

## Article

# Facile One-Pot Conversion of (poly)phenols to Diverse (hetero)aryl Compounds by Suzuki Coupling Reaction: A Modified Approach for the Synthesis of Coumarin- and Equol-Based Compounds as Potential Antioxidants

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**Abstract:** A series of 16 (hetero)aryl compounds based on coumarin and equol has been efficiently synthesized by exploring the palladium-catalyzed Suzuki cross-coupling reactions. Polyphenol based on coumarin (4-methyl-7-hydroxy coumarin) was initially converted to corresponding coumarin imidazylate and then subjected to Suzuki coupling reaction with 4-methoxyphenylboronic acid to obtain the coupled product. This modified approach was later developed into a one-pot methodology by directly reacting the polyphenol with 1,1-sulfonyldiimidazole (SDI) and boronic acid in situ to obtain the Suzuki coupled product in one step. Moreover, an array of (poly)phenols based on coumarin and equol were later converted to diverse (hetero)aryl compounds by this optimized step-economic protocol. The synthesized compounds were then subjected to the screening of their potential antioxidant activities by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. In our investigation, the compounds **4ah**, **4eh**, **4gh** and **4hh** exhibited promising antioxidant potential when compared to the reference standard, butylated hydroxytoluene (BHT). Structure activity relationship (SAR) studies revealed the importance of the presence of electron-donating substituents in enhancing the antioxidant activity of the synthesized compounds.

**Keywords:** coumarin; aryl imidazylates; Suzuki coupling; antioxidants; DPPH



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## 1. Introduction

The presence of highly reactive free radicals and oxygen species in the human body can cause numerous degenerative diseases [1–3] such as aging, atherosclerosis, cancer etc. One important reason for this issue is the fact that free radicals can abstract hydrogen atoms from membranes, lipids or DNA existing in biological systems [4]. In this scenario, the significance of eliminating free radicals from biological system has emerged as an urgent need. Accordingly, the sustainability of cellular machinery can be maintained, along with the prevention of oxidative diseases [5]. Free radicals can be effectively trapped and removed by providing antioxidants or free radical scavengers. Hence, oxidative damage can be mitigated by proper supplementation of compounds/molecules with excellent antioxidant properties [6,7]. A variety of natural and synthetic antioxidants has been reported so far and, among them, polyphenols are of utmost importance. Although most of the polyphenols are either extracted from plants or vegetable oils [8], they can also be synthesized in the laboratory on a large scale for various uses. Among the various types of available natural and synthetic polyphenols, coumarin-, equol- and daidzein-based compounds are highly important, owing to their varied applications in medicinal chemistry [9,10].

Coumarins, an important privileged class of benzopyrones, are reported to exhibit a wide spectrum of biological activities, including antimicrobial, antioxidant, anti-inflammatory, anti-tubercular and anticancer properties [11–14]. Coumarins are natural products found in green plants existing in a free or combined state. However, coumarins are also synthesized in the laboratory and their pharmacological significance is underlined by their presence in some important pharmaceutical drugs available in the market, such as warfarin (anti-coagulant), acenocoumarol (anti-coagulant), carbochromen (vasodilator), novobiocin (antibiotic), clorobiocin (antibiotic) and coumermycin A1 (antibiotic) [15–18]. Equol, an isoflavonoid belonging to polyphenols, is reported to display a wide range of pharmacological properties such as anti-androgenic, antioxidant and anti-inflammatory activities [19]. Equol is metabolized from daidzein in living organisms by intestinal bacteria. However, equol is also synthesized in laboratories in racemic form and as separate enantiomers [20].

In the modern arena of drug discovery, the role of palladium-catalyzed cross-coupling reactions, especially Suzuki coupling reactions, is highly significant [21–23]. A wide variety of heterocyclic architectures constituting diverse functional groups can be efficiently synthesized by Suzuki coupling reactions. Recently, we reported the utilization of aryl fluorosulfates as an efficient electrophilic coupling partner in Suzuki coupling for the synthesis of an array of coumarin derivatives [24]. However, our methodology required the initial conversion of phenols to a fluorosulfate-leaving group before subjecting it to Suzuki coupling reactions. This observation prompted us to develop a one-pot methodology for converting phenols directly to a leaving group in situ and react with Suzuki coupling conditions to obtain the desired biaryls as products in one step. In our successful trials, the (poly)phenols based on these natural products were directly converted to various (hetero)aryl compounds by a one-pot synthetic protocol. As a continuation of our ongoing research in the synthesis of biologically active molecules [25–27], we herein report a modified approach for the synthesis of a variety of compounds based on coumarin and equol. The antioxidant potential of these compounds was then evaluated by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay by considering the fact that it does not have to be generated prior to analysis. The structure activity relationship (SAR) studies of these compounds were also carried out at the later stage to get insights about the structural specificity and potency.

## 2. Materials and Methods

### 2.1. General Information

All chemicals were purchased from commercial suppliers and used as delivered. Palladium catalysts and sulfonyldiimidazole (SDI) was procured from Sigma Aldrich, Beijing, China. DMF (Finar AR dry grade) was used directly for all the procedures.  $^1\text{H}$  NMR (400 or 600 MHz) and  $^{13}\text{C}$  NMR (100 or 150 MHz) spectra were recorded on Bruker Avance II and Bruker Avance NEO spectrometer (Bruker, Billerica, MA, USA), respectively. Chemical shifts are reported in parts per million (ppm) and coupling constants in Hertz (Hz). Tetramethylsilane (TMS) ( $\delta = 0.00$  ppm) or residual solvent peak in DMSO- $d_6$  ( $\delta = 2.50$  ppm) and  $\text{CDCl}_3$  ( $\delta = 7.26$  ppm) served as the internal standard for recording [28]. Molecular weights of unknown compounds were determined by Shimadzu GCMS-QP2010 Ultra gas chromatograph operating at an ionization potential of 70 eV (EI), (Shimadzu, Kyoto, Japan). Microanalyses were performed on PerkinElmer Series II CHNS/O 2400 elemental analyzer (PerkinElmer, Waltham, MA, USA). Melting points were determined using a Stuart SMP 3 apparatus. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 TLC plates (Merck, Darmstadt, Germany).

### 2.2. Procedure for the Synthesis of Coumarin Imidazylate Intermediate 2a

In a sealed tube with screw cap, 4-methyl-7-hydroxy coumarin **1a** (1 mmol, 1 equiv.), 1,1'-sulfonyldiimidazole (1.5 mmol, 1.5 equiv.), cesium carbonate (1 mmol, 1 equiv.) and THF (4 mL) was added. The reaction mixture was heated at 80 °C for 8 h. After the completion of reaction monitored by TLC, the reaction mixture was filtered through celite and the filtrate was collected and distilled under reduced pressure. The resulting crude

product was purified by column chromatography to obtain the 4-methyl-2-oxo-2H-chromen-7-yl-1H-imidazole-1-sulfonate intermediate **2a** as white solid in 70% yield.

