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Citric acid-catalyzed three-component synthesis of (E)-3-aryl-2-styryl-2,3-dihydroquinazolin-4-(1H)-ones and their mild oxidation with I2/DMSO system into (E)-3-aryl-2-styrylquinazolin-4(3H)-ones

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Citric Acid-Catalyzed Three-Component Synthesis of (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4-(1*H*)-ones and Their Mild Oxidation with I_2/DMSO System Into (*e*)-3-aryl-2-styrylquinazolin-4(3*h*)-ones

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Abstract: We hereby report a simple and efficient method for the preparation of (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4-(1*H*)-ones, from isatoic anhydride, anilines and cinnamaldehydes in the presence of 20 mol% citric acid in methanol at 60 °C for 2 h. The styryl-dihydroquinazolin-4-(1*H*)-one products were obtained in moderate and good yields (30–80 %) through the three-component condensation reaction, under an environment-friendly protocol. The latter were easily transformed into styrylquinazolin-4-(3*H*)-one derivatives with 57–91 % yields using a mild oxidation with I_2/DMSO system for less than 60 min.

Keywords: three-component condensation reaction; 2,3-dihydroquinazolin-4-(1*H*)-ones; quinazolin-4-(3*H*)-ones; styryl derivatives; organocatalysis; citric acid; catalytic iodine/DMSO system.

1. Introduction

The quinazolinone skeletons (dihydroquinazolin-4-(1*H*)-ones and quinazolin-4-(3*H*)-ones are the main structural parts for numerous secondary metabolites and privileged scaffolds in medicinal chemistry [1–5], especially in cancer drug research [6, 7] and epilepsy treatment [8]. The chemical characteristics of the quinazolinone core (aromatic ring, two not equivalent nitrogen atoms in the pyrimidine ring, group C=O, π-conjugated lactam-aryl motif, and polarized endocyclic imine C=N function) make simple functionalized quinazolinones attractive, proper, and versatile models or/and precursors for diverse biological, pharmacological and agrochemical and fluorescent properties (Figure 1) [9–23].

Subsequently, there is a huge review literature on their synthesis [24–31]. Among them, environmentally benign approaches, i.e., solid acid catalyzed, nanocatalyzed or organocatalyzed syntheses stand out as promising green alternative methods for constructing quinazolinone skeletons [29–31]. Generally, the quinazolinones are easily prepared using different principal starting materials, 2-substituted aryl amines, such as anthranilic acid (2-aminobenzoic acid), its close derivatives, or 2-aminobenzaldehydes and 2-aminoaryl ketones. Direct synthesis of quinazolinone derivatives through cyclocondensation of 2-aminobenzamide derivatives and aldehydes in the presence of various metal catalysts remains the most popular method [27] although several new methods have been developed for the synthesis of the quinazolinones derivatives [32–35].

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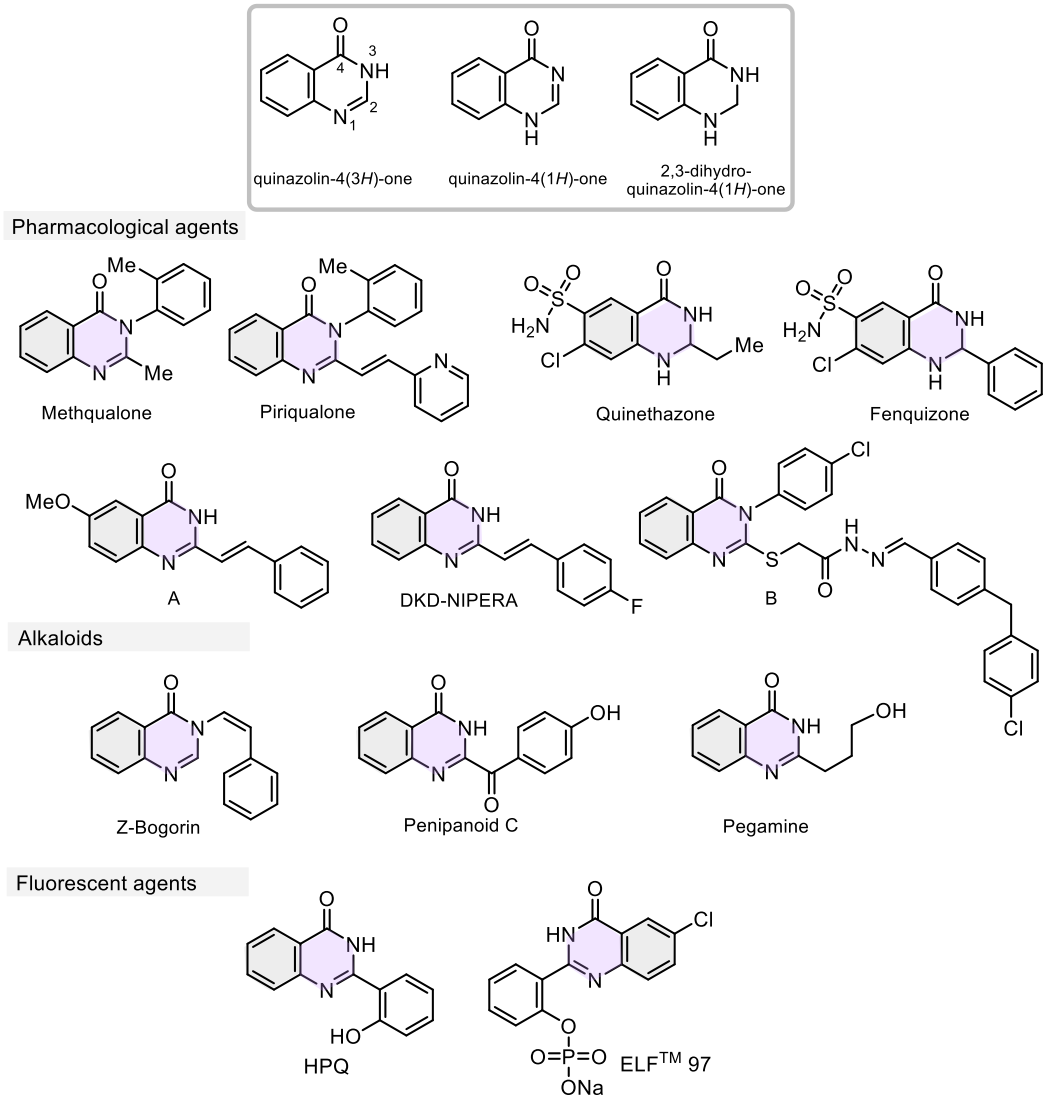

Figure 1. Structures of selected quinazolinone skeletons as pharmaceuticals and fluorophores. Methaqualone ("Quaaludes") is a sedative-hypnotic medication with effects resembling barbiturates. Today, it has no accepted medical use due to its addictive nature [13]. Piriqualone is an anticonvulsant agent for treating neurodegenerative and CNS-trauma-related conditions. It can be prepared from methaqualone and pyridine-2-carboxaldehyde condensation with acetic anhydride and anhydrous zinc chloride in refluxing dioxane [14]. Quinethazone and Fenquizone are diuretics used to treat hypertension [15]. 2-Styrylquinazolin-4(3*H*)-one-2 compound A inhibited tubulin polymerization and the growth of L12102 murine leukemia cells [16], while fluorinated 2-styryl quinazolinone DKD-NIPERA derivative is a promising hit for oral cancer, showing cytotoxicity in CAL-27 cancer cells (squamous cell carcinoma tumor) [17]. N'-(4–Arylidene)-2-((4-oxo-3-dihydroquinazolin-2-yl)thio)acetohydrazide derivative B displayed superior sub-micromolar antiproliferative activity towards NSC lung cancer cell line NCI-H460, being a potent EGFR inhibitor [18]. The alkaloid series (Bogorin, Penipanoid C, and Pegamine) also showed high cytotoxic activity [19–21]. Fluorophores HPQ and ELF™ 97 are insoluble in aqueous media but strongly fluorescent in the solid state [22, 23].

