemi, M.; Larijani, B.; Mahdavi, M.; Al-Harrasi, A. Synthetic Approaches to Chalcone Synthesis. *Asian J. Org. Chem.* **2025**, *14*, e00099. <https://doi.org/10.1002/ajoc.202500099>.
29. Shalaby, M.A.; Rizk, S.A.; Fahim, A.M. Synthesis, reactions and application of chalcones: A systematic review. *Org. Biomol. Chem.* **2023**, *21*, 5317–5346. <https://doi.org/10.1039/d3ob00792h>.
30. Stantliff, T.M.; Hill, A.; Kuo, M.E.; Neal, H.E.; Harrod, T.C.; Goens, K.; Mashuta, M.; Christianson, A.M.; Krzysiak, A.J. Flexibility in the Bridge of Chalcone Derivatives Is Important for the Inhibition of Cellular Growth. *Bioorg. Med. Chem. Lett.* **2023**, *95*, 129467. <https://doi.org/10.1016/j.bmcl.2023.129467>.
31. Iftikhar, S.; Khan, S.; Bilal, A.; Manzoor, S.; Abdullah, M.; Emwas, A.-H.; Sioud, S.; Gao, X.; Chotana, G.A.; Faisal, A.; et al. Synthesis and Evaluation of Modified Chalcone Based P53 Stabilizing Agents. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4101–4106. <https://doi.org/10.1016/j.bmcl.2017.07.042>.
32. Neha, K.; Wakode, S. Contemporary Advances of Cyclic Molecules Proposed for Inflammation. *Eur. J. Med. Chem.* **2021**, *221*, 113493. <https://doi.org/10.1016/j.ejmech.2021.113493>.
33. Eucerin: Nuestras Investigaciones | Base de Datos de Ingredientes. Available online: <https://www.eucerin.es/nuestras-investigaciones/base-de-datos-de-ingredientes/licochalcone-a> (accessed on 20 August 2024).
34. Chung, M.I.; Lai, M.H.; Yen, M.H.; Wu, R.R.; Lin, C.N. Phenolics from *Hypericum geminiflorum*. *Phytochemistry* **1997**, *44*, 943–947. [https://doi.org/10.1016/S0031-9422\(96\)00644-9](https://doi.org/10.1016/S0031-9422(96)00644-9).

35. Hamad, A.A.; Omer, R.A.; Kaka, K.N.; Amin, A.A.; Ahmed, K.M.; Rashid, R.F.; Aggarwal, T. A Review: New Synthesis of Chalcone Derivatives and Their Applications. *Chem. Rev. Lett.* **2025**, *8*, 329–351. <https://doi.org/10.22034/crl.2025.480229.1427>.
36. Antonio-Arias, J.E.; Díaz-Oliva, V.D.C.; Romero-Ceronio, N.; Gómez-Rivera, A.; Aguilar-Mariscal, H.; la Fuente, L.F.R.; Lobato-García, C.E. Monomodal vs. Multimodal Microwave Irradiation Applied in the Synthesis of Fluorochalcones. *Am. J. Org. Chem.* **2018**, *8*, 8–12. [10.5923/j.ajoc.20180801.02](https://doi.org/10.5923/j.ajoc.20180801.02)
37. Joshi, S.; Chaudhari, D.; Patel, A.; Vaghela, C.; Patel, J.; Patil, V.; Parikh, K.; Lakshmi, S.R. Recent advances from conventional to green synthetic approaches for chalcone derivatives. *J. Iran. Chem. Soc.* **2026**, *23*, 110. <https://doi.org/10.1007/s13738-026-03410-4>.
38. Marotta, L.; Rossi, S.; Ibba, R.; Brogi, S.; Calderone, V.; Butini, S.; Campiani, G.; Gemma, S. The Green Chemistry of Chalcones: Valuable Sources of Privileged Core Structures for Drug Discovery. *Front. Chem.* **2022**, *10*, 988376. <https://doi.org/10.3389/fchem.2022.988376>.
