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Short communication

Synthesis and inhibition of PGE_2 production of 6,8-disubstituted chrysin derivatives

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Abstract

A series of 6,8-disubstituted chrysin derivatives have been synthesized and evaluated for their PGE_2 inhibitory activities. 6,8-Disubstituted chrysin derivatives were obtained from naturally occurring chrysin by halogenation, oxidation, thiomethylation and C–C cross coupling reaction. Among the compounds investigated, 6,8-dibromochrysin (**2**), 6,8-diiodochrysin (**4**), 6,8-dimethylthiochrysin (**9**) and 6,8-dimethoxychrysin (**11**) showed as strong inhibitory activities of PGE_2 production from LPS-induced RAW 264.7 cells as wogonin, a well known natural flavone having strong and selective COX-2 inhibitory activity.

Keywords: Chrysin; PGE_2 production; Anti-inflammatory; COX-2; Wogonin; Flavonoids

1. Introduction

Chrysin (5,7-dihydroxyflavone), a naturally wide distributed flavonoid, has been reported to possess diverse biological activities such as anti-oxidant, anti-allergy, anti-inflammatory and anti-cancer [1–4]. It has been proposed that chrysin acts as an agonist of PPAR-γ which results in down-regulation of the key pro-inflammatory enzymes, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [5]. Furthermore, some natural flavone analogs such as wogonin, baicalein and oroxylin A (Fig. 1) showed much stronger inhibitory activities of PGE_2 production than that of chrysin [6,7]. These flavones have an extra 6- or 8-substituent group at the A ring of the flavone structures compared to the structure of chrysin. Therefore, we assumed that structural modification at both 6- and 8-positions of the A ring of chrysin could be tolerable to the bioactivity.

As an attempt to discover novel synthetic flavones with potent anti-inflammatory activity, recently we have synthesized flavone analogs modified at the A and B ring systems of chrysin and evaluated their inhibitory activities against prostaglandin production [8,9]. The results showed that methylation of 5,7-dihydroxy groups on the A ring as well as substitutions on the B ring of chrysin did not affect to the bioactivity. As part of our continuing research efforts directed at the SARs of natural flavones for the anti-inflammatory activity, we were interested in the effects of hydrophobic groups such as methylthio ($-SCH_3$), halogen (I, Br), alkyl and aryl groups substituted at the 6- and 8-positions of chrysin. Based on the structure–activity relationships (SARs) of these compounds for anti-inflammation, we visualized that the substitutions either at 6- or 8-position on the A ring of chrysin may play important roles in their bioactivities. These substituents are rarely seen in the basic structure of natural flavones, but it would be believed that they have important roles of bioactivities. In this paper, the synthesis of 6,8-disubstituted chrysin derivatives and evaluation of their inhibitory activities on PGE_2 production are reported. These compounds are more structurally similar to wogonin and oroxylin A than chrysin. As observed from the inhibitory activities of PGE_2 production of wogonin, baicalein and oroxylin A, substituention at 6- or 8-position did increase the bioactivity compared to that of chrysin. These results led us to design chrysin derivatives with substituents at 6- and 8-position. All the compounds were easily obtained from chrysin with excellent yields in a few steps.