Another equally popular starting material in synthesizing 2,3-dihydroquinazolinones, valuable intermediates in organic synthesis, are isatoic anhydrides. Several methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported, which are usually based on the condensation of isatoic anhydride, aldehydes, and ammonium salts or primary amines in the presence of numerous different catalysts [36], including organocatalysts such as *p*-TsOH [37], ethylene diamine diacetate [38], dodecylbenzenesulfonic acid [39], L-proline [40], β-cyclodextrin [41], room temperature ionic liquids [42], acetic [43], glutamic [44] or citric [45] acids, etc.

In light of the aforementioned facts and our ongoing commitment to exploring the synthesis of novel bioactive small heterocyclic molecules under environmentally friendly reaction conditions

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[46–48], we established a simple green procedure for the synthesis (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4-(1*H*)-ones and corresponding quinazoline-4(3*H*)-one derivatives.

Although 2-styrylquinazolinones, which combine the medicinally significant stilbene and quinazolinone frameworks, are of great interest to synthetic and medicinal chemists, their reported synthetic protocols often have notable limitations. Methods employing starting materials such as 2-aminobenzamide, 2-methyl-3,1-benzoxazin-4-one, or 2-methylquinazolin-4(3*H*)-one derivatives typically involve multi-step reactions, harsh conditions, extended reaction times, and reliance on toxic or expensive catalysts [49–54]. Notably, even the few reports describing one-pot procedures for synthesizing 2-styrylquinazolin-4(3*H*)-ones from readily available isatoic anhydride suffer similar drawbacks [55, 56].

Therefore, this study presents practical, direct syntheses of novel styryl-quinazolinone derivatives via a three-component condensation reaction involving isatoic anhydride, anilines, and cinnamaldehydes. The reaction, conducted in methanol with 20 mol% citric acid, yields (*E*)-3-aryl-2-styryl-2,3-dihydroquinazolin-4(1*H*)-ones. These intermediates are subsequently oxidized using an I_2/DMSO system to produce the corresponding 2-styryl-4(3*H*)-quinazolinones. A key highlight of our research is the development of two simple, cost-effective procedures under sustainable reaction conditions, enabling the preparation of a diverse series of styryl-quinazolinones. These compounds represent privileged scaffolds and valuable medicinal chemistry and organic synthesis building blocks.

2. Materials and Methods

2.1. Materials and Instruments

The solvents and reagents used for synthesizing both the intermediate and final compounds were of synthesis-grade purity. All chemicals were sourced from Merck, J.T. Baker, Sigma, and Aldrich Chemical Co. and were utilized without additional purification. Reaction progress and product purity were monitored using thin-layer chromatography (TLC) on Silufol UV254 plates (0.25 mm thickness). Visualization was done under UV light at 254 nm or using an ethanolic solution of phosphomolybdic-sulfuric acids. Melting points were determined with a Fisher-Johns apparatus and are reported as uncorrected values.

Nuclear magnetic resonance (NMR) spectra for ^{1}H and ^{13}C were acquired using a Bruker Avance–400 spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C). Chemical shifts (δ) are reported in parts per million (ppm), referenced to solvent signals (DMSO-d6: δ 2.50 ppm). Coupling constants (*J*) are provided in Hz, and signal multiplicity is denoted as follows: (s) singlet, (d) doublet, (dd) doublet of doublets, (ddd) doublet of doublet of doublets, and (m) multiplet. The coupling constants *J* are expressed in Hz. The aromatic protons of the N3-aryl fragment are designated as H_{Ph} and those of 2-styryl moiety shown as H_{Ar}.

Infrared spectra were recorded using a Bruker Tensor 27 FTIR spectrophotometer equipped with a platinum ATR cell, operating at 31 scans with a resolution of 2 cm^{-1}. Elemental analyses were performed on a Thermo Scientific CHNS-O analyzer (Model. Flash 2000), with results within ± 0.4 of theoretical values.

2.2. General Procedure for the Synthesis of (E)-3-aryl-2-styryl-2,3-dihydroquinazolin-4(1H)-one derivatives 4a–e

To a solution of isatoic anhydride **1** (1.4 mmol) in 1 mL of methanol, 20 mol% of citric acid monohydrate (CAM) was added, and the mixture was stirred for 20 minutes. Subsequently, the respective aniline derivatives **2a–e**, (1.6 mmol) and cinnamaldehydes **3a–b**, (1.3 mmol) were added sequentially. The resulting mixture was heated at 60°C for 2 hours, with progress monitored by TLC. After the reaction was complete, the mixture was cooled to room temperature. Methanol was distilled off, and the crude solids were washed with a cold solution of 85% ethanol and filtered to yield products **4a–e**. In some cases, purification by column chromatography was required, using alumina as the stationary phase and a petroleum ether: ethyl acetate (1:2) mixture as the eluent. Characterization data for the new compounds **4a–e** are provided below:

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2.2.1 3-Phenyl-2-styryl-2,3-dihydroquinazolin-4(1H)-one (4a)

was synthesized following the general procedure using isatoic anhydride **1** (0.25 g, 1.53 mmol), aniline **2a** (0.14 mL, 1.52 mmol), cinnamaldehyde **3a** (0.19 mL, 1.52 mmol), and 20 mol% CAM (69 mg, 0.33 mmol). After reaction, isolation, and recrystallization, a pale yellow solid (0.27 g, 0.83 mmol, 54% yield) was obtained. R_f = 0.23 (1:2, petroleum ether: ethyl acetate); Mp = 192–194 °C. IR (ATR, νmax): 3310 (N–H), 3058 (ArC–H), 1631 (C=O), 1488 (ArC=C), 1395 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm): 7.76 (1H, dd, *J* = 7.8, 1.6 Hz, 5-H), 7.43–7.38 (4H, m, H_{Ph}), 7.36–7.32 (5H, m, H_{Ar}), 7.28–7.21 (3H, m, 6-H, 7-H, and H_{Ph}), 6.85 (1H, d, *J* = 15.0 Hz, =$H_\alpha C_{Ar}$), 6.76 (1H, m, *J* = 15.0 Hz, =$H_\beta C_{Quin}$), 6.49 (2H, d, *J* = 4.7 Hz, 8-H and N-H), 5.73–5.66 (1H, m, 2-H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm): 161.7, 146.7, 140.6, 135.4, 133.6, 131.9, 128.7 (2), 128.6 (2), 128.1, 128.0, 127.0 (2), 126.7, 126.6 (2), 126.4, 117.5, 115.1, 114.8, 72.5. Anal. calcd. for $C_{22}H_{18}N_2O$ (326.40): C, 80.96; H, 5.56; N, 8.58 %. Found: C, 80.84; H, 5.71; N, 8.40 %.

2.2.2 3-(4-Methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (4b)

was synthesized following the general procedure using isatoic anhydride **1** (0.23 g, 1.32 mmol), 4-methoxyaniline **2c** (0.20 g, 1.62 mmol)), cinnamaldehyde **3a** (0.17 mL, 1.27 mmol), and 20 mol% CAM (65 mg, 0.31 mmol). After reaction, isolation, and recrystallization, a white solid (0.40 g, 1.12 mmol, 80 %) was obtained. R_f = 0.27 (1:2, petroleum ether: ethyl acetate); Mp = 234–236 °C. IR (ATR, νmax): 3311 (N–H), 2810 (OCH_3), 1630 (C=O), 1507 (ArC=C), 1389 (C–N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm): 7.72 (1H, d, *J* = 7.7 Hz, 5-H), 7.37–7.34 (2H, m, H_{Ar}), 7.34–7.31 (1H, m, 7-H), 7.27 (5H, m, H_{Ph} and H_{Ar}), 7.23 (1H, m, 6-H), 6.98–6.91 (2H, m, H_{Ph}), 6.82 (1H, d, *J* = 15.1 Hz, =$H_\alpha C_{Ar}$), 6.75 (1H, m, *J* = 15.0 Hz, =$H_\beta C_{Quin}$), 6.47 (2H, d, *J* = 3.1 Hz, 8-H and N–H), 5.61–5.57 (1H, m, 2-H), 3.74 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm): 161.8, 157.6, 146.8, 135.4, 133.5, 133.3, 131.9, 128.7 (2), 128.6 (2), 128.1, 127.9, 126.7, 126.6 (2), 117.4, 115.0, 114.7, 113.9 (2), 73.0, 55.2. Anal. calcd. for $C_{23}H_{20}N_2O_2$ (356.43): C, 77.51; H, 5.66; N, 7.86 %. Found: C, 77.76; H, 5.53; N, 7.61 %.

