VB₁ Promoted Green Synthesis of Chalcones and Its Neuroprotection Potency Evaluation

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Abstract: For the first time, thiamine hydrochloride (VB₁) has been employed as a catalyst for the synthesis of chalcones by metal-free Claisen–Schmidt condensation. Such an environmentally benign approach has several advantages such as a wide range of functional groups tolerance, a high yield of products, and the recoverability of this catalyst. Moreover, this unprecedented methodology enables the synthesis of the pharmaceutically important molecule 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (3f) and its derivatives. Moreover, 3f and its derivatives were screened for their preliminary in vitro neuroprotective activity against oxygen-glucose deprivation/reoxygenation (OGD/R)-induced apoptosis in SH-SY5Y cell lines. Most of the compounds exhibited the neuroprotective activity, and one of the prepared chalcones (3s), which incorporates prenyl moiety, showed the most potency by decreasing the expression of cleaved caspase-3, cleaved caspase-9, Bax, and p53 protein.

Keywords: chalcone; VB₁ catalyst; neuroprotective property; OGD/R

1. Introduction

Chalcones are widespread in plants, as precursors of flavonols and other flavonoid syntheses. They display various interesting biological activities [1] and are, hence, considered to be medicinally important. Of the many ways available for the synthesis of chalcones, the classic method is the base-catalysed Claisen–Schmidt condensation reaction [1]. However, when benzaldehyde and acetophenone with phenolic hydroxyl groups (except ortho hydroxyl groups) are substrates, the synthesis of chalcones by Claisen–Schmidt condensation via strong bases requires the protection of the phenolic hydroxyl groups [2]. Therefore, we sought to develop a more concise and efficient method of Claisen–Schmidt condensation with tolerance to base-sensitive functional groups, especially hydroxyl.

Cleistocalyx operculatus is a well-known medicinal plant [3], and its dried flower buds are commonly used as an ingredient for tonic drinks in Southern China for centuries [4]. 2′,4′-Dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (3f) (Figure 1), featuring a 3,5-dimethylsubstitution ring A, is the major active component in the buds of Cleistocalyx operculatus [5]. It has been shown to have antidrug efflux [6,7], antioxidant [8–10], antitumor [11–13], and antivirus effects [14] and antiacute liver injury [4].
Due to the poor accessibility of this material (0.69 g per 5 kg of dried flower buds) [15], the organic synthesis to get greater quantities of 3f was demanded. Until now, only one synthetic route has been reported by Hossain M. Amzad [16]. The reported synthesis of 3f by Claisen–Schmidt condensation via a strong base involves hydroxyl protection and deprotection. We now report the first time that chalcones can be produced in the presence of thiamine hydrochloride (VB1) in a mixed solvent of alcohol and water (v/v, 1:1).

VB1, which contains pyrimidine and thiazole moieties in its structure, is a nontoxic and inexpensive reagent (Figure 2). VB1 as a powerful catalyst has been successfully utilized in many organic transformations [17,18].

Some in vitro studies have reported that 3f showed a neuroprotective property via the regulation of oxidative stress [10]. However, the neuroprotective effects of 3f and its derivatives in oxygen-glucose deprivation/reoxygenation (OGD/R)-induced neuronal injury still remain to be defined. Therefore, in this work, we have designed a series of chalcone derivatives without methyl groups at the 3 and 5 positions of the ring A in order to obtain more effective novel neuroprotective agents against oxygen-glucose deprivation/reoxygenation and discussed their structure–activity relationship.

2. Results and Discussion

2.1. Optimization of the Reaction Conditions

To improve the yield and to optimize the reaction conditions, this Claisen–Schmidt condensation reaction was carried out under different conditions and the results are summarized in Table 1. Initially, the effect of solvents, such as 1,4-dioxane, tetrahydrofuran (THF), toluene, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), H2O, and ethanol (EtOH) on the condensation reaction was investigated. No desired products were detected except for EtOH as the solvent (Table 1, entries 1–6). These results can be explained due to that VB1 having a better solubility in EtOH than others. Inspired by this phenomenon, to increase the yield of 3a, the condensation reaction was carried out under similar conditions in a mixed solvent of EtOH–H2O. To our delight, the yields of 3a were increased substantially (78–84%) when using EtOH–H2O as a solvent (Table 1, entries 7–11), and EtOH–H2O (v/v, 1:1) gave the best result (Table 1, entry 8). Furthermore, the recyclable character of VB1 was also investigated. After the reaction was completed, the mixture was concentrated under vacuum and the desired product was isolated by a simple filtration. Next, the filtered solution containing the catalyst was again treated with the reactants, and the yields of the desired product were 84%, 84%, 83%, and 78% after 1–4 runs, respectively, indicating the catalyst could be reused without any loss of activity.
Table 1. The optimization of the reaction conditions