Mp 157–159 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.42 (s, 3H, CH<sub>3</sub>), 6.32 (s, 1H, ArH), 6.87 (dd, *J* = 2.4, 8.8 Hz, 1H, ArH), 6.98 (d, *J* = 2.4 Hz, 1H, ArH), 7.18 (s, 1H, ArH), 7.33 (s, 1H, ArH), 7.59 (d, *J* = 8.8 Hz, 1H, ArH), 7.75 (s, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.7 (CH<sub>3</sub>), 110.6 (C-aromatic), 116.0 (C-aromatic), 117.2 (C-aromatic), 118.2 (C-aromatic), 120.2 (C-aromatic), 126.4 (C-aromatic), 131.8 (C-aromatic), 137.5 (C-aromatic), 150.3 (C-aromatic), 151.1 (C-aromatic), 154.1 (C-aromatic), 159.4 (CO); MS (EI): *m/z* (%) = 306 (24) [M]<sup>+</sup>, 147 (100); Anal. Calcd for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>S: C, 50.98; H, 3.29; N, 9.15; S, 10.47%. Found: C, 50.92; H, 3.29; N, 9.39; S, 10.40%.

### 2.3. Synthesis of Products **4** from Phenols

In a sealed tube with screw cap, (poly)phenols **1a–i** (1 mmol, 1 equiv.), boronic acids **3a–h** (1.1 mmol, 1.1 equiv.), 1,1-sulfonyldiimidazole (1 mmol, 1 equiv.), Na<sub>2</sub>CO<sub>3</sub> (2 mmol, 2 equiv.) and DMF (2 mL) were added. The reaction mixture was degassed for 10 min under N<sub>2</sub> atmosphere and then Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol%, 0.05 equiv.) was added. The reaction mixture was heated at 90 °C for 8 h. After the specified time, the reaction mixture was filtered through celite, the filtrate was diluted with water (10 mL) and extracted thrice with ethyl acetate. The combined organic layers were washed with brine, dried in Na<sub>2</sub>SO<sub>4</sub> and distilled under reduced pressure to obtain the crude product. The crude product was purified by column chromatography in varying polarities to obtain the titled products **4aa–4ah** and **4bh–4ih** in varying yields. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of all the final compounds have been included in the supplementary information.

#### 7-(4-(1H-pyrazol-1-yl)phenyl)-4-methyl-2H-chromen-2-one (**4aa**)

Yield: 82% (248 mg); light yellow solid; mp 160–162 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.48 (d, *J* = 1.2 Hz, 3H, CH<sub>3</sub>), 6.31 (d, *J* = 1.2 Hz, 1H, ArH), 6.51 (t, *J* = 2.4 Hz, 1H, ArH), 7.55–7.57 (m, 2H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 7.72–7.74 (m, 2H, ArH), 7.76 (d, *J* = 1.6 Hz, 1H, ArH), 7.83 (d, *J* = 8.8 Hz, 2H, ArH), 7.99 (d, *J* = 2.8 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.7 (CH<sub>3</sub>), 108.0 (C-aromatic), 115.0 (C-aromatic), 119.1 (C-aromatic), 119.6 (C-aromatic), 122.8 (C-aromatic), 125.1 (C-aromatic), 126.7 (C-aromatic), 128.2 (C-aromatic), 137.0 (C-aromatic), 140.3 (C-aromatic), 141.5 (C-aromatic), 143.7 (C-aromatic), 152.1 (C-aromatic), 154.0 (C-aromatic), 160.8 (CO); MS (EI): *m/z* (%) = 302 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 75.48; H, 4.67; N, 9.27%; Found: C, 75.53; H, 4.42; N, 9.03%.

#### 4-Methyl-7-(*o*-tolyl)-2H-chromen-2-one (**4ab**)

Yield: 78% (195 mg); white solid; mp 135–137 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.31 (s, 3H, CH<sub>3</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 6.33 (s, 1H, ArH), 7.24–7.29 (m, 3H, ArH), 7.31–7.32 (m, 3H, ArH), 7.67 (d, *J* = 8 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.6 (CH<sub>3</sub>), 20.4 (CH<sub>3</sub>), 114.9 (C-aromatic), 117.6 (C-aromatic), 118.6 (C-aromatic), 124.3 (C-aromatic), 125.5 (C-aromatic), 126.1 (C-aromatic), 128.2 (C-aromatic), 129.5 (C-aromatic), 130.7 (C-aromatic), 135.2 (C-aromatic), 140.0 (C-aromatic), 146.0 (C-aromatic), 152.3 (C-aromatic), 153.4 (C-aromatic), 160.9 (CO); MS (EI): *m/z* (%) = 250 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>17</sub>H<sub>14</sub>O<sub>2</sub>: C, 81.58; H, 5.64%; Found: C, 81.37; H, 5.26%.

#### 7-(2-Ethoxyphenyl)-4-methyl-2H-chromen-2-one (**4ac**)

Yield: 80% (224 mg); white solid; mp 116–118 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.37 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 2.47 (s, 3H, CH<sub>3</sub>), 4.08 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.29 (s, 1H, ArH), 6.99–7.06 (m, 2H, ArH), 7.33–7.37 (m, 2H, ArH), 7.51 (dd, *J* = 1.6, 8.4 Hz, 1H, ArH), 7.58 (s, 1H, ArH), 7.62 (d, *J* = 8 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 14.7 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>), 64.0 (CH<sub>2</sub>), 112.6 (C-aromatic), 114.6 (C-aromatic), 117.8 (C-aromatic), 118.5 (C-aromatic), 121.0 (C-aromatic), 123.9 (C-aromatic),

125.7 (C-aromatic), 128.7 (C-aromatic), 129.7 (C-aromatic), 130.7 (C-aromatic), 142.7 (C-aromatic), 152.4 (C-aromatic), 153.3 (C-aromatic), 155.9 (C-aromatic), 161.2 (CO); MS (EI):  $m/z$  (%) = 280 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>18</sub>H<sub>16</sub>O<sub>3</sub>: C, 77.12; H, 5.75%. Found: C, 77.33; H, 6.06%.

#### 7-(3-Fluorophenyl)-4-methyl-2H-chromen-2-one (4ad)

Yield: 69% (175 mg); white solid; mp 140–143 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.48 (s, 3H, CH<sub>3</sub>), 6.32 (s, 1H, ArH), 7.10–7.14 (m, 1H, ArH), 7.33 (d,  $J$  = 10 Hz, 1H, ArH), 7.40–7.48 (m, 2H, ArH), 7.51–7.54 (m, 2H, ArH), 7.67 (d,  $J$  = 8.4 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.7 (CH<sub>3</sub>), 114.2 (d,  $J$  = 14 Hz, C-aromatic), 115.2 (C-aromatic), 115.3 (C-aromatic), 115.4 (C-aromatic), 119.4 (C-aromatic), 122.9 (d,  $J$  = 2 Hz, C-aromatic), 123.0 (C-aromatic), 125.1 (C-aromatic), 130.7 (d,  $J$  = 5 Hz, C-aromatic), 141.4 (d,  $J$  = 5 Hz, C-aromatic), 143.5 (d,  $J$  = 1 Hz, C-aromatic), 152.0 (C-aromatic), 154.0 (C-aromatic), 160.7 (CO), 163.2 (d,  $J$  = 164 Hz, CF); MS (EI):  $m/z$  (%) = 254 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>16</sub>H<sub>11</sub>FO<sub>2</sub>: C, 75.58; H, 4.36; F, 7.47%. Found: C, 75.80; H, 4.46; F, 7.62%.