2.2.3 3-(3,4-Dimethoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (4c)

was synthesized following the general procedure using isatoic anhydride **1** (0.21 g, 1.30 mmol), 3,4-dimethoxyaniline **2c** (0.22 g, 1.44 mmol), cinnamaldehyde **3a** (0.16 mL, 1.30 mmol), and 20 mol% CAM (58 mg, 0.28 mmol). After reaction, isolation, and recrystallization, a white solid (0.35 g, 0.90 mmol, 70 %) was obtained. R_f = 0.10 (1:2, petroleum ether: ethyl acetate); Mp = 227–228 °C. IR (ATR, νmax): 3306 (N–H), 2919 (OCH_3), 1630 (C=O), 1608 (C=C), 1507 (ArC=C), 1389 (C–N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm): 7.73 (1H, d, *J* = 7.8 Hz, 5-H), 7.39–7.35 (2H, m, H_{Ar}), 7.34–7.31 (1H, m, 7-H), 7.29 (3H, d, *J* = 3.7 Hz, H_{Ar}), 7.27–7.22 (1H, m, H_{Ph}), 6.98–6.95 (1H, m, 6-H), 6.94 (1H, s, H_{Ph}), 6.87 (1H, dd, *J* = 8.5, 2.3 Hz, H_{Ph}), 6.83 (1H, d, *J* = 15.0 Hz, =$H_\alpha C_{Ar}$), 6.75 (1H, m, *J* = 15.0 Hz, =$H_\beta C_{Quin}$), 6.50 (2H, d, *J* = 3.2 Hz, 8-H and N–H), 5.64–5.57 (1H, m, 2-H), 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm): 161.8, 148.5, 147.4, 146.8, 135.5, 133.5 (2), 132.0, 128.6 (2), 128.1, 128.0, 126.8, 126.6 (2), 119.6, 117.4, 115.0, 114.7, 111.8, 111.4, 73.0, 55.5 (2). Anal. calcd. for $C_{24}H_{22}N_2O_3$ (386.45): C, 74.59; H, 5.74; N, 7.25 %. Found: C, 74.40; H, 5.89; N, 7.13 %.

2.2.4 3-(4-Methoxyphenyl)-2-(2-methoxystyryl)-2,3-dihydroquinazolin-4(1H)-one (4d)

was synthesized following the general procedure using isatoic anhydride **1** (0.21g, 1.30 mmol), 4-methoxyaniline **2b** (0.17 g, 1.43 mmol), 3-(2-methoxyphenyl)acrylaldehyde **3b** (0.21 g, 1.29 mmol), and 20 mol% CAM (59 mg, 0.28 mmol). After reaction, isolation, and recrystallization, a brown solid (0.31 g, 0.80 mmol, 61 %) was obtained. R_f = 0.16 (1:2, petroleum ether: ethyl acetate); Mp = 162–164 °C. IR (ATR, νmax): 3306 (N–H), 2832 (OCH_3), 1628 (C=O), 1508 (C=C), 1391 (C–N), 1242 (ArC–H) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm): 7.72 (1H, dd, *J* = 7.8, 1.4 Hz, 5-H), 7.37 (1H, dd, *J* = 7.7, 1.6 Hz, H_{Ar}), 7.33–7.30 (1H, m, 7-H), 7.29–7.26 (3H, m, H_{Ar}), 7.25–7.20 (1H, m, 6-H), 6.97–6.92 (3H, m, 8-H and H_{Ph}), 6.88–6.80 (3H, m, H_{Ph} and N–H), 6.76–6.69 (1H, m, *J* = 15.0, =$H_\alpha C_{Ar}$), 6.43 (1H, m, *J* = 15.1, =$H_\beta C_{Quin}$), 5.60 (1H, m, 2-H), 3.74 (3H, s, OCH_3), 3.72 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm): 161.9, 157.5, 156.4, 146.9, 133.4, 133.3, 129.4, 128.7 (2), 127.9, 127.0, 126.7, 126.5, 123.9, 120.5, 117.3, 115.0, 114.7, 113.9 (2), 111.4, 73.3, 55.4, 55. Anal. calcd. for $C_{24}H_{22}N_2O$ (386.45): C, 74.59; H, 5.74; N, 7.25 %. Found: C, 74.68; H, 5.61; N, 7.33 %.

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2.2.5 3-(4-Bromophenyl)-2-styryl-2,3-dihydroquinazolin-4(1H)-one (4e)

was synthesized following the general procedure using isatoic anhydride **1** (0.20 g, 1.30 mmol), 4-bromoaniline **2d** (0.23 g, 1.35 mmol), cinnamaldehyde **3a** (0.15 mL, 1.23 mmol), and 20 mol% CAM (63 mg, 0.30 mmol). After reaction, isolation, and recrystallization, a white solid (0.14 g, 1.12 mmol, 30 %) was obtained. Rf = 0.46 (1:2, petroleum ether: ethyl acetate); Mp = 183–185 °C. IR (ATR, νmax): 3306 (N–H), 3067 (ArC–H), 1726 (C=O), 1613 (C=C), 1485 (ArC=C), 1010 (C–N), 751 (C–Br) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.92 (1H, dd, *J* = 7.9, 1.1 Hz, 5-H), 7.60–7.57 (2H, m, H_{Ph}), 7.38–7.34 (5H, m, H_{Ar}), 7.27–7.24 (2H, m, H_{Ph}), 7.16 (2H, d, *J* = 8.2 Hz, 6-H and 7-H), 6.84 (1H, d, *J* = 15.2 Hz, =$H_{\alpha}C_{Ar}$), 6.74–6.69 (1H, m,*J* = 15.0 Hz, =$H_{\beta}C_{Quin}$), 6.51–6.46 (2H, m, 8-H and N–H), 5.71 (1H, m, 2-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 161.8, 159.8, 147.0, 146.8, 141.3, 132.5, 132.1, 131.6 (2), 128.6 (2), 128.4, 128.2, 126.6 (2), 126.5, 123.4, 117.5, 115.32 (2), 114.9, 72.3. Anal. calcd. for $C_{22}H_{17}BrN_2O$ (405.30): C, 65.20; H, 4.23; N, 6.91 %. Found: C, 65.37; H, 4.11; N, 6.82 %.

2.3. General Procedure for the Synthesis of (E)-3-aryl-2-styrylquinazolin-4(3H)-one derivatives 5a–d

The oxidation of 2,3-dihydroquinazolin-4(3*H*)-ones (**4a–d**) was conducted as follows: 0.20 g (0.56 mmol) of the corresponding substrate, dissolved in 2 mL of DMSO was introduced into a vial under constant stirring. Subsequently, 20 mol% of I_2 was added, and the reaction was maintained at 100 °C, with progress monitored via TLC for 1 hour. The reaction mixture was then extracted with ethyl acetate and washed with brine (3 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Final purification was achieved through column chromatography (CC) using petroleum ether: ethyl acetate mixtures (10:1). Characterization data for the newly synthesized compounds **5a–d** are provided below:

2.3.1 3-Phenyl-2-styrylquinazolin-4(3H)-one (5a)

was synthesized following the general procedure using 2,3-dihydroquinazolinone **4a** (0.20 g, 0.61 mmol) and 20 mol% of I_2 (31 mg, 0.12 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow (0.11 g, 0.35 mmol, 57 %) was obtained. R_f = 0.50 (1:2, petroleum ether: ethyl acetate); Mp = 195–197 °C (lit. 196–197 °C [55]). IR (ATR, νmax): 3055 (ArC–H), 1665 (C=O), 1550 (ArC=C), 1352 (C–N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.31 (1H, d, *J* = 7.7 Hz, 5-H), 7.98 (1H, d, *J* = 15.5 Hz, =$H_{\alpha}C_{Ar}$), 7.81–7.78 (2H, m, 6-H and 7-H), 7.63–7.55 (3H, m, H_{Ph}), 7.47 (1H, d, *J* = 8.2 Hz, 8-H), 7.35–7.32 (2H, m, H_{Ph}), 7.32–7.29 (5H, m, H_{Ar}), 6.40 (1H, d, *J* = 15.5 Hz, =$H_{\beta}C_{Quin}$). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 162.4, 151.8, 147.9, 140.0, 137.1, 135.4, 134.7, 130.0 (2), 129.7, 129.4, 128.9 (2), 128.8 (2), 127.8 (2), 127.4, 127.2, 126.7, 121.0, 120.0. Anal. calcd. for $C_{22}H_{16}N_2O$ (324.38): C, 81.46; H, 4.97; N, 8.64 %. Found: C, 81.21; H, 4.82; N, 8.53 %.