| Entry | Solvent            | Temperature (°C) | Time (h) | Yield of 3a (%) |
|-------|--------------------|------------------|----------|-----------------|
| 1     | 1,4-Dioxane        | 80               | 24       | 0               |
| 2     | THF Reflux         | 24               |          | 0               |
| 3     | toluene            | 80               | 24       | 0               |
| 4     | DMF                | 80               | 24       | 0               |
| 5     | DMSO               | 80               | 24       | 0               |
| 6     | EtOH Reflux        | 24               |          | 64              |
| 7     | EtOH–H₂O = 2:3     | Reflux           | 10       | 77              |
| 8     | EtOH–H₂O = 1:1     | Reflux           | 10       | 84, 84, 83, 78  |
| 9     | EtOH–H₂O = 2:1     | Reflux           | 10       | 80              |
| 10    | EtOH–H₂O = 4:1     | Reflux           | 10       | 79              |
| 11    | EtOH–H₂O = 8:1     | Reflux           | 10       | 72              |

a Reaction conditions: 1.0 mmol of 1a, 1.0 mmol of 2a, 30 mol% VB₁, and 4.0 mL of solvent. b Isolated yields. c The catalyst was reused for up to four reactions.

Based on the above reaction conditions, the influence of the amount of VB₁ from 15 to 30 mol% was determined. As shown in Table 2, we found that the catalytic loading could be reduced to 20 mol% without a decrease of the yield (Table 2, entry 2).

Table 2. The optimization of the amount of catalyst

| Entry | VB₁ (mol%) | Time (h) | Yield of 3a (%) |
|-------|------------|----------|-----------------|
| 1     | 30         | 10       | 84              |
| 2     | 20         | 10       | 83              |
| 3     | 15         | 15       | 76              |

a Reaction conditions: 1.0 mmol of 1a, 1.0 mmol of 2a, and 4.0 mL, v/v = 1:1 of EtOH–H₂O at a reflux temperature. b Isolated yields.

2.2. The Scope of the Substrates

In order to gauge the scope and limitation of the process, we applied the optimized reaction conditions to a variety of substrates in the presence of 20 mol% VB₁ in a mixed solvent of EtOH–H₂O (v/v, 1:1) at a reflux temperature (Table 3). We discovered that heterocyclic aromatic aldehyde and the aromatic aldehydes carrying strong electron-withdrawing groups afforded relevant lower yields (70–79%). Most importantly, aromatic aldehydes carrying hydroxyl groups, which is a base-sensitive functional group, worked well to give high yields of products without a significant difference.
The plausible reaction mechanism for the chalcones synthesis.

Table 3. The synthesis of chalcones catalyzed by VB1.a.

| Entry | Product R1 | R2 | Time (h) | Yield (%) |
|-------|------------|----|----------|-----------|
| 1     | 3a         | H  | C6H5     | 10        | 82        |
| 2     | 3b         | 4Cl| C6H5     | 10        | 81        |
| 3     | 3c         | 2-OH-4,5-(C6H5) | 2-Furyl | 14        | 71        |
| 4     | 3d         | 2-OH-4,5-(C6H5) | 2-Thienyl | 14       | 73d       |
| 5     | 3e         | 2-OH-4,5-(C6H5) | 3-Pyridyl | 10       | 79        |
| 6     | 3f         | 2,4-(OH)2-6-OCH3 | -3,5-(CH3)2 | 10       | 82        |
| 7     | 3g         | 2,4-(OH)2-6-OCH3 | C6H5     | 10        | 80        |
| 8     | 3h         | 2,4-(OH)2-6-OCH3 | 3-OCH3C6H4 | 10      | 83        |
| 9     | 3i         | 2,4-(OH)2-6-OCH3 | 4-OCH3C6H4 | 10      | 85        |
| 10    | 3j         | 2,4-(OH)2-6-OCH3 | 3-OHCl2H4 | 10       | 82        |
| 11    | 3k         | 2,4-(OH)2-6-OCH3 | 4-OHCl2H4 | 10       | 82        |
| 12    | 3l         | 2,4-(OH)2-6-OCH3 | 3-ClC6H4  | 13        | 76        |
| 13    | 3m         | 2,4-(OH)2-6-OCH3 | 4-ClC6H4  | 13       | 77        |
| 14    | 3n         | 2-OH-4,6-(OCH3)2 | 4-OHCl2H4 | 10       | 83        |
| 15    | 3o         | 2-OH-4,6-(OCH3)2 | 3-NO2C6H4 | 13       | 79        |
| 16    | 3p         | 2-OH-4,6-(OCH3)2 | 4-OCH3C6H4 | 10      | 83        |
| 17    | 3q         | 2-OH-3,4,5-(OCH3)3 | 3,4-(OCH3)2C6H3 | 10 | 82        |
| 18    | 3r         | 3,4,5-(OCH3)3 | 3,4-(OCH3)2C6H3 | 10 | 87        |
| 19    | 3s         | 2-OH-4,6-(OCH3)2-3-CH2CH(CH3)2 | 3,4-(Methylenedioxy)C6H4 | 10 | 85        |
| 20    | 3t         | 2-OH-4,6-(OCH3)2-3-CH2CH(CH3)2 | 3,4,5-(OCH3)2C6H2 | 10 | 83        |

*a Reaction conditions: 1.0 mmol of 1, 1.0 mmol of 2, 20 mol% VB1, and 4.0 mL, v/o = 1:1 of EtOH–H2O at a reflux temperature. Isolated yields. The starting materials did not react completely, the amount of recovered starting materials was 0.041 mmol. The yield based on the recovered starting material.