#### 4-Methyl-7-(3-(trifluoromethoxy)phenyl)-2H-chromen-2-one (4ae)

Yield: 73% (234 mg); white solid; mp 65–67 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.47 (s, 3H, CH<sub>3</sub>), 6.31 (s, 1H, ArH), 7.28 (s, 1H, ArH), 7.46 (s, 1H, ArH), 7.49–7.56 (m, 4H, ArH), 7.68 (d,  $J$  = 8 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.6 (CH<sub>3</sub>), 115.3 (2 peaks, C-aromatic), 119.5 (C-aromatic), 119.8 (C-aromatic), 120.5 (q,  $J$  = 250 Hz, CF<sub>3</sub>), 120.7 (C-aromatic), 123.0 (C-aromatic), 125.2 (C-aromatic), 125.5 (C-aromatic), 130.5 (C-aromatic), 141.2 (C-aromatic), 143.1 (C-aromatic), 149.9 (C-aromatic), 151.9 (C-aromatic), 154.0 (C-aromatic), 160.6 (CO); MS (EI):  $m/z$  (%) = 320 (81) [M]<sup>+</sup>, 292 (100); Anal. Calcd for C<sub>17</sub>H<sub>11</sub>F<sub>3</sub>O<sub>3</sub>: C, 63.75; H, 3.46; F, 17.80%. Found: C, 63.35; H, 3.18; F, 17.81%.

#### 7-(3-Methoxyphenyl)-4-methyl-2H-chromen-2-one (4af)

Yield: 81% (215 mg); off white solid; mp 131–134 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.46 (s, 3H, CH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 6.29 (s, 1H, ArH), 6.96 (d,  $J$  = 8 Hz, 1H, ArH), 7.14 (s, 1H, ArH), 7.21 (d,  $J$  = 7.2 Hz, 1H, ArH), 7.39 (t,  $J$  = 8 Hz, 1H, ArH), 7.51–7.53 (m, 2H, ArH), 7.64 (d,  $J$  = 8.4 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.6 (CH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 113.0 (C-aromatic), 113.8 (C-aromatic), 114.8 (C-aromatic), 115.2 (C-aromatic), 119.0 (C-aromatic), 119.6 (C-aromatic), 123.1 (C-aromatic), 124.9 (C-aromatic), 130.1 (C-aromatic), 140.6 (C-aromatic), 144.8 (C-aromatic), 152.1 (C-aromatic), 153.9 (C-aromatic), 160.1 (C-aromatic), 160.9 (CO); MS (EI):  $m/z$  (%) = 266 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>17</sub>H<sub>14</sub>O<sub>3</sub>: C, 76.68; H, 5.30%. Found: C, 77.01; H, 5.12%.

#### 7-(4-Diethylaminophenyl)-4-methyl-2H-chromen-2-one (4ag)

Yield: 76% (233 mg); yellow solid; mp 154–157 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.21 (t,  $J$  = 6.8 Hz, 6H, 2CH<sub>3</sub>), 2.44 (s, 3H, CH<sub>3</sub>), 3.42 (q,  $J$  = 7.2 Hz, 4H, 2CH<sub>2</sub>), 6.22 (s, 1H, ArH), 6.76 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.50–7.59 (m, 5H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 12.6 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>), 44.4 (CH<sub>2</sub>), 111.8 (C-aromatic), 113.3 (C-aromatic), 113.7 (C-aromatic), 117.6 (C-aromatic), 121.8 (C-aromatic), 124.7 (C-aromatic), 125.2 (C-aromatic), 128.1 (C-aromatic), 145.1 (C-aromatic), 148.1 (C-aromatic), 152.4 (C-aromatic), 154.2 (C-aromatic), 161.3 (CO); MS (EI):  $m/z$  (%) = 307 (53) [M]<sup>+</sup>, 292 (100); Anal. Calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>: C, 78.15; H, 6.89; N, 4.56%. Found: C, 78.02; H, 6.97; N, 4.37%.

#### 7-(4-Methoxyphenyl)-4-methyl-2H-chromen-2-one (4ah)

Yield: 85% (226 mg); off white solid; mp 133–136 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.46 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 6.27 (s, 1H, ArH), 7.01 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.49–7.51 (m, 2H, ArH), 7.58 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.63 (d,  $J$  = 8.4 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 18.6 (CH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 114.4 (C-aromatic), 114.5 (C-aromatic), 114.6 (C-aromatic), 118.4 (C-aromatic),

122.5 (C-aromatic), 124.9 (C-aromatic), 128.3 (C-aromatic), 131.5 (C-aromatic), 144.5 (C-aromatic), 152.2 (C-aromatic), 154.0 (C-aromatic), 160.1 (C-aromatic), 161.0 (CO); MS (EI):  $m/z$  (%) = 266 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>17</sub>H<sub>14</sub>O<sub>3</sub>: C, 76.68; H, 5.30%. Found: C, 76.71; H, 5.08%.

#### 7-(4-Methoxyphenyl)-2H-chromen-2-one (4bh)

Yield: 80% (202mg); off white solid; mp 158–161 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 3.86 (s, 3H, OCH<sub>3</sub>), 6.39 (d,  $J$  = 9.6 Hz, 1H, ArH), 7.00 (d,  $J$  = 8.8 Hz, 2H, ArH), 7.46–7.51 (m, 3H, ArH), 7.56 (d,  $J$  = 8.8 Hz, 2H, ArH), 7.71 (d,  $J$  = 9.6 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 55.4 (OCH<sub>3</sub>), 114.4 (C-aromatic), 114.6 (C-aromatic), 115.9 (C-aromatic), 117.3 (C-aromatic), 122.8 (C-aromatic), 128.1 (C-aromatic), 128.4 (C-aromatic), 131.5 (C-aromatic), 143.2 (C-aromatic), 144.7 (C-aromatic), 154.6 (C-aromatic), 160.2 (C-aromatic), 161.0 (CO); MS (EI):  $m/z$  (%) = 252 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>16</sub>H<sub>12</sub>O<sub>3</sub>: C, 76.18; H, 4.79%. Found: C, 76.42; H, 4.65%.

#### 7-(4-Methoxyphenyl)-4-(trifluoromethyl)-2H-chromen-2-one (4ch)

Yield: 75% (240 mg); off white solid; mp 154–157 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 3.88 (s, 3H, OCH<sub>3</sub>), 6.77 (s, 1H, ArH), 7.03 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.56–7.61 (m, 4H, ArH), 7.76 (d,  $J$  = 8 Hz, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 55.4 (OCH<sub>3</sub>), 111.9 (C-aromatic), 114.7 (C-aromatic), 114.8 (C-aromatic), 115.0 (q,  $J$  = 6 Hz, C-aromatic), 121.6 (q,  $J$  = 274 Hz, CF<sub>3</sub>), 123.3 (C-aromatic), 125.6 (C-aromatic), 128.4 (C-aromatic), 130.7 (C-aromatic), 141.4 (q,  $J$  = 33 Hz, C-aromatic), 145.8 (C-aromatic), 154.9 (C-aromatic), 159.1 (C-aromatic), 160.6 (CO); MS (EI):  $m/z$  (%) = 320 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>17</sub>H<sub>11</sub>F<sub>3</sub>O<sub>3</sub>: C, 63.75; H, 3.46; F, 17.80%. Found: C, 63.70; H, 3.81; F, 17.93%.