2.3.2 3-(4-Methoxyphenyl)-2-styrylquinazolin-4(3H)-one (5b)

was synthesized following the general procedure using 2,3-dihydroquinazolinone **4b** (0.20 g, 56 mmol) and 20 mol% of I_2 (28 mg, 0.11 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.18 g, 0.52 mmol, 91 %) was obtained. R_f = 0.53 (1:2, petroleum ether: ethyl acetate); Mp = 166–168 °C. IR (ATR, νmax): 2922 (ArC–H), 2838 (OCH_3), 1671 (C=O), 1548 (C–N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.30 (1H, d, *J* = 7.9 Hz, 5-H), 7.97 (1H, d, *J* = 15.5 Hz, =$H_{\alpha}C_{Ar}$), 7.80–7.76 (2H, m, 6-H and 7-H), 7.46 (1H, d, *J* = 8.2 8-H), 7.38–7.29 (5H, m, H_{Ar}), 7.25–7.19 (2H, m, H_{Ph}), 7.11–7.05 (2H, m, H_{Ph}), 6.47 (1H, d, *J* = 15.5 Hz, =$H_{\beta}C_{Quin}$), 3.91 (3H, s, 4′-OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 162.7, 160.0, 152.2, 147.9, 139.9, 135.4, 134.6, 129.8 (2), 129.7, 129.5, 128.9 (2), 127.9 (2), 127.4, 127.3, 126.6, 121.0, 120.1, 115.2 (2), 55.7. Anal. calcd. for $C_{23}H_{18}N_2O_2$ (354.41): C, 77.95; H, 5.12; N, 7.90 %. Found: C, 77.82; H, 5.37; N, 7.76 %.

2.3.3 3-(3,4-Dimethoxyphenyl)-2-styrylquinazolin-4(3H)-one (5c)

was synthesized following the general procedure using 2,3-dihydroquinazolinone **4c** (0.20 g, 52 mmol) and 20 mol% of I_2 (26 mg, 0.10 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.17 g, 0.47 mmol,

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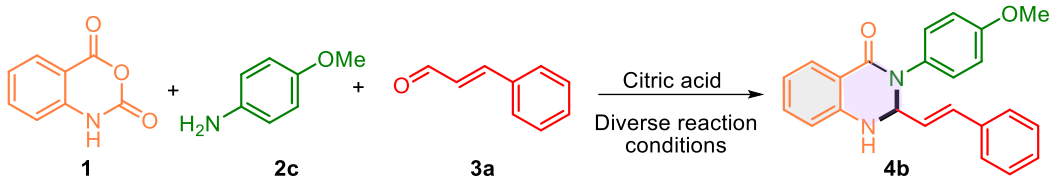
87 %) was obtained. R_f = 0.30 (1:2, petroleum ether: ethyl acetate); Mp = 232–233 °C. IR (ATR, νmax): 3005 (ArC–H), 2915 (OCH_3), 1673 (C=O), 1551 (C–N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.30 (1H, d, *J*= 7.9 Hz, 5-H), 7.98 (1H, d, *J* = 15.5 Hz, $=H_\alpha C_{Ar}$), 7.82–7.75 (2H, m, 6-H and 7-H), 7.50–7.43 (1H, m, 8-H), 7.37–7.30 (5H, m, H_{Ar}), 7.03 (1H, d, *J* = 8.4 Hz, H_{Ph}), 6.87 (1H, dd, *J* = 8.4, 2.3 Hz, H_{Ph}), 6.82 (1H, d, *J* = 2.4 Hz, H_{Ph}), 6.48 (1H, d, *J* = 15.5 Hz, $=H_\beta C_{Quin}$), 3.98 (3H, s, OCH_3), 3.88 (3H, s, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 162.7, 152.1, 150.0, 149.6, 147.9, 140.0, 135.4, 134.7, 129.8, 129.7, 128.9 (2), 127.9 (2), 127.4, 127.2, 126.7, 121.0 (2), 120.0, 111.7, 111.6, 56.2 (2). Anal. calcd. for $C_{24}H_{20}N_2O_3$ (384.44): C, 74.98; H, 5.24; N, 7.29 %. Found: C, 74.71; H, 5.37; N, 7.40 %.

2.3.4 3-(4-Methoxyphenyl)-2-(2-methoxystyryl)-quinazolin-4(3H)-one (5d)

was synthesized following the general procedure using 2,3-dihydroquinazolinone **4c** (0.20 g, 52 mmol) and 20 mol% of I_2 (26 mg, 0.10 mmol), dissolved in 2 mL of DMSO. The reaction mixture was heated at 100 °C. After reaction, isolation, and recrystallization, a pale yellow solid (0.17 g, 0.45 mmol, 86%) was obtained. R_f = 0.43 (1:2, petroleum ether: ethyl acetate); Mp = 189–190 °C. IR (ATR, νmax): 3057 (ArC–H), 2935 (OCH_3), 1671 (C=O), 1550 (C–N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.29 (1H, ddd, *J* = 8.0, 1.4, 0.6 Hz, 5-H), 8.19 (1H, d, *J* = 15.6 Hz, $=H_\alpha C_{Ar}$), 7.82–7.74 (2H, m, 6-H and 7-H), 7.44 (1H, d, *J* = 8.2, 6.6, 1.7 Hz, 8-H), 7.29–7.25 (2H, m, H_{Ar}), 7.23 (2H, d, *J* = 9.0 Hz, H_{Ph}), 7.08 (2H, d, *J* = 9.0 Hz, H_{Ph}), 6.92–6.84 (2H, m, H_{Ar}), 6.67 (1H, d, *J* = 15.6 Hz, $=H_\beta C_{Quin}$), 3.90 (3H, s, OCH_3), 3.76 (3H, s, 4OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 162.8, 159.9, 158.3, 152.9, 148.0, 135.6, 134.5, 130.8, 129.9, 129.8 (2), 129.5, 127.5, 127.2, 126.4, 124.5, 121.3, 120.9, 120.7, 115.1 (2), 111.1, 55.7, 55.3. Anal. calcd. for $C_{24}H_{20}N_2O_3$ (384.44): C, 74.98; H, 5.24; N, 7.29 %. Found: C, 74.83; H, 5.41; N, 7.11 %.

3. Results and Discussion

Drawing on previous reports of 3-aryl-2,3-dihydroquinazolione synthesis catalyzed by organocatalyst [37–45], we selected citric acid as the catalyst. This naturally occurring Brønsted acid is inexpensive, readily available, and has demonstrated good performance in preparing such heterocycles [45]. To explore its efficacy, we investigated the reaction of isatoic anhydride **1**, 4-methoxyaniline **2c**, and *trans*-cinnamaldehyde **3a** to synthesize 3-(4-methoxyphenyl)-2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **4b** using citric acid under varying reaction conditions (Scheme 1, Table 1).



Scheme 1. The model reaction of isatoic anhydride **1**, 4-methoxyaniline **2c**, and *trans*-cinnamaldehyde **3a** to afford 2-styryl-2,3-dihydroquinazolin-4(1*H*)-one **4b** evaluating reaction parameters.

Table 1. Study of the optimal reaction conditions for the preparation of 2-styryl-2,3-dihydroquinazolin-4(1*H*)-one (**4b**)[a].