39. Popatkar, B.B.; Yadav, S.; Manjare, S.B.; Borge, V.V. Green methods for the synthesis of chalcones: An overview with appraisal to sustainable development and bioactive compounds. *Org. Commun.* **2025**, *18*, 38–59. <http://doi.org/10.25135/acg.oc.189.2504.3495>.
40. Mulugeta, D. A Review of Synthesis Methods of Chalcones, Flavonoids, and Coumarins. *Sci. J. Chem.* **2022**, *10*, 41–52. <http://doi.org/10.11648/j.sjc.20221002.12>.
41. Henderson, R.K.; Hill, A.P.; Redman, A.M.; Sneddon, H.F. Development of GSK's Acid and Base Selection Guides. *Green Chem.* **2015**, *17*, 945–949. <https://doi.org/10.1039/C4GC01481B>.
42. Masmoudi, N.; Chtourou, M. Green and Ultrasound-Assisted Synthesis of 1,3-Diaryl-2-Propenones Catalyzed by Amberlyte IRA-410 and Amberlyte IRA-400 Basic Resins. *Lett. Org. Chem.* **2023**, *20*, 362–369. <https://doi.org/10.2174/1570178620666221103105347>.
43. Tang, L.; Gao, Y.; Chen, J.; Yang, L.; Xiao, B.; Shen, G.; Ouyang, Y.; Han, W. Ligand-Free Palladium-Catalyzed Substoichiometric Base Mediated Carbonylation of Aryl Iodides with Alkenylboronic Acids under Ambient Conditions. *Synlett* **2023**, *34*, 1280–1284. <https://doi.org/10.1055/a-2007-2958>.
44. Karaman, İ.; Gezezen, H.; Gürdere, M.B.; Dingil, A.; Ceylan, M. Screening of Biological Activities of a Series of Chalcone Derivatives against Human Pathogenic Microorganisms. *Chem. Biodivers.* **2010**, *7*, 400–408. <https://doi.org/10.1002/cbdv.200900027>.
45. Zhao, P.-L.; Liu, C.-L.; Huang, W.; Wang, Y.-Z.; Yang, G.-F. Synthesis and Fungicidal Evaluation of Novel Chalcone-Based Strobilurin Analogues. *J. Agric. Food Chem.* **2007**, *55*, 5697–5700. <https://doi.org/10.1021/jf071064x>.
46. Chintakrindi, A.S.; Gohil, D.J.; Kothari, S.T.; Chowdhary, A.S.; Kanyalkar, M.A. Design, Synthesis and Evaluation of Chalcones as H1N1 Neuraminidase Inhibitors. *Med. Chem. Res.* **2018**, *27*, 1013–1025. <https://doi.org/10.1007/s00044-017-2124-2>.
47. Jacob, K.C.; Jadhav, G.V.; Vakharia, M.N. Synthesis of 2-hydroxy-4-methyl-5-chlorochalcones and their derivatives. *Pesticides* **1972**, *6*, 94–96.
48. Qiu, X.Y.; Li, S.Z.; Shi, A.R.; Yue, Q.L. Synthesis, Characterized and Biological Activities of Chalcone Derivatives. *Adv. Mater. Res.* **2012**, 535–537, 2540–2543. <https://doi.org/10.4028/www.scientific.net/AMR.535-537.2540>.
49. Balaji, S.; Manikandan, V.; Senbagam, R.; Vijayakumar, R.; Rajarajan, M.; Vanangamudi, G.; Thirunarayanan, G. Synthesis, evaluation of antimicrobial activities of some (e)-1-(5-chloro- 2-hydroxyphenyl)-3-phenylprop-2-en-1-one compounds. *Mintage J. Pharm. Med. Sci.* **2016**, *5*, 24–32.