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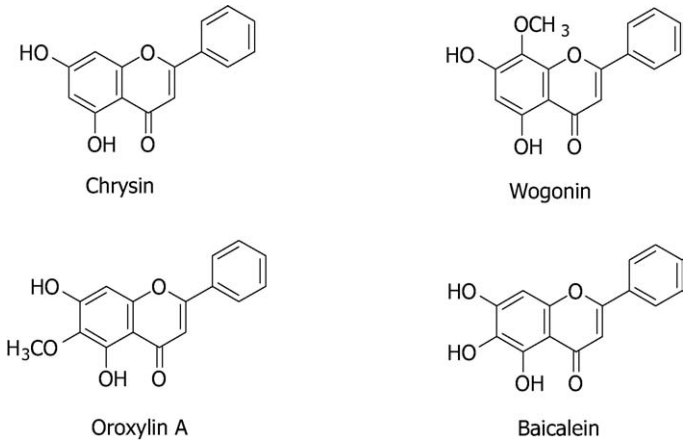
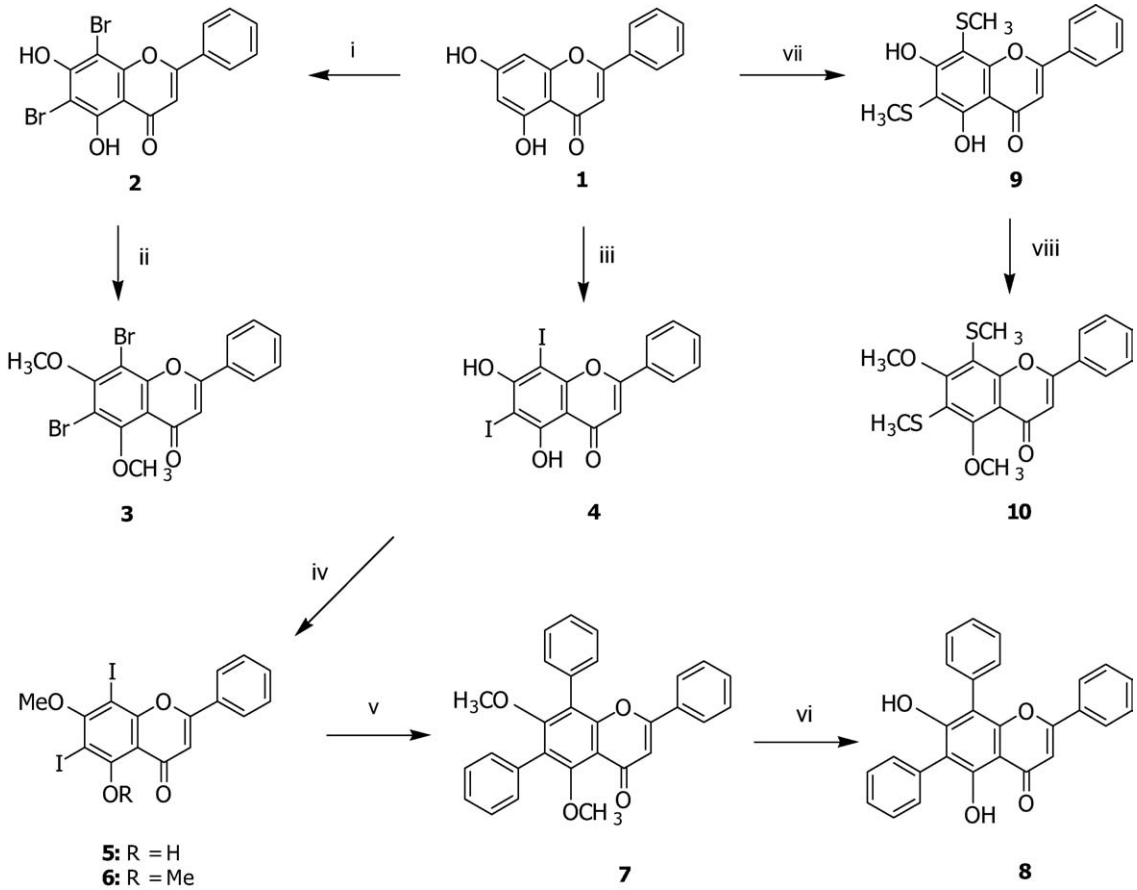


Fig. 1. Structures of some natural flavone analogs.

2. Chemistry

The synthetic procedures and reaction conditions for all investigated compounds are shown in Schemes 1 and 2. Chrysin (**1**) was directly halogenated by process of bromination [10] to form 6,8-dibromochrysin (**2**), or iodination [11] to form 6,8-diiodochrysin (**4**). Methylation reaction of the 6,8-dihalogenated chrysin derivatives with either 1 or 2 M equivalents of dimethylsulfate in anhydrous acetone and potassium carbonate gave 5,7-dimethoxy-6,8-dibromoflavone (**3**), 5-hydroxy-7-methoxy-6,8-diiodoflavone (**5**), and 6,8-diiodo-5,7-dimethoxyflavone (**6**). Suzuki coupling reaction [12] of **6**, benzeneboronic acid and catalytic amount of $Pd(PPh_3)_4$ afforded 5,7-dimethoxy-6,8-diphenylflavone (**7**). Deprotection reaction of **7** with BBr_3 in anhydrous methylene chloride gave 5,7-dihydroxy-6,8-diphenylflavone (**8**). Thiomethylation reaction [13] of chrysin (**1**) gave 6,8-dimethylthiochrysin (**9**) and followed by methylation with dimethylsulfate yielded



Scheme 1. i: Bromine, $CHCl_2$, Me_2S, 0 °C; ii: Me_2SO_4 (2 equiv.), K_2CO_3, acetone, reflux; iii: iodine, acetic acid, 0 °C; iv: Me_2SO_4 (1 equiv. For **5**; 2 equiv. for **6**), K_2CO_3, acetone, reflux; v: benzeneboronic acid, DMF, Pd $(PPh_3)_4$, 90 °C; vi: BBr_3, chloroform, reflux; vii: DMDS, $FeCl_3$, toluene, reflux; viii: Me_2SO_4 (2.5 equiv.), K_2CO_3, acetone, reflux.