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One-pot green synthesis of 1,3,5-triarylpentane-1,5-dione and triarylmethane derivatives as a new class of tyrosinase inhibitors

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ABSTRACT

A new method was developed for one-pot green synthesis 1,3,5-triarylpentane-1,5-dione, triarylmethane, and flavonoid derivatives from the reaction between 2,4-dihydroxybenzaldehyde and hydroxyacetophenones via Aldol, Michael, and Friedel–Crafts additions using boric acid as catalyst in polyethylene glycol 400. The synthetic compounds demonstrated significant tyrosinase inhibitory activities much stronger than that of kojic acid. More important, 1,3,5-triarylpentane-1,5-dione and triarylmethane derivatives were found to be a new class of tyrosinase inhibitors.

Tyrosinase plays a key role in enzymatic browning in vegetables and fruits and the formation of skin melanin.[1,2] Enzymatic browning causes great loss in fruits and vegetables.[3] On the other hand, excessive secretion of melanin in the skin may also cause serious aesthetic problems in human beings.[4] Inhibition of tyrosinase activity will contribute to reduce these adverse effects in vegetables and fruits and in the skin. Application of tyrosinase inhibitors therefore gets a lot of attention due to its capable to inhibit the activity of tyrosinase and possess the great potential market profits and enormous application prospects. Up to now, numerous tyrosinase inhibitors identified from natural or synthetic origins have been reported.[5,6] However, only a few of them are sufficiently potent for practical use due to poor inhibitory activity, solubility, instability, and safety concerns. Therefore, finding a novel, stronger, and safer tyrosinase inhibitor remains challenge in food and medicinal chemistry.

Flavonoids have a variety of biological activities, such as antityrosinase, antimicrobial, anticancer, and antioxidants.[7–10] Many flavonoid derivatives have been found to be strong inhibitory activity against tyrosinase in the course of our searching potent inhibitors from natural sources, such as 2,4,2′,4′-tetrahydroxychalcone, morachalcone A, norartocarpetin, and steppogenin.[11–14] However, the low isolated yields from natural source greatly restrict the application of these flavonoids. Therefore, a robust synthetic method would be better to developed to obtain these tyrosinase inhibitors. Although many methods have been developed to synthetize flavonoids, their application are still suffered from harsh reaction conditions, toxic reagents and metal catalysts, strong acidic/basic conditions, prolonged reaction time, oily product, and tedious extraction procedure.[15–19] More worse, most synthetic methods to polyhydroxy flavonoids require extra protection/deprotection steps for the hydroxyl, leading to a waste of effort and unnecessary expense of chemical reagents. Recently, some green methods focused on tackling these problems on the basis of an increasing economic and ecological pressure.[20–22] However, lack of production and tedious manipulation did not only urgent an eco-friendly approach, but also an easy handling procedures with short reaction time and economic reaction.

Herein, we reported one-pot green synthesis of one 1,3,5-triarylpentane-1,5-dione and one triarylmethane derivative, together with four flavonoid derivatives by Aldol, Michael, and Friedel–Crafts additions between 2,4-dihydroxybenzaldehyde and hydroxyacetophenones using boric acid as catalyst in polyethylene glycol 400 (Scheme 1). Meanwhile, the products were also subjected to tyrosinase inhibitory activity tests.

Scheme 1 depicted the synthetic route of new 1,3,5-triarylpentane-1,5-dione (**3a**), triarylmethane derivatives (**3b**), and four known flavonoids (**4a**, **5a**, **4b**, **5b**). In Scheme 1(1), substrates **1** and **2a** were chosen as the starting materials. The reaction was conducted with the mixture of 2,4-dihydroxybenzaldehyde (**1**),

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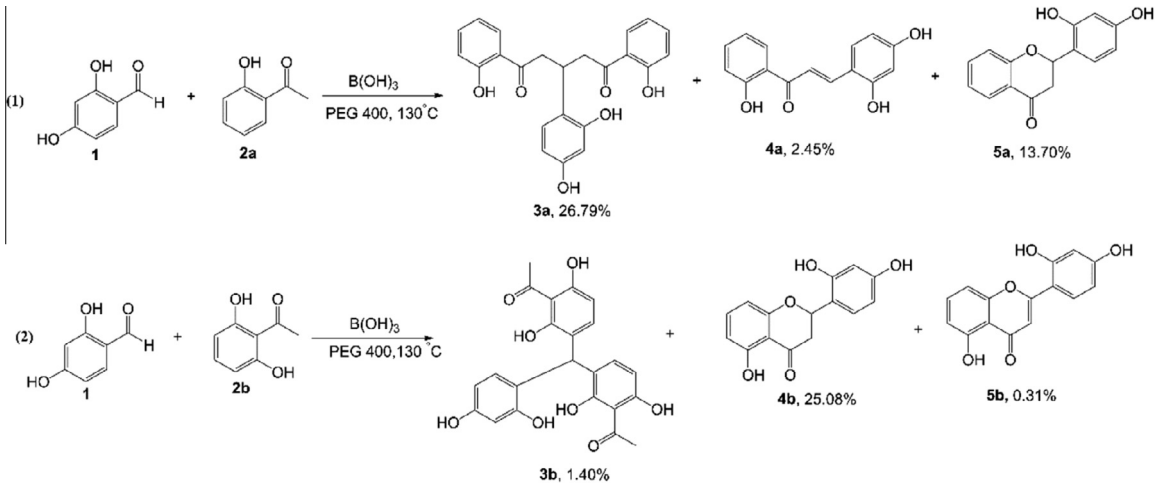