Entry	Citric acid (mol %)	Dissolvent	t, °C	T (h)	Yield, %
1	40	Methanol	60	2	76
2	40	Methanol	100[b]	10 min	40
3	40	Methanol	160[b]	15 min	20
4	20	Methanol	60	2	80
5	--	Urea/$ZnCl_2$	110	1	20[c]

[a] Reaction conditions: 4-methoxyaniline **2c** (1.62 mmol, 1.1 equiv), isatoic anhydride **1** (1.39 mmol, 1 equiv), *trans*-cinnamaldehyde **3a** (1.27 mmol, 1 equiv), mol % of citric acid monohydrate, 1 mL of methanol (MeOH), time and temperature. [b] Microwave heating (min). [c] Catalytic system with eutectic solvent Urea/$ZnCl_2$ (3.5:1).

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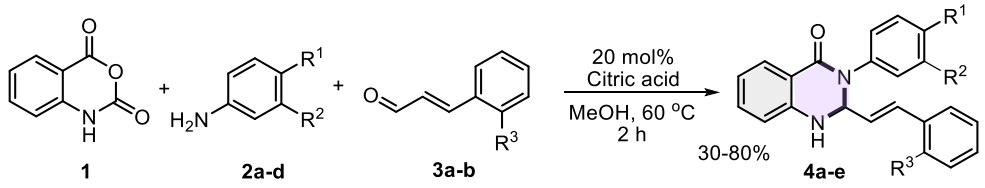
Based on prior literature on the construction of similar systems, the formation of the target compound **4b** was initially investigated using 40 mol% citric acid as a catalyst, yielding 76% (Entry 1, Table 1). Despite this promising result, our goal was to develop a more user-friendly and efficient protocol to accelerate the reaction rate and improve the selective synthesis of dihydroquinazolinones. To this end, microwave radiation (MW) was employed as a heating source under various time and temperature conditions. While MW-assisted synthesis of 2,3-diaryl-2,3-dihydroquinazolinones has been documented [57–59], no reports exist for synthesizing 2-styryl derivatives. Experiments using MW revealed a significant decrease in yield (40% and 20%, respectively) as the temperature and reaction time increased (Entries 2–3, Table 1), indicating that these conditions adversely affected the reaction's progress toward the desired quinazoline systems. Subsequently, the citric acid catalyst loading was reduced to 20 mol% under conventional heating. The reaction, monitored via TLC and completed in two hours, successfully yielded **4b** with an improved 80% yield (Entry 4, Table 1). Finally, a urea/zinc chloride eutectic solvent system (3.5:1molar ratio) was tested, inspired by recent reports on synthesizing 2,3-diaryl-dihydroquinazolinones in deep eutectic solvents [60]. However, under these conditions, the efficient formation of **4b** could not be achieved (Entry 5, Table 1).

Following the optimization of reaction conditions, a small series of 2-styryl-dihydroquinazolinones **4a–e** was successfully synthesized (Scheme 2, Table 2). The reaction employed isatoic anhydride (1), selected anilines **2a–d**, and cinnamaldehydes **3a–b** in the presence of 20 mol% citric acid as a catalyst using methanol as the solvent at 60 °C for 2 hours. The resulting 2,3-dihydroquinazolin-4(1*H*)-ones **4a–e** were obtained in yields ranging from 30% to 80%. The lowest yield (30%) was observed for molecule **4e**, likely due to the diminished nucleophilicity of 4-bromoaniline **2d**, which impeded its interaction with isatoic anhydride during the initial condensation step. Moreover, no product was formed with 4-nitroaniline (not shown in the scheme), underscoring the essential role of aniline nucleophilicity in successfully forming the target compounds.



Scheme 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **4a–e** using citric acid as catalyst.

Table 2. 2-Styryl-dihydroquinazolinone derivatives obtained via a citric acid-catalyzed three-component condensation reaction.

Comp.	R^1	R^2	R^3	Mp., °C	Yield, %
4a	H	H	H	192–194	54
4b	OMe	H	H	234–236	80
4c	OMe	OMe	H	227–228	70
4d	OMe	H	OMe	162–164	61
4e	Br	H	H	183–185	30

In contrast, 2,3-dihydroquinazolin-4(1*H*)-one **4a** and those bearing electron-donating substituents **4b–c** were obtained in moderate to excellent yields. As noted in previous studies [36], the synthesis of the 2,3-dihydroquinazolin-4(1*H*)-one series depends mainly on the balance between the acidity of the reaction medium and the nucleophilicity of the starting anilines. In the initial step, the carbonyl group at the C-4 position of isatoic anhydride **1** undergoes protonation by citric acid, which enhances its electrophilicity and promotes a nucleophilic attack by the amino group of aniline (**2a**). This reaction produces the intermediate 2-amino-N-phenylbenzamide (AFB), which then progresses to form the desired product. Under the same conditions, the second step proceeds as the carbonyl group of cinnamaldehyde **3a**, activated by citric acid, reacts with the amino group at the C-2 position of the intermediate AFB. This nucleophilic attack is followed by dehydration and

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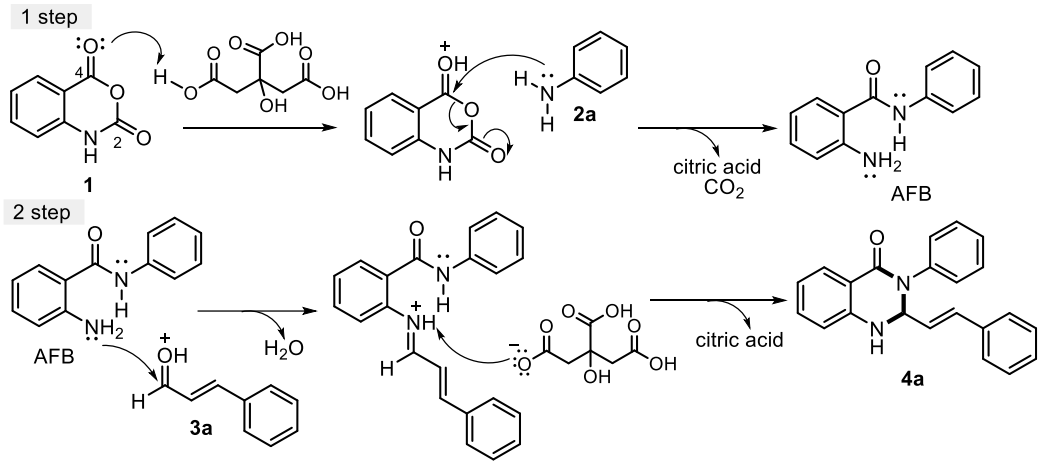
subsequent protonation facilitated by citric acid in the reaction medium. These steps culminate in cyclization, yielding 2,3-dihydroquinazolin-4(1*H*)-one **4a** (Scheme 3).



Scheme 3. Proposed mechanism of 2,3-dihydroquinazolin-4(1*H*)-ones via multicomponent reaction.

The 2-styryl-2,3-dihydroquinazolin-4(1*H*)-ones **4a–e** were obtained as stable solids (Table 2). Their structures were elucidated using a combination of spectroscopic and analytical techniques, including IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. The ^{1}H NMR spectra provided clear evidence for the molecular structure, with all proton signals and their couplings consistent with the spatial arrangement of the molecule. Key features confirming the skeleton construction included the C-2 proton and the olefinic protons of the styryl fragment, =$H_{\alpha}C_{Ar}$ and =$H_{\beta}C_{Quin,}$ which were observed in the regions of 5.57–5.73 ppm, 6.67–6.85 ppm, and 6.43–6.76 ppm, respectively. The olefinic protons were confirmed to have a *trans*-configuration, as indicated by the H_{α} signals appearing as doublets with coupling constants J = 15.0–15.2 Hz. Meanwhile, the H_{β} protons were deshielded and appeared as multiplets due to interactions with the two quinazolinone nitrogen atoms and the adjacent C-2 proton.