50. Ammaji, S.; Masthanamma, S.; Bhandare, R.R.B.; Annadurai, S.; Shaik, A. Antitubercular and Antioxidant Activities of Hydroxy and Chloro Substituted Chalcone Analogues: Synthesis, Biological and Computational Studies. *Arab. J. Chem.* **2021**, *15*, 103581. <https://doi.org/10.1016/j.arabjc.2021.103581>.
51. Dofe, V.S.; Sarkate, A.P.; Kathwate, S.H.; Gill, C.H. Synthesis, Antimicrobial Activity and Anti-Biofilm Activity of Novel Tetrazole Derivatives. *Heterocycl. Commun.* **2017**, *23*, 325–330. <https://doi.org/10.1515/hc-2017-0016>.
52. Dofe, V.S.; Sarkate, A.P.; Lokwani, D.K.; Shinde, D.B.; Kathwate, S.H.; Gill, C.H. Novel O-Alkylated Chromones as Antimicrobial Agents: Ultrasound Mediated Synthesis, Molecular Docking and ADME Prediction. *J. Heterocycl. Chem.* **2017**, *54*, 2678–2685. <https://doi.org/10.1002/jhet.2868>.
53. Chandrasekhar, S.; Vijeender, K.; Reddy, K.V. New Synthesis of Flavanones Catalyzed by L-Proline. *Tetrahedron Lett.* **2005**, *46*, 6991–6993. <https://doi.org/10.1016/j.tetlet.2005.08.066>.
54. Muller, B.M.; Mai, J.; Yocum, R.A.; Adler, M.J. Impact of Mono- and Disubstitution on the Colorimetric Dynamic Covalent Switching Chalcone/Flavanone Scaffold. *Org. Biomol. Chem.* **2014**, *12*, 5108–5114. <https://doi.org/10.1039/C4OB00398E>.
55. Jesus, A.R.; Marques, A.P.; Rauter, A.P. An Easy Approach to Dihydrochalcones *via* Chalcone *in Situ* Hydrogenation. *Pure Appl. Chem.* **2016**, *88*, 349–361. <https://doi.org/10.1515/pac-2016-0303>.

56. De, R.; Savarimuthu, A.; Ballav, T.; Singh, P.; Nanda, J.; Hasija, A.; Chopra, D.; Bera, M.K. DBU-Catalyzed Rearrangement of Secondary Propargylic Alcohols: An Efficient and Cost-Effective Route to Chalcone Derivatives. *Synlett* **2020**, *31*, 1587–1592. <https://doi.org/10.1055/s-0040-1707909>.
57. Ciupa, A.; Mahon, M.F.; De Bank, P.A.; Caggiano, L. Simple Pyrazoline and Pyrazole “Turn on” Fluorescent Sensors Selective for Cd^{2+} and Zn^{2+} in MeCN. *Org. Biomol. Chem.* **2012**, *10*, 8753. <https://doi.org/10.1039/c2ob26608c>.
58. Bat, D.G.; Goodman, R.; Jones, D.G.; Kerr, J.S.; Mantegna, L.R.; McAllister, C.; Newton, R.C.; Nurnberg, S.; Welch, P.K.; Covington, M.B. 2-Substituted Chalcone Derivatives as inhibitors of Interleukin-1 Biosynthesis. *J. Med. Chem.* **1993**, *36*, 1434–1442. <https://doi.org/10.1021/jm00062a016>.
59. Kitanosono, T.; Kobayashi, S. Reactions in Water Involving the “On-Water” Mechanism. *Chem. Eur. J.* **2020**, *26*, 9408–9429. <https://doi.org/10.1002/chem.201905482>.
60. Shaik, A.B.; Bhandare, R.R.; Nissankararao, S.; Edis, Z.; Tangirala, N.R.; Shahanaaz, S.; Rahman, M.M. Design, Facile Synthesis and Characterization of Dichloro Substituted Chalcones and Dihydropyrazole Derivatives for Their Antifungal, Antitubercular and Antiproliferative Activities. *Molecules* **2020**, *25*, 3188. <https://doi.org/10.3390/molecules25143188>.