#### Ethyl-2-(7-(4-methoxyphenyl)-2-oxo-2H-chromen-4-yl)acetate (4dh)

Yield: 74% (250 mg); off white solid; mp 130–133 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.27 (t,  $J$  = 7.2 Hz, 3H, CH<sub>3</sub>), 3.78 (s, 2H, CH<sub>2</sub>), 3.86 (s, 3H, CH<sub>3</sub>), 4.21 (q,  $J$  = 7.2 Hz, 2H, OCH<sub>2</sub>), 6.37 (s, 1H, ArH), 7.01 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.49–7.51 (m, 2H, ArH), 7.56–7.62 (m, 3H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 14.1 (CH<sub>3</sub>), 38.2 (CH<sub>2</sub>), 55.4 (OCH<sub>3</sub>), 61.8 (OCH<sub>2</sub>), 114.6 (C-aromatic), 114.7 (C-aromatic), 116.3 (C-aromatic), 117.3 (C-aromatic), 122.7 (C-aromatic), 124.9 (C-aromatic), 128.3 (C-aromatic), 131.3 (C-aromatic), 144.8 (C-aromatic), 147.9 (C-aromatic), 154.3 (C-aromatic), 160.2 (C-aromatic), 160.6 (CO), 168.7 (CO); MS (EI):  $m/z$  (%) = 338 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>20</sub>H<sub>18</sub>O<sub>5</sub>: C, 70.99; H, 5.36%. Found: C, 71.30; H, 5.22%.

#### 9-(4-Methoxyphenyl)-1-methyl-3H-benzof[chromen-3-one (4eh)

Yield: 78% (246 mg); light yellow solid; mp 174–177 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 3.01 (s, 3H, CH<sub>3</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 6.40 (s, 1H, ArH), 7.06 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.46 (d,  $J$  = 8.8 Hz, 1H, ArH), 7.64 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.77 (d,  $J$  = 8.4 Hz, 1H, ArH), 7.97 (t,  $J$  = 8.8 Hz, 3H, ArH), 8.75 (s, 1H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 26.5 (CH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 114.6 (C-aromatic), 116.5 (C-aromatic), 117.5 (C-aromatic), 122.8 (C-aromatic), 124.8 (C-aromatic), 128.6 (C-aromatic), 130.1 (2 peaks, C-aromatic), 130.7 (C-aromatic), 133.3 (C-aromatic), 133.5 (C-aromatic), 140.4 (C-aromatic), 154.0 (C-aromatic), 155.1 (C-aromatic), 159.7 (C-aromatic), 160.4 (CO); MS (EI):  $m/z$  (%) = 316 (100) [M]<sup>+</sup>; Anal. Calcd for C<sub>21</sub>H<sub>16</sub>O<sub>3</sub>: C, 79.73; H, 5.10%. Found: C, 79.98; H, 5.34%.

#### 6-Acetyl-7-(4-methoxyphenyl)-4-methyl-2H-chromen-2-one (4fh)

Yield: 75% (231 mg); off white solid; mp 180–182 °C.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ = 2.00 (s, 3H, CH<sub>3</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 6.33 (s, 1H, ArH), 7.00 (d,  $J$  = 7.8 Hz, 2H, ArH), 7.29 (d,  $J$  = 7.8 Hz, 2H, ArH), 7.32 (s, 1H, ArH), 7.79 (s, 1H, ArH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ = 18.7 (CH<sub>3</sub>), 30.4 (CH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 114.6 (C-aromatic), 115.5 (C-aromatic), 118.1 (C-aromatic), 118.6 (C-aromatic), 125.2 (C-aromatic), 130.0 (C-aromatic), 131.3 (C-aromatic), 137.2 (C-aromatic), 144.1 (C-aromatic),

152.1 (C-aromatic), 154.5 (C-aromatic), 160.2 (C-aromatic), 160.4 (CO), 203.6 (CO); MS (EI):  $m/z$  (%) = 308 (100)  $[M]^+$ ; Anal. Calcd for  $C_{19}H_{16}O_4$ : C, 74.01; H, 5.23%. Found: C, 73.61; H, 5.11%.

#### 7-Methoxy-3-(4'-methoxy [1,1'-biphenyl]-4-yl)chroman (4gh)

Yield: 68% (235 mg); white solid; mp 157–160 °C.

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 3.02 (d,  $J$  = 9.6 Hz, 2H,  $CH_2$ ), 3.26–3.28 (m, 1H, CH), 3.79 (s, 3H,  $OCH_3$ ), 3.86 (s, 3H,  $OCH_3$ ), 4.06 (t,  $J$  = 10.4 Hz, 1H, CH), 4.38 (d,  $J$  = 10.4 Hz, 1H, CH), 6.46 (s, 1H, ArH), 6.50 (d,  $J$  = 8.4 Hz, 1H, ArH), 6.98–7.02 (m, 3H, ArH), 7.30 (d,  $J$  = 8 Hz, 2H, ArH), 7.52–7.55 (m, 4H, ArH);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 31.7 ( $CH_2$ ), 38.4 (CH), 55.4 (2 peaks,  $OCH_3$ ), 70.9 ( $CH_2$ ), 101.4 (C-aromatic), 107.4 (C-aromatic), 114.1 (C-aromatic), 114.3 (C-aromatic), 127.1 (C-aromatic), 127.8 (C-aromatic), 128.1 (C-aromatic), 130.2 (C-aromatic), 133.3 (C-aromatic), 139.7 (C-aromatic), 139.8 (C-aromatic), 155.1 (C-aromatic), 159.2 (2 peaks, C-aromatic); MS (EI):  $m/z$  (%) = 346 (45)  $[M]^+$ , 210 (100); Anal. Calcd for  $C_{23}H_{22}O_3$ : C, 79.74; H, 6.40%. Found: C, 79.48; H, 6.49%.

#### 3,7-Bis(4-methoxyphenyl)chromane (4hh)

Yield: 70% (242 mg); white solid; mp 160–162 °C.