The possible mechanism of the reaction is depicted in Scheme 1. It has been postulated that acetophenone 1 tautomerised to enol 1’ under the action of VB1. Further, the Claisen–Schmidt condensation reaction between 1’ and 2 furnished the β-hydroxyl ketone 3’. Eventually, the elimination of water from β-hydroxyl ketone 3’ yielded the final chalcone.
2.3. Synthesis of Natural Product 3f

Starting with compound 4 in the reported synthetic route (Scheme 2), they were able to obtain 5 by a Vilsmeier–Haack reaction. Thus, 5 was reduced with Zn/Hg to deliver 6. Following, Hoesch’s acylation of 6 with acetonitrile in the presence of phosphorus oxychloride gave acetophenone 7. With anhydrous K$_2$CO$_3$ being chosen as the base, 8 with hydroxyl groups protected by methyl methyl ether was generated. Eventually, 3f was achieved by the deprotection of hydroxyl groups of compound 9, which stemmed from 8 by a Claisen–Schmidt condensation under strongly basic conditions. No yields are given in the original reference for this reaction.

![Scheme 2](image)

**Scheme 2.** The reported synthetic route of 3f. Reagents and conditions: (a) ZnCN, HCl, ether, (room temperature (r.t.)); (b) Zn/Hg, HCl, MeOH, r.t.; (c) dimethyl sulfate (DMS), K$_2$CO$_3$, Acetone, reflux; (d) chloromethyl methyl-ether (MOMOCl), K$_2$CO$_3$, Acetone, reflux; (e) 50% KOH, ethanol (EtOH), r.t.; (f) 3N HCl, methanol (MeOH), reflux.

In this paper, we designed a novel synthetic route beginning with the methylation of 10 (Scheme 3). The subsequent Vilsmeier–Haack reaction of 11 and the Zn–Cu-mediated Clemmensen reduction of 12 respectively afforded the key compounds 12 and 13 in a yield of 85%. Hoesch’s acylation of 13 with acetonitrile in the presence of phosphorus oxychloride gave ketone 7. Eventually, a formation of the desired chalcone 3f was accomplished in good yield (82%) by a VB$_1$-catalyzed condensation. The synthesis features the application of VB$_1$ as a catalyst to synthesize the desired chalcone 3f in one step, avoiding the protection and deprotection of hydroxyl groups.

![Scheme 3](image)

**Scheme 3.** The total synthesis of compound 3f. Reagents and conditions: (a) TsOCH$_3$, K$_2$CO$_3$, ethanol (EtOH), reflux, 71%; (b) POC$_3$, N,N-dimethylformamide (DMF), N$_2$, Dioxane, r.t. 93%; (c) Zn/Cu, HCl, methanol (MeOH), r.t. 85%; (d) POC$_3$, CH$_3$CN, 40 °C, 82%; (e) VB$_1$, EtOH–H$_2$O = 1:1, reflux, 82%.
2.4. Biological Activity

2.4.1. Neuroprotection Against Oxygen-Glucose Deprivation/Reperfusion Injury of 3f and Derivatives 3g–t

A short period of oxygen-glucose deprivation (OGD) conditions can lead to great damage to neuronal cells, while a subsequent reoxygenation, the restoration of the blood supply, can aggravate the neuronal injury, even neuronal death [19]. The neuroprotection against OGD/R of 3f and derivatives (3g–t) without 3,5-dimethyl on ring A was investigated.

First, the cytotoxicity of the above compounds was evaluated against SH-SY5Y cells at 5 μM. Compound 3f and its derivatives did not demonstrate a significant cytotoxicity at the used concentrations without a decrease of cell viability (Figures 3 and 4). Therefore, we chose 5 μM as the concentration in the following experiments. Next, the biological activity of 3f and derivatives to enhance the viability of human neuronal SH-SY5Y cells exposed to OGD/R was investigated by an 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Except 3l–m, all tested compounds reversed the effects of OGD/R through different extents, recovering the cell viability in Figure 3. Unexpectedly, all the derivatives resulted in a decreased activity compared with the 3f, suggesting the importance of 3,5-dimethyl to the potency of 3f. Further, structure–activity relationship (SAR) studies found that the substitution pattern on the aromatic ring played an important role in the neuroprotective activity. Compounds 3l–m with electron-withdrawing groups on ring B had no reversal effect, whereas, when electron-donating groups were used as substitutions, 3h–k displayed an increased reversal activity compared with 3g. Therefore, in the further structural modification studies of 3f, we investigated the effects of multiple substitutions with methoxy groups in Figure 4.

![Figure 3](image_url)

**Figure 3.** The effect of 3f–m on the cell viability of human neuronal SH-SY5Y cells: The cells were pretreated with different concentrations of 3f–m for 24 h and then exposed to oxygen-glucose deprivation/reoxygenation (OGD/R) for 5.5 h and then reoxygenated for 4 h further. All data are presented as means ± SD (n = 3). ### $p < 0.001$ vs. control group, * $p < 0.05$, *** $p < 0.001$ vs. OGD/R group.