The products obtained hold significant value not only for medicinal applications but also for their synthetic potential. Typically, 2,3-diaryl-dihydroquinazolinones can be converted into their corresponding 4(3*H*)-quinazolinone derivatives through oxidation. Established methods include potassium *tert*-butoxide and tetrabutylammonium bromide in dry THF [61] or $KMnO_4$ in acetone [62]. Additionally, a catalyzed cyclization–oxidation coupling of isatoic anhydride with benzaldehydes and amines in the presence of iodine (1 equiv.) and acetic acid (10 mol%) in a MeCN-H_2O mixture was reported in 2010, yielding 2,3-diaryl-4(3*H*)-quinazolinones [63]. Seeking an efficient method for the oxidation of 2-styryl-2,3-dihydro-4(1*H*)-quinazolinones **4** to their respective 2-styrylquinazolinones **5**, we explored the I_2/DMSO catalytic system. This system has gained considerable attention due to its green chemistry attributes, high efficiency, atom economy, low cost, and mild reaction conditions [64,65]. Drawing on these advantages and our prior experience with the system [66], we subjected compounds **4** to oxidation using 20 mol% iodine in DMSO at 100°C for 1 hour. This approach successfully produced the corresponding 4(3*H*)-quinazolinone derivatives **5** in good to excellent yields, demonstrating that this oxidative catalytic system is also reproducible for this type of quinazoline system (Scheme 4).

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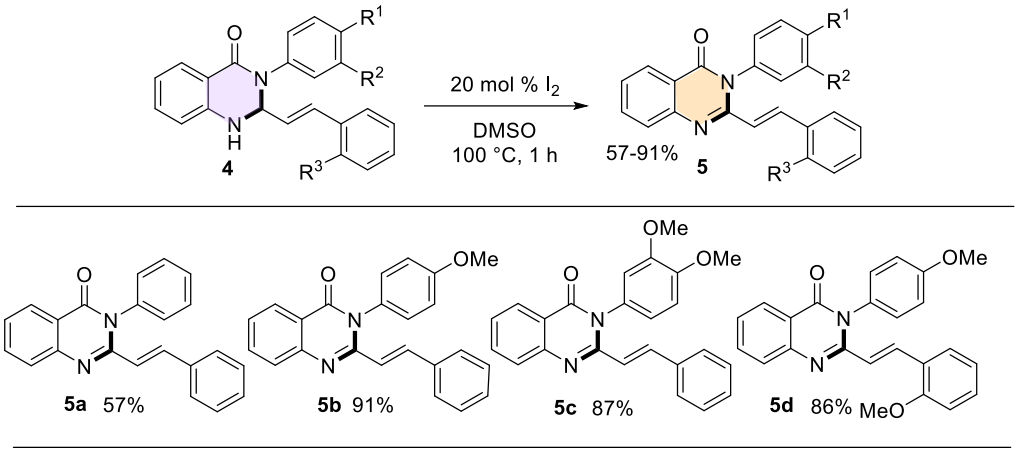

Scheme 4. Preparation of 3-aryl-2-styryl-4(3*H*)-quinazolinones **5** promoted by the I_2/DMSO catalytic system.

The obtained 4(3*H*)-quinazolinones **5a-d** were isolated as stable solids, facilitating the determination of their physical properties and characterization through infrared spectroscopy and nuclear magnetic resonance analysis. A clear comparison of the IR spectra of the dehydro-product **4d** and oxidized counterpart **5d** reveals the absence of the characteristic peak at 3306 cm^{-1}, corresponding to the NH group. This confirms the successful and complete oxidation of dihydroquinazolinone **4d** (Figure S10). Additionally, the NMR spectra of the oxidized products display well-defined signals for the olefinic protons. The olefinic H_β protons (=$H_\beta C_{Quin}$) appear as doublets at 6.40–6.67 ppm (J = 15.5–15.6 Hz), while the H_α protons (=$H_\alpha C_{Ar}$) are observed as doublets at 7.97–8.19 ppm, exhibiting identical coupling constants.

4. Conclusions

In summary, we have developed an organocatalytic approach for synthesizing 3-aryl-quinazolinones incorporating a *trans*-stilbene unit. This method, executed in a straightforward and eco-friendly one-pot process, represents a novel contribution to the field. Citric acid, serving as the catalyst, exhibited remarkable efficiency in facilitating these dehydro-products. These intermediates were then efficiently transformed into 2-styryl-quinazolinones through a metal-free catalytic system using iodine/DMSO under mild oxidative conditions. The synthetic strategies introduced here enable the construction of two diverse series of saturated and aromatic N3-aryl-quinazolinone frameworks featuring a styryl group at the C-2 position. Moreover, the workup procedures are simple, cost-effective, and rely on readily available commercial reagents. Both structural series hold significant potential in medicinal chemistry, particularly in cancer drug discovery. This study provides an accessible and practical route for generating novel libraries of styryl-quinazolinones from various amines and cinnamaldehydes.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, synthetic procedures FT-IR and NMR.

Author Contributions: Conceptualization, V.V.K.; methodology, A.P.G.; formal analysis, A.P.G., C.E.P.G. and V.V.K.; writing—original draft preparation, V.V.K; writing—review and editing, C.E.P.G. and V.V.K. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Synthetic procedures and FT-IR and NMR are reported in Supplementary Materials.

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Conflicts of Interest: The authors declare no conflict of interest.

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References

1. He, D.; Wang, M.; Zhao, S.; Shu, Y.; Zeng, H.; Xiao, C.; Lu, C.; Liu, Y. Pharmaceutical prospects of naturally occurring quinazolinone and its derivatives. *Fitoterapia* **2017**, *119*, 136–149.
2. Hameed, A.; Al-Rashida, M.; Uroos, M.; Ali, S. A.; Arshia; Ishtiaq, M.; Khan, K. M. Quinazoline and quinazolinone as important medicinal scaffolds: a comparative patent review (2011–2016). *Expert Opin. Ther. Pat*. **2018**, *28*(4), 281–297.
3. Alsibaee, A. M.; Al-Yousef, H. M.; Al-Salem, H. S. Quinazolinones, the winning horse in drug discovery. *Molecules* **2023**, *28*(3), 978.
4. Tiwary, B. K.; Pradhan, K.; Nanda, A. K.; Chakraborty, R. Implication of Quinazoline-4(3*H*)-Ones in Medicinal Chemistry: A Brief Review. *J. Chem. Biol. Ther.* **2015**, *1*(1), 1000104.
5. Mahato, A.; Srivastava, B.; Nithya, S. Chemistry Structure Activity Relationship and Biological Activity of Quinazoline-4 (3*H*)-One Derivatives. *Inventi Rapid Med. Chem*. **2011**, *2*(1), 13–19.
6. Kaur, J.; Kaur, S.; Muskan; Kaur, N.; Kumar, V.; Anand, A. Unveiling the Therapeutic Potential of Quinazolinone Derivatives in Cancer Treatment: A Comprehensive Exploration. *ChemistrySelect* **2024**, *9*(32), e202401366.
7. Upadhyay, R.; Tandel, P.; Patel, A. B. Halogen-based quinazolin-4 (3*H*)-one derivatives as MCF-7 breast cancer inhibitors: Current developments and structure–activity relationship. *Arch. Pharm.* **2024**, e2400740.
8. Ugale, V. G.; Bari, S. B. Quinazolines: new horizons in anticonvulsant therapy. *Eur. J. Med. Chem.* 2014, *80*, 447–501.
9. Utreja, D.; Salotra, R.; Kaur, G.; Sharma, S.; Kaushal, S. Chemistry of quinolines and their agrochemical potential. *Curr. Org. Chem.* **2022**, *26*(20), 1895–1913.
10. An, L.; Yang, L.; Yan, T.; Yi, M.; Liu, S.; Li, H.; Bao, X. Synthesis and agricultural antimicrobial evaluation of new quinazoline derivatives containing both a piperazine linker and the N-acetyl moiety. *Pest Manag. Sci.* **2024**, *80*(10), 5307–5321.
11. Ma, J.; Li, P.; Li, X.; Shi, Q.; Wan, Z.; Hu, D.; Jin, L.; Song, B. Synthesis and antiviral bioactivity of novel 3-((2-((1E,4E)-3-oxo-5-arylpenta-1,4-dien-1-yl) phenoxy) methyl)-4(3*H*)-quinazolinone derivatives. *J. Agric. Food Chem.* **2014**, *62*(36), 8928–8934.
12. Xing, Z.; Wu, W.; Miao, Y.; Tang, Y.; Zhou, Y.; Zheng, L.; Fu, Y.; Song, Z.; Peng, Y. Recent advances in quinazolinones as an emerging molecular platform for luminescent materials and bioimaging. *Org. Chem. Front*. **2021**, *8*(8), 1867–1889.
13. Inger, J. A.; Mihan, E. R.; Kolli, J. U.; Lindsley, C. W.; Bender, A. M. DARK classics in chemical neuroscience: methaqualone. *ACS Chem. Neurosci.* **2023**, *14*(3), 340–350.
14. Welch, W. M.; Ewing, F. E.; Huang, J.; Menniti, F. S.; Pagnozzi, M. J.; Kelly, K.; Seymour, P. A.; Guanowsky, V.; Guhan, S.; Guinn, M. R.; Critchett, D.; Lazzaro, J.; Ganong, A. H.; DeVries, K. M.; Staigers, T. L.; Chenard, B. L. Atropisomeric quinazolin-4-one derivatives are potent noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*(2), 177–181.
15. Selvam, T. P.; Kumar, P. V. Quinazoline marketed drugs. *Res. Pharm.* **2015**, *1*(1), https://updatepublishing.com/journal/index.php/rip/article/view/204.
16. Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. Synthesis and biological evaluation of 2-styrylquinazolin-4 (3*H*)-ones, a new class of antimitotic anticancer agents which inhibit tubulin polymerization. *J. Med. Chem.* **1990**, *33*(6), 1721–1728.
17. Satpute, D. P.; Shirwadkar, U.; Tharalla, A. K.; Shinde, S. D.; Vaidya, G. N.; Joshi, S.; Vatsa, P. P.; Jain, A., Singh, A. A., Garg, R., Mandoli, A., Kumar, D. Discovery of fluorinated 2-Styryl-4(3*H*)-quinazolinone as potential therapeutic hit for oral cancer. *Bioorg. Med. Chem.* **2023**, *81*, 117193.
18. Sonousi, A.; Hassan, R. A.; Osman, E. O.; Abdou, A. M.; Emam, S. H. Design and synthesis of novel quinazolinone-based derivatives as EGFR inhibitors with antitumor activity. *J. Enzyme Inhib. Med. Chem.* **2022**, *37*(1), 2644–2659.
19. Seger, C.; Vajrodaya, S.; Greger, H.; Hofer, O. Structure elucidation and synthesis of a new bioactive quinazolone derivative obtained from *Glycosmis Cf. Chlorosperma*. *Chem. Pharm. Bull*. **1998**, *46*(12), 1926–1928.
20. Ma, C.; Li, Y.; Niu, S.; Zhang, H.; Liu, X.; Che, Y. N-hydroxypyridones, phenylhydrazones, and a quinazolinone from *Isaria farinosa*. *J. Nat. Prod.* **2011**, *74*(1), 32–37.
21. Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y. J. Two new quinazoline-quinoline alkaloids from *Peganum nigellastrum*. *Heterocycles* **1999**, *8*(51), 1883–1889.
22. Zhang, X. B.; Waibel, M.; Hasserodt, J. An Autoimmolative Spacer Allows First-Time Incorporation of a Unique Solid-State Fluorophore into a Detection Probe for Acyl Hydrolases. *Chem. Eur. J. 3*(16), 792–795.