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 3.04 (d,  $J$  = 8 Hz, 2H,  $CH_2$ ), 3.23–3.28 (m, 1H, CH), 3.81 (s, 3H,  $OCH_3$ ), 3.85 (s, 3H,  $OCH_3$ ), 4.03 (t,  $J$  = 10.8 Hz, 1H, CH), 4.36 (d,  $J$  = 10.8 Hz, 1H, CH), 6.91 (d,  $J$  = 8.4 Hz, 2H, ArH), 6.97 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.07–7.15 (m, 3H, ArH), 7.19 (d,  $J$  = 8.8 Hz, 2H, ArH), 7.52 (d,  $J$  = 8.8 Hz, 2H, ArH);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 32.4 ( $CH_2$ ), 37.9 (CH), 55.3 (2 peaks,  $OCH_3$ ), 71.2 ( $CH_2$ ), 114.3 (C-aromatic), 114.4 (C-aromatic), 114.6 (C-aromatic), 118.9 (C-aromatic), 120.5 (C-aromatic), 128.0 (C-aromatic), 128.3 (C-aromatic), 130.0 (C-aromatic), 133.5 (2 peaks, C-aromatic), 140.4 (C-aromatic), 154.7 (C-aromatic), 158.8 (C-aromatic), 159.3 (C-aromatic); MS (EI):  $m/z$  (%) = 346 (63)  $[M]^+$ , 134 (100); Anal. Calcd for  $C_{23}H_{22}O_3$ : C, 79.74; H, 6.40%. Found: C, 80.13; H, 6.51%.

#### 2-(4-Methoxyphenyl)naphthalene (4ih)

Yield: 85% (199 mg); off white solid; mp 140–143 °C.

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 3.88 (s, 3H,  $OCH_3$ ), 7.03 (d,  $J$  = 8.8 Hz, 2H, ArH), 7.45–7.52 (m, 2H, ArH), 7.67 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.73 (d,  $J$  = 8.4 Hz, 1H, ArH), 7.85–7.91 (m, 3H, ArH), 8.00 (s, 1H, ArH);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 55.4 ( $OCH_3$ ), 114.3 (C-aromatic), 125.1 (C-aromatic), 125.5 (C-aromatic), 125.7 (C-aromatic), 126.2 (C-aromatic), 127.6 (C-aromatic), 128.1 (C-aromatic), 128.4 (2 peaks, C-aromatic), 132.3 (C-aromatic), 133.7 (C-aromatic), 133.8 (C-aromatic), 138.2 (C-aromatic), 159.3 (C-aromatic); MS (EI):  $m/z$  (%) = 234 (100)  $[M]^+$ ; Anal. Calcd for  $C_{17}H_{14}O$ : C, 87.15; H, 6.02%. Found: C, 87.17; H, 6.05%.

#### 2.4. Procedure for Determining Antioxidant Potential of the Synthesized Compounds

The conventional colorimetric DPPH• scavenging capacity assay was carried out according to a previously reported laboratory protocol [29]. Briefly, a 100  $\mu$ L (100  $\mu$ g concentration) sample of organic compounds prepared in methanol was added to 3 mL of 0.004% w/v DPPH• solution. Each test tube was made up to a 4 mL final volume. The reference standard BHT was also dissolved in methanol to make the same concentration as that of the tested compounds. Each mixture was vortexed for some time and left to stand in the dark for 10 min at ambient temperature. The absorbance of each reaction mixture was measured at 517 nm against a blank of methanol using a UV-visible spectrometer (Shimadzu UV-1800). The level of DPPH• remaining for each experiment was calculated by the following equation:

$$\% \text{Scavenging Activity} = \frac{\text{Absorbance of the control} - \text{Absorbance of the test sample}}{\text{Absorbance of the control}} \times 100$$

The inhibition curve was plotted for triplicate experiments and represented as percentage of mean inhibition  $\pm$  standard deviation.

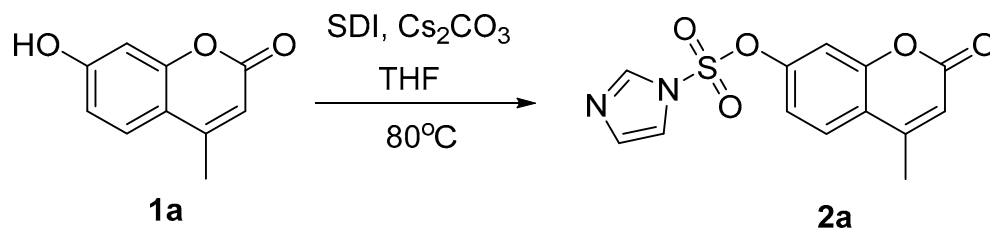


### 3. Results

#### 3.1. Chemistry and Pharmacological Studies

##### 3.1.1. Synthesis of Coumarin Derivatives by One-Pot Suzuki Coupling

As illustrated in Scheme 1, our synthetic strategy started from preparing the coumarin imidazylate intermediate **2a** from 4-methyl-7-hydroxy coumarin **1a** in the presence of 1,1-sulfonyldiimidazole (SDI) and cesium carbonate in THF solvent at 80 °C. This intermediate was then planned to react with different arylboronic acids for synthesizing a series of 4-methyl-7-substituted coumarins by Suzuki coupling.

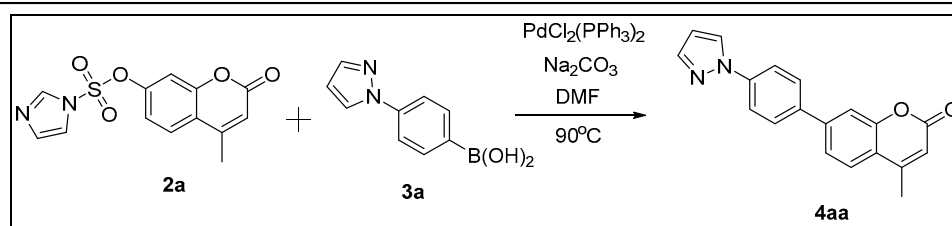


**Scheme 1.** Synthesis of coumarin imidazylate intermediate.

As a model reaction, we took **2a** and (4-(1*H*-pyrazol-1-yl)phenyl)boronic acid **3a** to optimize the reaction conditions. A series of palladium catalysts, ligands, base and solvents were screened in our optimization studies (Table 1). Gratifyingly, we obtained the expected product **4aa** in 85% isolated yield when the reaction was carried out at 90 °C in DMF solvent by employing PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst and Na<sub>2</sub>CO<sub>3</sub> as base. All other catalyst-ligand combinations rendered the desired product in lower yields. Among the various bases screened, cesium carbonate procured the required product in slightly better yield. However, Na<sub>2</sub>CO<sub>3</sub> was found to be better than Cs<sub>2</sub>CO<sub>3</sub> and other organic bases for this reaction. Similarly, DMF was found to be the best solvent for our reactions when compared to dioxane, water and THF. The reaction was found to be sluggish at 60 °C and a slightly lower yield of the expected product was obtained at 110 °C.