Similarly, the reversal activity of 3p–t in cellular damage caused by OGD/R was evaluated (Figure 4). In comparison with the parent 3i, chalcones 3p–q in which the A-ring was substituted by multiple methoxy groups kept an excellent protective activity. While 3r displayed no inhibition at all, indicating the 2-OH on ring A is a distinct advantage to the protective activity and trisubstitution on ring B was a disadvantage. In view of the importance of methyl in 3f, we introduced isopentenyl on ring A and got derivatives 3s–t. Surprisingly, 3s presented a more remarkable restored effect on OGD/R with a much higher cell viability than 3f. However, the activity of 3t was in a slightly increase. Therefore, we can conclude the structure–activity relationship of all target compounds is...
that the methoxy groups and isopentenyl on ring A have positive contribution; monosubstitution and
disubstitution with methoxy groups on ring B served greatly in the increase in reversal activity.

![Figure 4](image-url)

**Figure 4.** The effect of derivatives 3p–t on the cell viability of human neuronal SH-SY5Y cells: The cells were pretreated with different concentrations of derivatives 3p–t for 24 h, then exposed to OGD/R for 5.5 h, and then reoxygenated for 4 h further. All data are presented as means ± SD (n = 3). ### p < 0.001 vs. control group, * p < 0.05, ** p < 0.01 *** p < 0.001 vs. OGD/R group.

On the basis of the above result, to better comprehend the molecular mechanism by which 3s reverses OGD/R responses, we additionally studied the influence of 3s on the protein levels of cleaved caspase-3, cleaved caspase-9, Bax, and p53-inducing apoptosis or necrosis [20] using a Western blotting analysis in Figure 5. The expression of cleaved caspase-3 cleaved, caspase-9, Bax, and p53 proteins increased dramatically after a treatment of OGD/R alone. On the contrary, a pretreatment with 3s at 5 μM observably attenuated OGD/R-induced cleaved caspase-3, cleaved caspase-9, Bax, and p53 levels. The results clearly suggested that possibly 3s’s effect on cleaved caspase-3, cleaved caspase-9, Bax, and p53 proteins played an important role in the neuroprotection of SH-SY5Y cells from OGD/R to apoptosis and cell damage. To our knowledge, its influence on OGD/R-induced cell death and the underlying molecular mechanism had not been reported.

![Figure 5](image-url)

**Figure 5.** The mechanism of 3s reverses OGD/R responses. (a) 3s downregulated the expression of cleaved caspase-3, cleaved caspase-9 in cells treated with OGD/R; (b) 3s downregulated the expression of Bax, and p53 proteins in cells treated with OGD/R. Changes in the levels of proteins were analysed by a Western blotting with antibodies.
3. Experimental

3.1. Biological Assays

The cell viability assays were conducted using a standard MTT-based protocol as described previously. Western blotting was performed as described previously [20].

3.2. Chemistry

All nonaqueous reactions were performed under a constant stream of dry nitrogen using oven-dried glassware. All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Room temperature refers to ambient temperature. Temperatures of 0 °C were maintained using an ice-water bath. All reactions were stirred magnetically. 1H and 13C NMR spectra were recorded on a Bruker AV-400 instrument made by Bruker in Switzerland in CDCl3, (CD3)2CO-d6, and DMSO-d6. Chemical shifts were given in parts per million (ppm) down field from the internal reference Me4Si in 6 units, and the coupling constants (J) were given in hertz (Hz). The selected data were reported in the following manner: chemical shift, multiplicity, and coupling constant. The high resolution mass (High resolution mass spectrometry (HRMS), electrospray ionization (ESI)) spectral data were acquired by use of a Bruker Daltonics 7T mass spectrometer made by Bruker in Switzerland in the positive ion mode. The solvents were removed by rotary evaporation under a vacuum using a standard rotovap equipped with a cold alcohol condenser. All filtrations were performed with a vacuum unless otherwise noted.

3.2.1. General Procedure for the Synthesis of Compounds 3a–e, 3g–r

A solution of benzaldehyde (2 mmol), acetophenone (2 mmol), and VB1 (135 mg, 0.4 mmol, and 20 mol%) in EtOH–H2O (20 mL, v/v = 1:1) was stirred for 10 h at reflux. After cooling to room temperature, the mixture was concentrated in a vacuum, during which time a precipitate formed. The product was dissolved in EtOH, and the catalyst was dissolved in water. The EtOH was removed under reduced pressure, and the water was left. This precipitate was then filtered off and washed with more water. The crude product was purified by flash column chromatography (AcOEt/PE = 1/10 to 1/30, v/v) to give chalcone derivatives.

Compounds 3a [21,22], 3b [21,23], 3g [24,25], 3h [26], 3i [27], 3k [27], 3m [27], 3n [28,29], 3o [30], 3p [31], and 3r [32] were known and synthesized previously. The NMR data of 3a [21], 3b [21], 3g [24], 3h, 3i, 3n [28], and 3r in our paper are inconsistent with their corresponding references due to the different deuterated solvent. The 13C NMR data of 3k and 3m are consistent with their corresponding references. The NMR data of 3o and 3p are consistent with their corresponding references. Although compounds 3q, 3s, and 3t were known, the NMR data were not provided in the references.