 doi:10.20944/preprints202502.0465.v1

23. Zi-Jun, C. A. I.; Kuang, Y. Q.; Dan, P. A. N.; Wei, L. I. U.; Jiang, J. H. Synthesis and characterization of a novel ELF-97-based fluorescent probe for hydrogen peroxide detection. *Chin. J. Anal. Chem.* **2015**, *43*(11), 1671–1675.
24. Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Synthesis of quinazolinones and quinazolines. *Tetrahedron* **2005**, *61*(43), 10153–10202.
25. Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications. *Eur. J. Med. Chem.* **2014**, *76*, 193–244.
26. Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue. *Eur. J. Med. Chem.* **2015**, *90*, 124–169.
27. Maiden, T. M. M.; Harrity, J. P. A. Recent developments in transition metal catalysis for quinazolinone synthesis. *Org. Biomol. Chem.* **2016**, *14*(34), 8014–8025.
28. Reddy, M. M.; Sivaramakrishna, A. Remarkably flexible quinazolinones—synthesis and biological applications. *J. Heterocyclic Chem.* **2020**, *57*(3), 942–954.
29. Kumar, P.; Tomar, V.; Joshi, R. K.; Nemiwal, M. Nanocatalyzed synthetic approach for quinazoline and quinazolinone derivatives: A review (2015–present). *Synth. Commun.* **2022**, *52*(6), 795–826.
30. Lodhi, A.; Maheria, K. C. Solid acid catalysed synthesis of biologically potent quinazolinones: Environmentally benign approaches. *Sustain. Chem. Pharm.* **2023**, *36*, 101265.
31. Borah, B.; Swain, S.; Patat, M.; Chowhan, L. R. Recent advances and prospects in the organocatalytic synthesis of quinazolinones. *Front. Chem.* **2022**, *10*, 991026.
32. Peng, J.-B.; Geng, H.-Q.; Wang, W.; Qi, X.; Ying, J.; Wu, X.-F. Palladium-catalyzed four-component carbonylative synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones: Convenient methaqualone preparation. *J. Catal.* **2018**, *365*, 10–13.
33. Wang, L. C.; Du, S.; Chen, Z.; Wu, X. F. $FeCl_3$-Mediated Synthesis of 2-(Trifluoromethyl) quinazolin-4(3*H*)-ones from Isatins and Trifluoroacetimidoyl Chlorides. *Org. Lett.* **2020**, *22*(14), 5567–5571.
34. Chen, Z.; Wang, L. C.; Zhang, J.; Wu, X. F. Palladium-catalyzed three-component carbonylative synthesis of 2-(trifluoromethyl) quinazolin-4(3*H*)-ones from trifluoroacetimidoyl chlorides and amines. *Org. Chem. Front.* **2020**, *7*(17), 2499–2504.
35. Wang, L. C.; Zhang, Y.; Chen, Z.; Wu, X. F. Palladium-Catalyzed Carbonylative Synthesis of 2-(Trifluoromethyl) quinazolin-4(3*H*)-ones from Trifluoroacetimidoyl Chlorides and Nitro Compounds. *Adv. Synth. Catal.* **2021**, *363*(5), 1417–1426.
36. Abbas, S. Y.; El-Bayouki, K. A.; Basyouni, W. M. Utilization of isatoic anhydride in the syntheses of various types of quinazoline and quinazolinone derivatives. *Synth. Commun.* **2016**, *46*(12), 993–1035.
37. Baghbanzadeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. Water-accelerated synthesis of novel bis-2, 3-dihydroquinazolin-4(1*H*)-one derivatives. *Synthesis* **2006** *2006*(02), 344–348.
38. Narasimhulu, M.; Lee, Y. R. Ethylenediamine diacetate-catalyzed three-component reaction for the synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones and their spirooxindole derivatives. *Tetrahedron* **2011**, *67*(49), 9627–9634.
39. Chen, B. H.; Li, J. T.; Chen, G. F. Efficient synthesis of 2, 3-disubstituted-2, 3-dihydroquinazolin-4(1*H*)-ones catalyzed by dodecylbenzenesulfonic acid in aqueous media under ultrasound irradiation. *Ultrason. Sonochem.* **2015**, *23*, 59–65.
40. Mehta, H. B.; Dixit, B. C.; Dixit, R. B. L-Proline catalyzed one-pot multi-component synthesis of 2-(1, 3-diphenyl-1*H*-pyrazol-4-yl) quinazolin-4(3*H*)-one derivatives and their biological studies. *Chin.Chem. Lett.* **2014**, *25*(5), 741–744.
41. Ramesh, K.; Karnakar, K. G. K. H. V.; Satish, G.; Reddy, K. H. V.; Nageswar, Y. V. D. Tandem supramolecular synthesis of substituted 2-aryl-2, 3-dihydroquinazolin-4(1*H*)-ones in the presence of β-cyclodextrin in water. *Tetrahedron Lett.* **2012**, *53*(45), 6095–6099.
42. Baghbanzadeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. Water-accelerated synthesis of novel bis-2, 3-dihydroquinazolin-4 (1*H*)-one derivatives. *Synthesis* 2006, *2006*(02), 344–348.
43. Karimi-Jaberi, Z.; Arjmandi, R. Acetic acid-promoted, efficient, one-pot synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones. *Monatsh. Chem.* **2011**, *142*, 631–635.
44. Mane, R.; Yaraguppi, D. A.; Ashok, A. K.; Gangadharappa, B.; Chandrakala, K. B.; Kamanna, K. Glutamic acid-catalyzed synthesis of dihydroquinazolinone: anticancer activity, electrochemical behavior, molecular docking, dynamics, simulations and drug-likeness studies. *Res. Chem. Intermed.* **2024**, 1–33.
45. Fahimi, N.; Sardarian, A. R. Citric acid: A green bioorganic catalyst for one-pot three-component synthesis of 2, 3-dihydroquinazoline-4 (1*H*)-ones. *Curr. Organocatal.* **2016**, *3*(1), 39–44.
46. Rosado-Solano, D. N.; Barón-Rodríguez, M. A.; Sanabria-Florez, P. L.; Luna-Parada, L. K.; Puerto-Galvis, C. E.; Zorro-González, A. F.; Kouznetsov, V. V.; Vargas-Méndez, L. Y. Synthesis, biological evaluation and in silico computational studies of 7-chloro-4-(1*H*-1,2,3-triazol-1-yl)quinoline