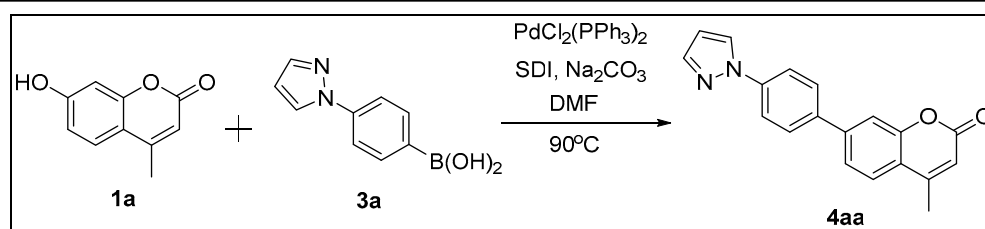
After the detailed optimization studies, our next task was to evaluate the substrate scope by synthesizing an array of 4-methyl-7-substituted coumarin derivatives. However, we planned to do some control experiments to explore the possibility of developing a one-pot protocol for converting 4-methyl-7-hydroxy coumarin **1a** to Suzuki coupled product **4aa**. The feasibility of our optimized Suzuki coupling reaction in the Cs<sub>2</sub>CO<sub>3</sub> base and THF solvent (albeit in slightly lower yield) further encouraged us to screen some conditions for one-pot methodology. Accordingly, we treated **1a** with boronic acid **3a**, SDI and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> catalyst in different bases and solvents (Table 2). To our delight, we obtained the desired product **4aa** in 82% isolated yield when the reaction was carried out in DMF at 90 °C. Even though the yield of the isolated product was slightly lower than the previously optimized two-step methodology, this one-pot protocol was found to be facile, convenient and step-economic.

After the successful development of one-pot synthesis, we shifted our attention to evaluate the substrate scope. Accordingly, 4-methyl-7-hydroxy coumarin **1a** was treated with diverse arylboronic acids **3a–h** in view of synthesizing an assortment of 4-methyl-7-substituted coumarin derivatives (Scheme 2). Gratifyingly, all the boronic acids reacted well enough to procure the expected products **4aa–4ah** in good to acceptable yields (69–85% isolated yield). Later, it was planned to evaluate the antioxidant potential of these synthesized compounds by DPPH assay.

**Table 1.** Optimization of reaction conditions for Suzuki coupling <sup>1</sup>.

Entry	Catalyst	Ligand	Base	Solvent	Yield <sup>2</sup> 4aa (%)
1	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	DMF	85
2	Pd(OAc) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	DMF	trace
3	Pd(OAc) <sub>2</sub>	Xantphos	Na <sub>2</sub> CO <sub>3</sub>	DMF	55
4	Pd(dppf)Cl <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	DMF	60
5	Pd(OAc) <sub>2</sub>	BINAP	Na <sub>2</sub> CO <sub>3</sub>	DMF	40
6	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Cs <sub>2</sub> CO <sub>3</sub>	DMF	70
7	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	K <sub>3</sub> PO <sub>4</sub>	DMF	40
8	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Et <sub>3</sub> N	DMF	55
9	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	DBU	DMF	60
10	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	THF	68
11	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	1,4-Dioxane	25
12	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	40
13	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	1,4-Dioxane-H <sub>2</sub> O (1:1)	60
14 <sup>3</sup>	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	DMF	50
15 <sup>4</sup>	PdCl <sub>2</sub> ·(PPh <sub>3</sub> ) <sub>2</sub>	----	Na <sub>2</sub> CO <sub>3</sub>	DMF	80

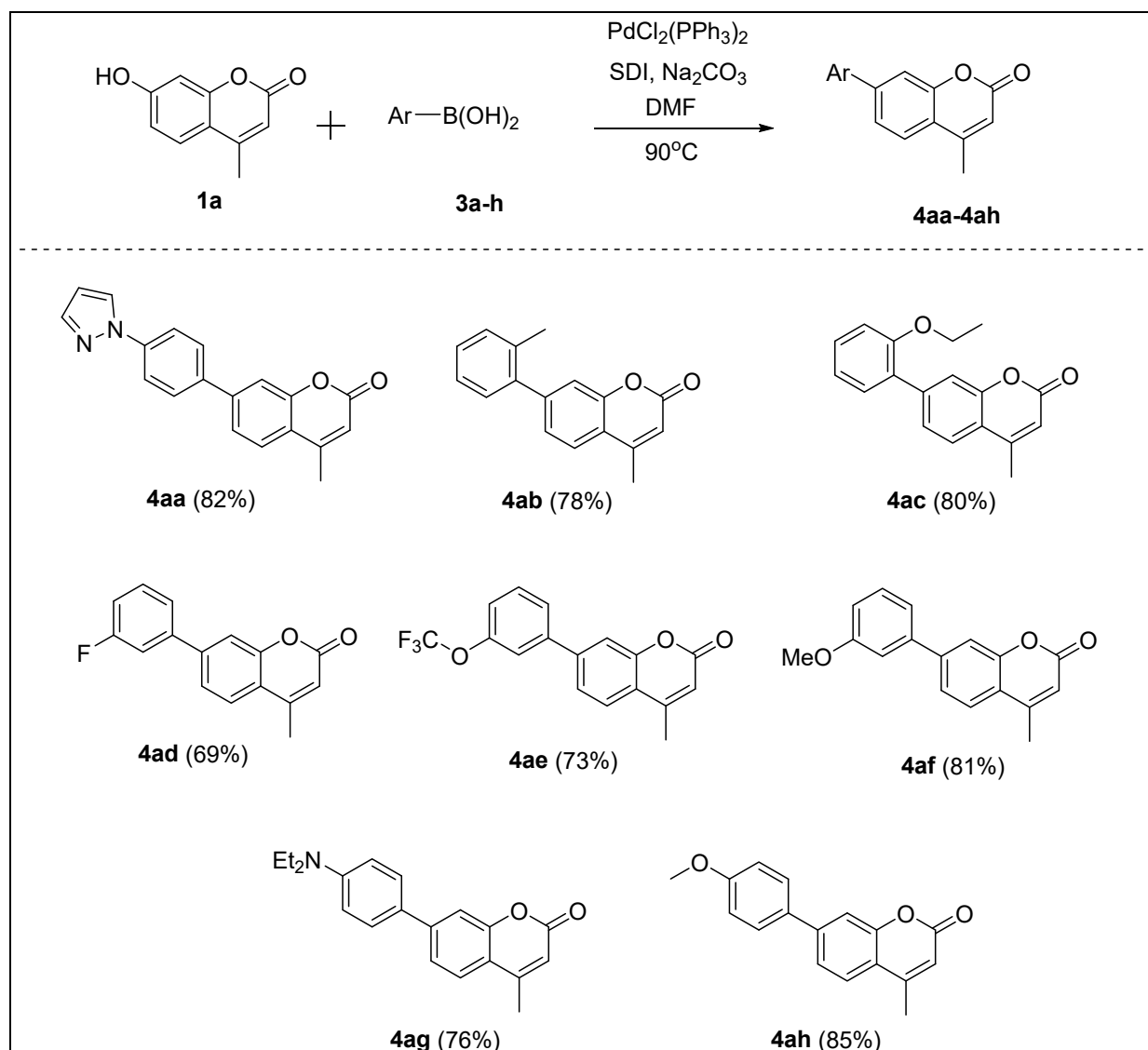
<sup>1</sup> Reaction conditions: **2a** (1 mmol), **3a** (1.1 mmol), catalyst (5 mol%), ligand (10 mol%), base (2 mmol), 2 mL solvent at given temperature for 8 h. <sup>2</sup> Isolated yield. <sup>3</sup> Reaction at 60 °C. <sup>4</sup> Reaction at 110 °C.