(E)-1-(Phenyl)-3-(phenyl)prop-2-en-1-one (3a). Isolated as a yellow solid; yield: 82%, 0.34 g; m.p. = 57–58 °C (lit. 55 °C [22]); 1H-NMR (400 MHz, DMSO-d6) δ 8.21–8.17 (m, 2H), 7.97 (d, J = 15.7 Hz, 1H), 7.91 (dd, J = 6.6, 2.9 Hz, 2H), 7.78 (d, J = 15.7 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.60 (t, J = 7.6 Hz, 2H), 7.50–7.46 (m, 3H); 13C-NMR (150 MHz, DMSO-d6) δ 189.7, 144.5, 138.1, 135.1, 133.6, 131.1, 129.4, 129.3, 129.0, 122.5. HRMS (ESI): Calcd for C15H12O [M + H]+ 209.0966; Found: 209.0967.

(E)-1-(4-Chlorophenyl)-3-(phenyl)prop-2-en-1-one (3b). Isolated as a yellow solid; yield: 81%, 0.39 g; m.p. = 97–98 °C (lit. 96–98 °C [23]); 1H-NMR (400 MHz, DMSO-d6) δ 8.22–8.17 (m, 2H), 7.96 (d, J = 15.6 Hz, 1H), 7.91 (dd, J = 6.5, 3.0 Hz, 2H), 7.77 (d, J = 15.6 Hz, 1H), 7.66 (dd, J = 8.9, 2.0 Hz, 2H), 7.51–7.45 (m, 3H); 13C-NMR (150 MHz, DMSO-d6) δ 188.6, 145.0, 138.6, 136.7, 135.0, 131.2, 130.9, 129.5, 129.4, 129.2, 122.2. Calcd for C15H12ClO [M + H]+ 243.0576; Found: 243.0577.

(E)-1-(2-Hydroxy-4,5(cyclohexyl)phenyl)-3-(2-furyl)prop-2-en-1-one (3c). Isolated as a yellow solid; yield: 71%, 0.38 g; m.p. = 127–130 °C; 1H-NMR (400 MHz, CDCl3) δ 7.65 (d, J = 15.1 Hz, 1H), 7.59 (s, 1H),
7.56 (s, 1H), 7.53 (d, J = 15.2 Hz, 1H), 6.75 (d, J = 3.4 Hz, 1H), 6.72 (s, 1H), 6.54 (dd, J = 3.4, 1.8 Hz, 1H), 2.84–2.69 (m, 1H), 1.88–1.73 (m, 1H); 13C-NMR (150 MHz, CDCl3) δ 192.5, 161.2, 151.2, 150.1, 148.1, 140.8, 134.6, 130.6, 129.7, 128.0, 123.8, 122.4, 118.0, 117.9, 30.1, 28.7, 23.2, 22.6. HRMS (ESI): Calcd for C17H16O3 [M + H]+ 269.1177; Found: 269.1178.

(E)-1-(2-Hydroxy-4,5(cyclohexyl)phenyl)-3-(phenyl)prop-2-en-1-one (3e). Isolated as a yellow solid; yield: 79%, 0.40 g; m.p. = 130–131 °C; 1H-NMR (400 MHz, CDCl3) δ 8.89 (d, J = 2.0 Hz, 1H), 6.65 (dd, J = 4.8, 1.5 Hz, 1H), 7.98 (dt, J = 7.9, 1.8 Hz, 1H), 7.87 (d, J = 15.6 Hz, 1H), 7.70 (d, J = 15.6 Hz, 1H), 7.57 (s, 1H), 7.39 (dd, J = 7.9, 4.8 Hz, 1H), 6.75 (s, 1H), 2.87 – 2.70 (m, 1H), 1.86–1.75 (m, 1H); 13C-NMR (150 MHz, CDCl3) δ 192.7, 161.1, 151.7, 147.5, 145.2, 130.5, 129.7, 127.8, 118.3, 117.9, 117.7, 116.7, 112.8, 30.0, 28.7, 23.2, 22.7. HRMS (ESI): Calcd for C18H16O3S [M + H]+ 285.0949; Found: 285.0947.

(E)-1-(2-Hydroxy-4,5(cyclohexyl)phenyl)-3-(3-pyridyl)prop-2-en-1-one (3f). Isolated as a yellow solid; yield: 80%, 0.43 g; m.p. = 192–195 °C (lit. 207 °C [25]); 1H-NMR (400 MHz, Acetone-d6) δ 8.03 (d, J = 15.6 Hz, 1H), 7.75 (dd, J = 11.6, 7.2 Hz, 3H), 7.46 (d, J = 6.7 Hz, 3H), 6.10 (d, J = 2.0 Hz, 1H), 6.01 (d, J = 2.0 Hz, 1H), 3.99 (s, 3H); 13C-NMR (150 MHz, DMSO-d6) δ 192.2, 166.8, 165.5, 163.2, 143.2, 135.4, 130.8, 129.5, 128.9, 128.0, 105.6, 96.3, 92.2, 56.5. HRMS (ESI): Calcd for C16H14O4 [M + H]+ 271.0970; Found: 271.0971.