Scheme 1. One pot synthesis of 1,3,5-triarylpentane-1,5-dione, triarylmethane, and flavonoid derivatives.

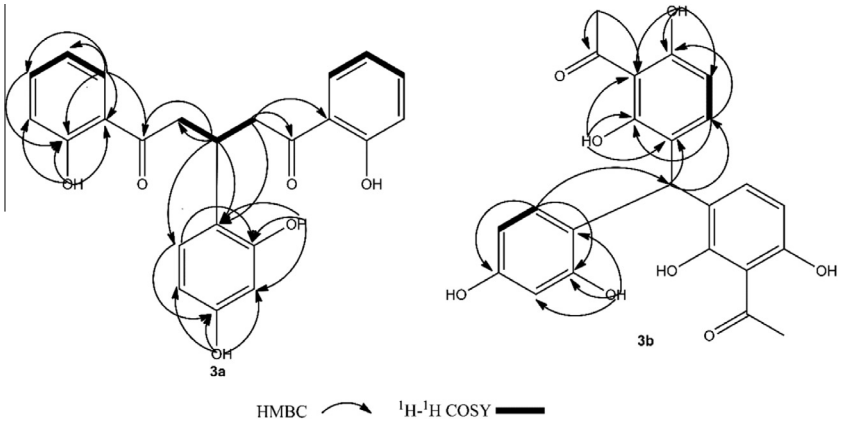
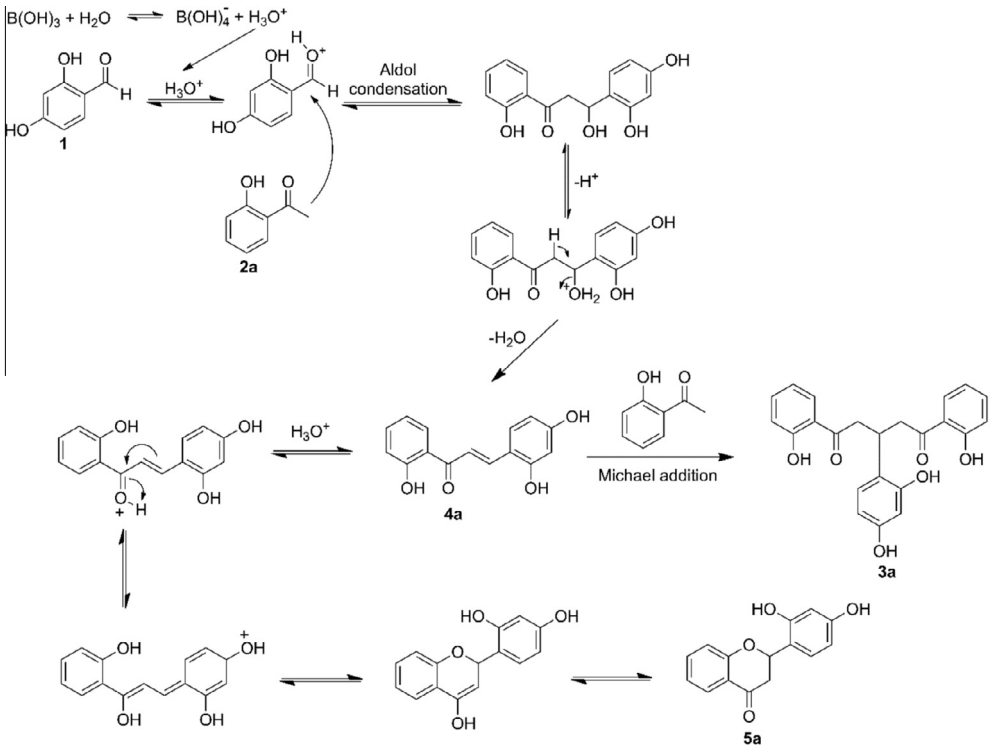


Figure 1. The key ^{1}H–^{1}H COSY and HMBC correlations of **3a** and **3b**.



Scheme 2. Proposed mechanism for the synthesis of 1,3,5-triarylpentane-1,5-dione and flavonoid derivatives.