61. Kohler, E.P.; Chadwell, H.M. Benzalacetophenone [chalcone]. *Org. Synth.* **1922**, *2*, 1. <https://doi.org/10.15227/orgsyn.002.0001>.
62. Tanemura, K.; Rohand, T. Activated Charcoal-Mediated Synthesis of Chalcones Catalyzed by NaOH in Water. *Tetrahedron Lett.* **2021**, *71*, 152918. <https://doi.org/10.1016/j.tetlet.2021.152918>.
63. Shakil, N.A.; Singh, M.K.; Kumar, J.; Sathiyendiran, M.; Kumar, G.; Singh, M.K.; Pandey, R.P.; Pandey, A.; Parmar, V.S. Microwave Synthesis and Antifungal Evaluations of Some Chalcones and Their Derived Diaryl-Cyclohexenones. *J. Environ. Sci. Health Part B* **2010**, *45*, 524–530. <https://doi.org/10.1080/03601234.2010.493482>.
64. Kitawat, B.S.; Singh, M.; Kale, R.K. Robust Cationic Quaternary Ammonium Surfactant-Catalyzed Condensation Reaction for (E)-3-Aryl-1-(3-Alkyl-2-Pyrazinyl)-2-Propenone Synthesis in Water at Room Temperature. *ACS Sustain. Chem. Eng.* **2013**, *1*, 1040–1044. <https://doi.org/10.1021/sc400102e>.
65. Dotta, D.; Gastaldi, M.; Fin, A.; Barbero, N.; Barolo, C.; Cardano, F.; Rossi, F.; Brunelli, F.; Viscardi, G.; Tron, G.C.; et al. Chalcone synthesis by Green Claisen–Schmidt reaction in cationic and nonionic micellar media. *J. Org. Chem.* **2025**, *90*, 2915–2926. <https://doi.org/10.1021/acs.joc.4c02616>.
66. Dasari, G.K.; Sunkara, S.; Gadupudi, P.C.R. Green and Ecofriendly Synthesis of Indole-condensed Benzimidazole Chalcones in Water and Their Antimicrobial Evaluations. *J. Heterocycl. Chem.* **2020**, *57*, 1201–1210. <https://doi.org/10.1002/jhet.3856>.
67. Armenise, N.; Malferrari, D.; Ricciardulli, S.; Galletti, P.; Tagliavini, E. Multicomponent Cascade Synthesis of Biaryl-Based Chalcones in Pure Water and in an Aqueous Micellar Environment. *Eur. J. Org. Chem.* **2016**, *2016*, 3177–3185. <https://doi.org/10.1002/ejoc.201600095>.
68. Cravotto, G.; Nano, G.M.; Palmisano, G.; Tagliapietra, S.; Demetri, A.; Penoni, A. The aldol reaction under high-intensity ultrasound: A novel approach to an old reaction. *Eur. J. Org. Chem.* **2003**, *22*, 4438–4444. <https://doi.org/10.1002/ejoc.200300369>.
69. Shen, Y.R.; Ostroverkhov, V. Sum-Frequency Vibrational Spectroscopy on Water Interfaces: Polar Orientation of Water Molecules at Interfaces. *Chem. Rev.* **2006**, *106*, 1140–1154. <https://doi.org/10.1021/cr040377d>.
70. Cortes-Clerget, M.; Yu, J.; Kincaid, J.R.A.; Walde, P.; Gallou, F.; Lipshutz, B.H. Water as the Reaction Medium in Organic Chemistry: From Our Worst Enemy to Our Best Friend. *Chem. Sci.* **2021**, *12*, 4237–4266. <https://doi.org/10.1039/D0SC06000C>.

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