(E)-1-(2-Hydroxy-4,5(cyclohexyl)phenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (3h). Isolated as a yellow solid; yield: 83%, 0.50 g; m.p. = 156–158 °C (lit. 159–162 °C [26]); 1H-NMR (400 MHz, CDCl3) δ 7.86 (d, J = 15.6 Hz, 1H), 7.74 (d, J = 15.5 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.13 (s, 1H), 6.95 (dd, J = 8.2, 1.9 Hz, 1H), 6.03 (d, J = 2.2 Hz, 1H), 5.96 (d, J = 2.2 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H); 13C-NMR (150 MHz, CDCl3) δ 130.8, 136.0, 128.4, 121.1, 116.6, 113.9, 105.7, 96.3, 92.2, 56.5, 55.6. HRMS (ESI): Calcd for C17H16O3 [M + H]+ 301.1076; Found: 301.1080.

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(E)-1-(2,4-Dihydroxy-6-methoxyphenyl)-3-(3-chlorophenyl)prop-2-en-1-one (3I). Isolated as a yellow solid; yield: 76%, 0.46 g; m.p. = 143–149 °C; δ 8.02 (d, J = 15.6, 1H), 7.81–7.66 (m, 3H), 7.46 (d, J = 7.4 Hz, 2H), 6.08 (d, J = 11.9 Hz, 1H), 5.98 (d, J = 26.0 Hz, 1H), 3.99 (s, 3H); δ 13C-NMR (150 MHz, DMSO-d$_6$) δ 192.1, 166.8, 165.7, 163.2, 140.3, 135.4, 134.3, 131.3, 129.5, 128.9, 128.7, 127.0, 105.6, 96.3, 92.2, 56.6. HRMS (ESI): Calcd for C$_{16}$H$_{13}$ClO$_4$ [M + H]$^+$ 305.0580; Found: 305.0582.

(E)-1-(2,4-Dihydroxy-6-methoxyphenyl)-3-(4-chlorophenyl)prop-2-en-1-one (3m). Isolated as a yellow solid; yield: 77%, 0.47 g; m.p. = 185–188 °C (lit. 209–211 °C [27]); δ 7.84 (d, J = 15.6 Hz, 1H), 7.72 (d, J = 15.6 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.04 (d, J = 2.3 Hz, 1H), 5.96 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H); δ 13C-NMR (150 MHz, DMSO-d$_6$) δ 192.1, 166.7, 165.6, 163.2, 140.7, 135.2, 134.4, 130.6, 129.6, 128.7, 105.6, 96.3, 92.2, 56.5. HRMS (ESI): Calcd for C$_{16}$H$_{13}$ClO$_4$ [M + H]$^+$ 305.0580; Found: 305.0582.

(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3-chlorophenyl)prop-2-en-1-one (3n). Isolated as a yellow solid; yield: 83%, 0.50 g; m.p. = 180–182 °C (lit. 179–182 °C [29]); δ 8.05 (d, J = 15.8 Hz, 1H), 7.96 (d, J = 15.8 Hz, 1H), 7.55 (d, J = 6.7 Hz, 1H), 7.27–7.24 (m, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.12 (d, J = 2.3 Hz, 1H), 5.97 (d, J = 2.3 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H); δ 13C-NMR (150 MHz, CDCl$_3$) δ 192.0, 167.3, 165.2, 161.5, 154.0, 136.4, 130.2, 128.1, 127.4, 121.8, 120.0, 115.5, 105.4, 92.7, 90.3, 54.8, 54.6. HRMS (ESI): Calcd for C$_{16}$H$_{15}$NO$_6$ [M + H]$^+$ 330.0971; Found: 330.0973.

(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-chlorophenyl)prop-2-en-1-one (3p). Isolated as a yellow solid; yield: 83%, 0.52 g; m.p. = 169–172 °C (lit. 171–172 °C [30]); δ 8.10 (d, J = 15.6 Hz, 1H), 7.77 (d, J = 15.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.10 (d, J = 2.4 Hz, 1H), 5.95 (d, J = 2.4 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H); δ 13C-NMR (100 MHz, CDCl$_3$) δ 192.6, 168.4, 166.0, 162.5, 161.4, 142.5, 150.1, 128.3, 125.1, 114.4, 106.3, 93.8, 91.2, 55.8, 55.6, 55.4. HRMS (ESI): Calcd for C$_{18}$H$_{15}$NO$_5$ [M + H]$^+$ 315.1232; Found: 315.1230.

(E)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3,4-methoxyphenyl)prop-2-en-1-one (3q). Isolated as a yellow solid; yield: 82%, 0.61 g; m.p. = 109–111 °C (lit. 110–112 °C [31]); δ 7.89 (d, J = 15.3 Hz, 1H), 7.84 (d, J = 15.3 Hz, 1H), 7.50 (s, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.42 (dd, J = 8.3, 1.9 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 1H), 3.89 (s, 1H), 3.88 (s, 1H), 3.87 (s, 1H); δ 13C-NMR (150 MHz, Acetone-d$_6$) δ 193.3, 154.7, 152.7, 150.1, 145.7, 141.9, 128.1, 124.2, 118.7, 115.1, 111.9, 111.8, 108.4, 60.8, 60.5, 56.9, 55.7, 55.6. HRMS (ESI): Calcd for C$_{20}$H$_{22}$O$_7$ [M + H]$^+$ 375.1444; Found: 375.1445.