**Table 2.** Optimization of reaction conditions for one-pot Suzuki coupling <sup>1</sup>.

Entry	Deviation from Standard Conditions	Yield <sup>2</sup> 4aa (%)
1	None	82
2	Cs <sub>2</sub> CO <sub>3</sub> instead of Na <sub>2</sub> CO <sub>3</sub>	78
3	Et <sub>3</sub> N instead of Na <sub>2</sub> CO <sub>3</sub>	60
4	THF instead of DMF	70
5	Reaction at 80 °C	70
6	Reaction at 100 °C	75

<sup>1</sup> Reaction conditions: **2a** (1 mmol), **3a** (1.1 mmol), SDI (1 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%), base (2 mmol), 2 mL solvent at given temperature for 8 h. <sup>2</sup> Isolated yield.





**Scheme 2.** Scope of boronic acids in one-pot synthesis.

### 3.1.2. Antioxidant Activity of Coumarin Derivatives **4aa–4ah**

One of the most effective methods for evaluating the antioxidant potential of organic compounds is DPPH assay. The radical scavenging activity can be easily determined in terms of percentage inhibition by this assay [30]. Accordingly, we evaluated the antioxidant capacity of the synthesized coumarin derivatives **4aa–4ah** by DPPH radical scavenging activity studies [31]. Butylated hydroxytoluene (BHT) was used as the reference standard in our investigation. It is worth noting that the coumarin derivatives have an extended  $\pi$ -conjugated system that could possibly be favorable for enhanced antioxidant potential. The percentage inhibition at  $100\ \mu\text{g}$  concentration has been evaluated and our results are summarized in Table 3.

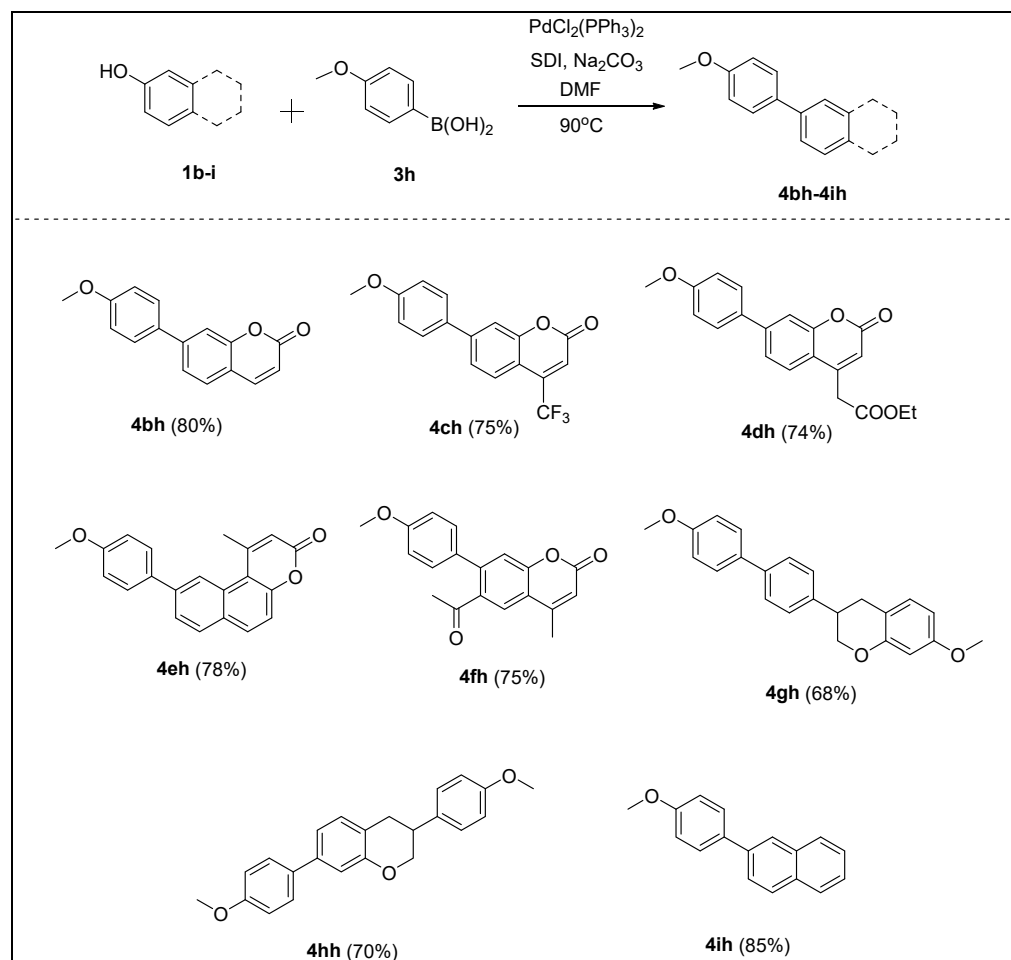
From our studies, the reference standard BHT exhibited a strong antioxidant activity of 90.4% at  $100\ \mu\text{g}$  concentration. Among the compounds screened, **4ah** showed the highest radical scavenging capacity of 81.7% at  $100\ \mu\text{g}$  concentration. However, the compounds **4aa** (75.3%), **4af** (77.6%) and **4ag** (76%) also demonstrated promising antioxidant potential at the same concentration. To our disappointment, the compounds **4ad** and **4ae** exhibited significantly lower potency. Other tested compounds in this series, such as **4ab** and **4ac**, possessed moderate radical scavenging activity, which indicates the possibility of their improved potential at higher concentrations.

**Table 3.** Determination of the antioxidant activity of the synthesized compounds.

Entry	Compound	% Inhibition at 100 $\mu$ g Concentration
1	4aa	75.3
2	4ab	60.5
3	4ac	70.6
4	4ad	42.1
5	4ae	51.3
6	4af	77.6
7	4ag	76.0
8	4ah	81.7
9	Standard (BHT)	90.4

### 3.1.3. Synthesis of Coumarin- and Equol-Based Compounds

After identifying **4ah** as the most potent antioxidant among the tested compounds, it was planned to synthesize some additional compounds from available (poly)phenols. Accordingly, different (poly)phenols based on coumarins and equols **1b–i** were treated with 4-methoxyphenylboronic acid **3h** in our optimized one-pot Suzuki coupling conditions (Scheme 3). Fortunately, we obtained the required final products **4bh–4ih** in good to satisfactory yields (68–85% isolated yield). The antioxidant potential of these synthesized compounds was then evaluated by DPPH assay.

**Scheme 3.** Scope of (poly)phenols in one-pot synthesis.

### 3.1.4. Antioxidant Activity of 4bh–4ih by DPPH Assay

After the successful synthesis of the coumarin- and equol-based final products, **4bh–4ih**, the antioxidant capacity of these molecules was subsequently determined by DPPH assay employing BHT as the standard (Table 4). From our results, we identified the need for the presence of electron-donating functionalities in enhancing the antioxidant activity. Among the compounds screened, **4eh**, **4gh** and **4hh** showed promising potential that was comparable to the reference standard, BHT. The compounds **4ch**, **4dh** and **4fh** exhibited lower potency when compared with other tested compounds. Moreover, the compounds **4bh** and **4ih** displayed moderate antioxidant potential. The SAR studies were then carried out to understand the relationship between the antioxidant capacity and the structural features of the tested compounds.