 doi:10.20944/preprints202502.0465.v1

derivatives. Search for new controlling agents against *Spodoptera frugiperda* (Lepidoptera: Noctuidae) larvae. *J. Agric. Food Chem*. **2019**, *67*(33), 9210–9219.

47. Villamizar-Mogotocoro, A. F.; Bonilla-Castañeda, S. M.; Kouznetsov, V. V. Green conditions for the efficient two-step synthesis of new 6-arylphenanthridines from 2-bromoacetoanilides based on microwave-assisted Suzuki-Miyaura cross-coupling and modified Pictet-Spengler dehydrogenative cyclization in a zinc chloride/[Bmim]BF_4 mixture. *Green Chem.* **2022**, *24*(20), 7996–8004.
48. Becerra-Anaya, S. J.; Merchán Arenas, D. R.; Kouznetsov, V. V. A simple and effective protocol for the Pechmann reaction to obtain 4-methylcoumarin derivatives using a high-speed mixer ball mill process. *Chemistry* **2023**, *5*(2), 1077–1088.
49. Jatav, V.; Mishra, P.; Kashaw, S.; Stables, J. P. Synthesis and CNS depressant activity of some novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4 (3*H*)-ones. *Eur. J. Med. Chem.* **2008**, *43*(1), 135–141.
50. Raffa, D.; Edler, M. C.; Daidone, G.; Maggio, B.; Merickech, M.; Plescia, S.; Schillaci, D.; Bai, R.; Hamel, E. Synthesis, cytotoxicity, and inhibitory effects on tubulin polymerization of a new 3-heterocyclo substituted 2-styrylquinazolinones. *Eur. J. Med. Chem.* **2004**, *39*(4), 299–304.
51. Ovchinnikova, I. G.; Kim, G. A.; Matochkina, E. G.; Kodess, M. I.; Barykin, N. V.; El′tsov, O. S.; Nosova, E. V.; Rusinov, G. L.; Charushin, V. N. Synthesis, photochemical and luminescent properties of (E)-2-(2-hydroxyarylethylene)-3-phenylquinazolin-4 (3*H*)-ones. *Russ. Chem. Bull.* **2014**, *63*, 2467–2477.
52. Baghbanzadeh, M.; Molnar, M.; Damm, M.; Reidlinger, C.; Dabiri, M.; Kappe, C. O. Parallel microwave synthesis of 2-styrylquinazolin-4 (3*H*)-ones in a high-throughput platform using HPLC/GC vials as reaction vessels. *J. Comb. Chem*. **2009**, *11*(4), 676–684.
53. Srinivasa Reddy, B.; Naidu, A.; Dubey, P. K. PEG-600-mediated, green and efficient, tandem syntheses of N-subtituted-2-styrylquinazolin-4-ones. *Green Chem. Lett. Rev.* **2013**, *6*(3), 254–261.
54. Trashakhova, T. V.; Nosova, E. V.; Valova, M. S.; Slepukhin, P. A.; Lipunova, G. N.; Charushin, V. N. Synthesis and photophysical properties of 2-styrylquinazolin-4-ones. *Russ. J. Org. Chem.* **2011**, *47*, 753–761.
55. Kumar, D.; Jadhavar, P. S.; Nautiyal, M.; Sharma, H.; Meena, P. K.; Adane, L.; Pancholia, S.; Chakraborti, A. K. Convenient synthesis of 2, 3-disubstituted quinazolin-4 (3*H*)-ones and 2-styryl-3-substituted quinazolin-4 (3*H*)-ones: Applications towards the synthesis of drugs. *RSC Adv.* **2015**, *5*(39), 30819–30825.
56. Dabiri, M.; Baghbanzadeh, M.; Delbari, A. S. Novel and efficient one-Pot tandem synthesis of 2-Styryl-Substituted 4 (3*H*)-Quinazolinones. *J. Comb. Chem.* **2008**, *10*(5), 700–703.
57. Gupta, A. D.; Sepay, N.; Mallik, A. K. An efficient microwave-assisted synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones by a three component reaction under catalyst-and solvent-free conditions. *Eur. Chem. Bull.* **2016**, *5*, 185–188.
58. Rupnar, B. D.; Kachave, T. R.; Jawale, P. D.; Shisodia, S. U.; Pawar, R. P. Green and efficient synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones in aqueous medium using $ZnFe_2O_4$ catalyst under microwave irradiation. *J. Iran. Chem. Soc.* **2017**, *14*, 1853–1858.
59. Dutta, A.; Sarma, D. Base promoted metal-free approach towards synthesis of quinazolin-4 (3H)-ones and 2, 3-dihydroquinazolin-4 (1H)-ones under microwave irradiation. *Sustain. Chem. Pharm.* **2021**, *20*, 100402.
60. Peña-Solórzano, D.; Guilombo, C. E. G.; Ochoa-Puentes, C. Rapid and eco-friendly high yield synthesis of dihydroquinazolinones mediated by urea/zinc chloride eutectic mixture. *Sustain. Chem. Pharm.* **2019**, *14*, 100167.
61. Mahdavi, M.; Pedrood, K.; Safavi, M.; Saeedi, M.; Pordeli, M.; Ardestani, S. K.; Emami, S.; Adib, M.; Foroumadi, A.; Shafiee, A. Synthesis and anticancer activity of N-substituted 2-arylquinazolinones bearing trans-stilbene scaffold. *Eur. J. Med. Chem.* **2015**, *95*, 492–499.
62. Mehta, H. B.; Dixit, B. C.; Dixit, R. B. L-Proline catalyzed one-pot multi-component synthesis of 2-(1, 3-diphenyl-1H-pyrazol-4-yl) quinazolin-4 (3H)-one derivatives and their biological studies. *Chin. Chem. Lett*. **2014**, *25*(5), 741–744.
63. Wang, J. Q.; Zuo, Z. Y.; He, W. Recent advances of green catalytic system I_2/DMSO in C–C and C–Heteroatom bonds formation. *Catalysts* **2022**, *12*(8), 821.
64. Singhal, R.; Choudhary, S. P.; Malik, B.; Pilania, M. I_2/DMSO-mediated oxidative C–C and C–heteroatom bond formation: a sustainable approach to chemical synthesis. *RSC Adv.* **2024**, *14*(9), 5817–5845.
65. Peñaranda Gómez, A.; Puerto Galvis, C.E.; Macías, M.A.; Ochoa-Puentes, C.; Kouznetsov, V.V. I_2/DMSO-Promoted the synthesis of chromeno[4,3-*b*]quinolines through an imine formation/aza-Diels-Alder/aromatization tandem reaction under metal-catalyst and photosensitizer-free conditions *Synthesis* **2022**, *54*(7), 1857–1869.

 doi:10.20944/preprints202502.0465.v1

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