(E)-1-(3,4,5-Trimethoxyphenyl)-3-(3,4-methoxyphenyl)prop-2-en-1-one (3r). Isolated as a yellow solid; yield: 87%, 0.62 g; m.p. = 131–133 °C (lit. 127–129 °C [32]); δ 7.77 (d, J = 15.6 Hz, 1H), 7.33 (d, J = 15.6 Hz, 1H), 7.28–7.25 (m, 3H), 7.16 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 3.96 (s, 9H), 3.94 (s, 6H); δ 13C-NMR (150 MHz, Acetone-d$_6$) δ 188.2, 153.8, 152.2, 150.0, 144.5, 142.9, 134.2, 128.4, 123.6, 120.0, 111.9, 111.6, 106.5, 60.2, 56.2, 55.7, 55.6. HRMS (ESI): Calcd for C$_{20}$H$_{22}$O$_6$ [M + H]$^+$ 359.1494; Found: 359.1493.

3.2.2. General Procedure for the Synthesis of Compound 3f

(1) 5-Methoxyresorcinol (11)

To a stirred solution of phloroglucinol (1.42 g, 11.3 mmol) in dry ethanol (10 mL) were added anhydrous K$_2$CO$_3$ (1.66 g, 12 mmol) and methyl p-toluenesulfonate (1.83 mL, 12 mmol). The reaction
mixture was heated at reflux with stirring for 3 h. The resulting mixture was allowed to cool to room temperature, diluted with 200 mL water, and was extracted with ethyl acetate (EtOAc). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/PE = 1/5, v/v) to afford 5-methoxyresorcinol (1.12 g, 71%) as a yellow oil. $^{1}H$-NMR (400 MHz, Acetone-$d_{6}$) $\delta$ 10.14 (s, 1H), 10.06 (s, 1H), 6.13 (s, 1H), 4.06 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_{3}$) $\delta$ 158.4, 156.1, 155.6, 106.1, 106.0, 93.4, 56.8, 9.5, 9.4. HRMS (ESI): Calcd for C$_{10}$H$_{9}$O$_{3}$ [M + H]$^{+}$ 197.0450; Found: 197.0450.

(2) 2,6-Dihydroxy-4-methoxyisophthalaldehyde (12)

Phosphoryl chloride (1.6 mL, 16.7 mmol) was added dropwise to DMF (1.3 mL, 16.7 mmol) with strong stirring at room temperature under a nitrogen atmosphere. Stirring was continued for 30 min. This Vilsmeier reagent was then slowly added to a stirred solution of 11 (1.1 g, 7.9 mmol) in dioxane (5 mL) at room temperature under a nitrogen atmosphere. This solution was then stirred at room temperature for 12 h, whereupon it turned into a yellow amorphous solid. This solid mixture was cooled to 0 °C before being added to ice-water slurry (40 mL). The solution was allowed to slowly warm to room temperature and stirring was continued for a further 4 h, during which time a cream precipitate formed. This precipitate was then filtered off and washed with more water to give 2,6-dihydroxy-4-methoxyisophthalaldehyde (1.39 g, 93%) as a cream colored solid. $^{1}H$-NMR (400 MHz, Acetone-$d_{6}$) $\delta$ 6.11 (s, 1H), 3.68 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_{3}$) $\delta$ 192.0, 191.9, 172.0, 169.6, 168.7, 104.5, 104.4, 91.0, 56.5. HRMS (ESI): Calcd for C$_{9}$H$_{8}$O$_{3}$ [M + H]$^{+}$ 197.0450; Found: 197.0451.

(3) 2,4-Dimethyl-5-methoxyresorcinol (13)

To a solution of 12 (1.39 g, 7.11 mmol) and Zn–Cu (3.5 g) in MeOH (20 mL) was added 9 mL HCl–H$_{2}$O (2:1, v/v) at 0 °C. After stirring for 15 min at room temperature, the reaction was quenched with saturated aqueous NaHCO$_{3}$. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (AcOEt/PE = 1/15, v/v) to give 2,4-dimethyl-5-methoxyresorcinol (1 g, 85%) as a pale-yellow oil. $^{1}H$-NMR (400 MHz, Acetone-$d_{6}$) $\delta$ 6.11 (s, 1H), 3.68 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_{3}$) $\delta$ 158.4, 156.1, 155.6, 106.1, 106.0, 93.4, 56.8, 9.5, 9.4. HRMS (ESI): Calcd for C$_{10}$H$_{12}$O$_{3}$ [M + H]$^{+}$ 169.0864.2440; Found: 169.0866.