**Table 4.** Determination of antioxidant activity of the synthesized compounds **4bh–4ih**.

Entry	Compound	% Inhibition at 100 µg Concentration
1	<b>4bh</b>	70.1
2	<b>4ch</b>	45.5
3	<b>4dh</b>	58.6
4	<b>4eh</b>	80.1
5	<b>4fh</b>	54.3
6	<b>4gh</b>	83.8
7	<b>4hh</b>	81.6
8	<b>4ih</b>	65.3
9	Standard (BHT)	90.6

## 4. Discussion

### 4.1. Antioxidant Activity of Phenolic Compounds 1a–i by DPPH Assay

In order to understand the actual need for derivatization of phenolic compounds by Suzuki coupling for developing novel antioxidants, we decided to determine the antioxidant activity evaluation of the parent phenolic compounds **1a–i** by DPPH assay. The results of antioxidant screening of **1a–i** has been illustrated in Table 5. The phenolic compound **1g** displayed the highest antioxidant potential (80.3%); however, the corresponding Suzuki coupled product **4gh** showed better antioxidant activity (83.8%). It is noteworthy that the parent phenol **1b** possessed better antioxidant potential when compared to the corresponding Suzuki coupled product **4bh**. Nevertheless, most of the phenolic compounds **1a–i** displayed lower antioxidant potential when compared to the Suzuki coupled products **4ah–4ih**, which highlights the need for derivatization of parent phenolic compounds.

**Table 5.** Determination of antioxidant activity of phenolic compounds **1a–i**.

Entry	Compound	% Inhibition at 100 µg Concentration
1	<b>1a</b>	79.4
2	<b>1b</b>	73.8
3	<b>1c</b>	40.3
4	<b>1d</b>	54.8
5	<b>1e</b>	77.3

Table 5. Cont.

Entry	Compound	% Inhibition at 100 µg Concentration
6	<b>1f</b>	51.0
7	<b>1g</b>	80.3
8	<b>1h</b>	79.6
9	<b>1i</b>	60.0
10	Standard (BHT)	90.4

#### 4.2. SAR Studies

The structure activity determination (SAR) studies help us to understand the importance of some critical structural features in enhancing the overall pharmacological potential of the tested compounds. In this communication, we have reported the step-economic one-pot synthesis of coumarin- and equol-based compounds and the evaluation of their biological potential as antioxidants. The results of free radical scavenging capacity of all the compounds tested have been summarized in Figure 1. Some of the compounds such as **4ah**, **4eh**, **4gh** and **4hh** exhibited comparable antioxidant capacity. The SAR studies were carried out to get more insights about the profound antioxidant activity of these promising compounds.

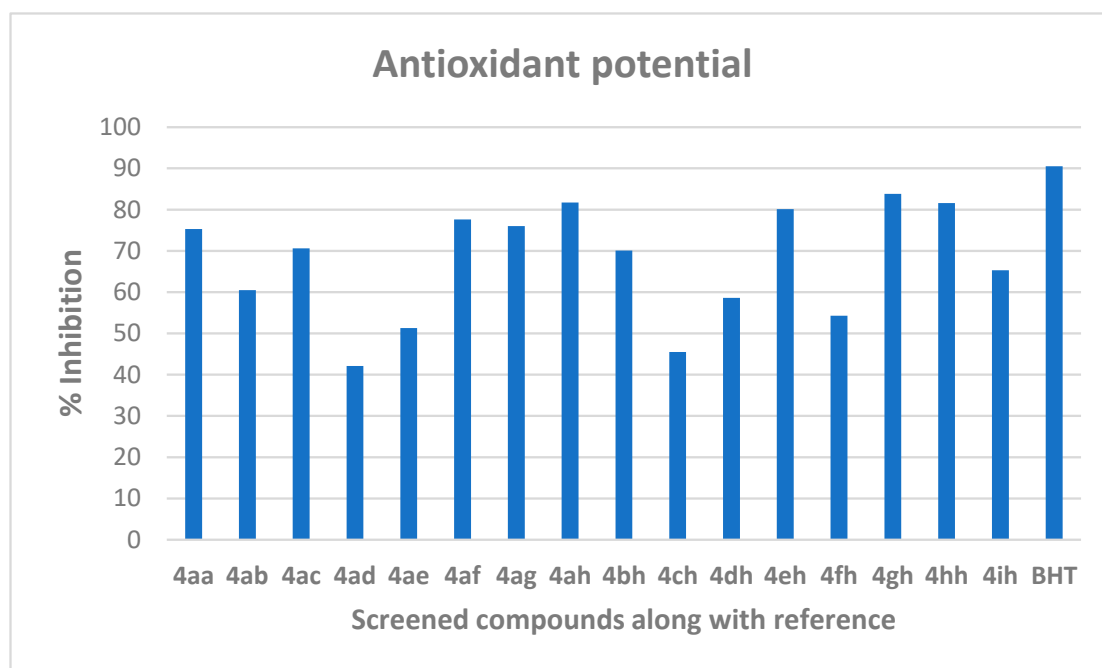


Figure 1. Results of antioxidant screening of synthesized compounds.

From the SAR studies, it was found that the compounds **4ah**, **4gh** and **4hh** contain the electron-donating methoxy group, and the compound **4eh** has three aromatic rings fused together. Moreover, the most promising compounds **4gh** and **4hh** comprises two electron-donating methoxy groups. Hence, in this study, the presence of electron-donating functionalities and extended  $\pi$ -conjugation are crucial for enhancing the radical scavenging activity of the tested compounds. Moreover, the compounds **4ad**, **4ae**, **4ch**, **4dh** and **4fh**, containing electron-withdrawing groups, displayed lower activity profiles. It is presumed that the hydrophilic electron-donating functionalities enable the stabilization of the oxygen-centered radical and thereby reduce the O–H bond dissociation enthalpy (BDE). This

will possibly increase the radical scavenging activity by abstraction of hydrogen [32,33]: a plausible reason for the promising antioxidant potential of **4ah**, **4gh** and **4hh** when compared to other synthesized molecules.

## 5. Conclusions

In summary, we have developed a facile, convenient and step-economic one-pot protocol for direct conversion of (poly)phenols based on coumarin and equol to various (hetero)aryl compounds by palladium-catalyzed Suzuki coupling reaction. The antioxidant capacity of the synthesized compounds was evaluated by DPPH assay, employing BHT as the reference. Among the compounds screened, **4ah**, **4eh**, **4gh** and **4hh** were found to be the most potent ones as they exhibited comparable activity with the employed reference standard. The parent phenolic compounds were also subjected to antioxidant screening for understanding the actual need for their derivatization by Suzuki coupling. Most of the phenolic compounds displayed a slightly lower activity profile when compared to the newly synthesized Suzuki coupled derivatives. The more active compounds were subjected to SAR studies, which revealed the significance of the presence of electron-donating substituents in increasing their overall antioxidant properties. The synthesis of additional compounds, including various natural product derivatives from oils and fats, focusing on the development of new antioxidants with improved potency is currently in process in our laboratory.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/antiox13101198/s1>, File S1: The  $^1\text{H}$  and  $^{13}\text{C}$  spectra of intermediate **2a** and all final compounds.

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