(4) 2,4-Dihydroxy-6-methoxy-3,5-dimethylacetophenone (7)

Phosphoryl chloride (1.8 mL, 18 mmol) was added dropwise to 2,4-dimethyl-5-methoxyresorcinol (1 g, 6 mmol) in acetonitrile (10 mL) with strong stirring at room temperature under a nitrogen atmosphere. Stirring was continued for 30 min and then changed to 40 °C for 24 h, whereupon it turned into an amorphous solid. The resulting mixture was diluted with 200 mL water, and stirring was continued at 100 °C for a further 1 h, during which time precipitate formed. This precipitate was then filtered off and washed with more water to give 2,4-dihydroxy-6-methoxy-3,5-dimethylacetophenone (1.03 g, 82%), which could be used directly for the next step without further purification.

(5) 2′,4′-Dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (3f)

3f were synthesized using a Claisen–Schmidt reaction as previously described in the synthesis of 3a.
3.2.3. General Procedure for the Synthesis of Compounds 3s-t

To a stirred solution of 2,4,6-trihydroxyacetophenone (1.68 g, 0.01 mol) in dry methylbenzene (150 mL) was added prenyl bromide (1.17 mL, 0.01 mol) in the presence of DBU (1.49 mL, 0.1 mol) as a base at room temperature under nitrogen atmosphere for 48 h. After the completion of the reaction as indicated by TLC, the mixture was diluted with water and extracted with ethyl acetate (3 × 150 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated under vacuum; the residue was chromatographed on silica gel column (MeOH/DCM = 50/1, v/v) to afford 2,4,6-trihydroxy-3-(3-methylbut-2-en-1-yl)acetophenone (1.18 g, 50%).

To a mixture of the above compound (1.18 g, 5 mmol) and K₂CO₃ (1.4 g, 10 mmol) in ethanol (150 mL) was added TsOCH₃ (1.9 mL, 12.5 mmol) dropwise at room temperature and then refluxed for 3 h. The resulting solution was cooled, was added H₂O (2 mL), and was extracted with CH₂Cl₂ (3 × 150 mL). The organic layer was concentrated under vacuum, and the residue was subjected to column chromatography (AcOEt/MeOH = 100/1) to afford the desired product (1.21 g, 92%).

3s-t were synthesized using a Claisen–Schmidt reaction as previously described in the synthesis of 3a.

Compound 3t was known and synthesized elsewhere.

(E)-1-(2-Hydroxy-4,6-dimethoxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(3,4-(methylenedioxy)phenyl)prop-2-en-1-one (3s). Isolated as a yellow solid; yield: 85%; 0.67 g; m.p. = 158–162 °C; 1H-NMR (400 MHz, DMSO-d₆) δ 7.75 (d, J = 15.5 Hz), 7.67 (d, J = 15.5 Hz, 1H), 7.36 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.27 (s, 1H), 6.11 (s, 2H), 5.10 (t, J = 7.0 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.16 (d, J = 7.0 Hz, 2H), 1.70 (s, 3H), 1.61 (s, 3H); ¹³C-NMR (150 MHz, DMSO-d₆) δ 192.9, 163.8, 163.2, 161.7, 149.9, 148.6, 142.7, 130.7, 129.8, 125.9, 125.6, 123.2, 109.2, 108.8, 107.3, 106.1, 102.1, 88.1, 56.7, 56.4, 25.9, 21.4, 18.1. HRMS (ESI): Calcd for C₃₈H₂₃O₇ [M + H]⁺ 597.1651; Found: 597.1650.

(E)-1-(2-Hydroxy-4,6-dimethoxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3t). Isolated as a yellow solid; yield: 83%; 0.73 g; m.p. = 158–162 °C; 1H-NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 15.5 Hz, 1H), 7.68 (d, J = 15.5 Hz, 1H), 6.83 (s, 2H), 6.00 (s, 1H), 5.21 (s, 1H), 3.94 (s, 3H), 3.91 (s, 6H), 3.30 (d, J = 6.7 Hz, 1H), 1.78 (s, 1H), 1.68 (s, 1H); ¹³C-NMR (150 MHz, DMSO-d₆) δ 192.9, 163.9, 163.2, 161.7, 153.6, 142.7, 140.0, 131.0, 130.8, 127.4, 123.1, 108.9, 106.3, 106.1, 88.2, 60.6, 56.7, 56.4, 25.9, 21.4, 18.1. HRMS (ESI): Calcd for C₃₅H₂₃O₈ [M + H]⁺ 443.2070; Found: 443.2071.

4. Conclusions

In summary, a metal-free and highly efficient protocol for the synthesis of chalcones by Claisen–Schmidt condensation using recoverable VB₄ as a catalyst has been developed. Thus, the method is characterized by the use of a convenient source of VB₄ and a green mixed solvent EtOH–H₂O to enable it to have these advantages including a tolerance for base-sensitive functional groups (hydroxy), high yields, and no side reactions. We also presented, for the first time, that natural product chalcone 3f treatment protected cells from OGD/R-induced apoptosis. Furthermore, we designed and synthesized 12 derivatives of 3f. Most compounds displayed restored activity against OGD/R, and the most active prepared chalcone 3s, which incorporates prenyl moiety, demonstrated a further neuroprotective activity by modulating the expression of the cell death signal factor. These findings provided important evidence for further basic and clinical research of 3s to as a potential agent against neurodegenerative diseases.

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