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Original article

Synthesis and anti-cancer activity evaluation of novel prenylated and geranylated chalcone natural products and their analogs

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ABSTRACT

Four natural chalcones bearing prenyl or geranyl groups, i.e., bavachalcone (**1a**), xanthoangelol (**1b**), isobavachalcone (**1c**), and isoxanthoangelol (**1d**) were synthesized by using a regio-selective iodination and the Suzuki coupling reaction as key steps. The first total synthesis of isoxanthoangelol (**1d**) was achieved in 36% overall yield. A series of diprenylated and digeranylated chalcone analogs were also synthesized by alkylation, regio-selective iodination, aldol condensation, Suzuki coupling and [1,3]-sigmatropic rearrangement. The structures of the 11 new derivatives were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The anticancer activity of these new chalcone derivatives against human tumor cell line K562 were evaluated by MTT assay *in vitro*. SAR studies suggested that the 5′-prenylation/geranylation of the chalcones significantly enhance their cytotoxic activity. Among them, Bavachalcone (**1a**) displayed the most potent cytotoxic activity against K562 with IC_{50} value of 2.7 μM. The morphology changes and annexin-V/PI staining studies suggested that those chalcone derivatives inhibited the proliferation of K562 cells by inducing apoptosis.

1. Introduction

Chalcones containing prenyl or geranyl groups are an abundant subclass of flavonoids which are widely found in nature and display a variety of biological and pharmacological activities. Isobavachalcone (**1c**), first isolated from *Psoralea corylifolia* [1], showed antibacterial, antifungal, anticancer, anti-reverse transcriptase, antitubercular, and antioxidant activities [2–4]. Bavachalcone (**1a**), also isolated from *soraleaorylifolia* [1,5], was shown to display a significant inhibitory effect on baculovirus-expressed BACE-1 *in vitro* [6] as well as osteoclast differentiation [7]. These natural chalcones also exhibit extremely high α-glucosidase inhibitory activity [8]. Xanthoangelol (**1b**), isolated from fresh roots of *Angelica keiskei* [9], exhibits antibacterial activity against Gram-Positive pathogenic bacteria [10], antitumor-promoting activity and cytotoxicity against neuroblastoma cells, which induced apoptotic cell death via the mitochondrial pathway and had no cytotoxicity against normal cells [11]. The newly discovered compound **1d**, 2′, 4′, 4-trihydroxy- 5-geranyl chalcone, coined here as isoxanthoangelol, was isolated from the leaves of *Artocarpus communis*, and reported to possess anticancer activity in SW 872 human liposarcoma cells (Fig. 1) [12].

Due to their structural uniqueness and potent bioactivity, the synthesis of prenylated and geranylated chalcone natural products has attracted much attention in recent years. In 2010, Jung reported the first total synthesis of **1b** with a total yield of 16.8% starting from 4-dihydroxyacetophenone (**1**) [13]. Sugamoto subsequently finished the total synthesis of **1a**, **1b** and **1c** with 12.4%, 28.1% and 17.2% overall yield respectively [14]. All of these syntheses used O-alkylation followed by Claisen rearrangement as the key steps to

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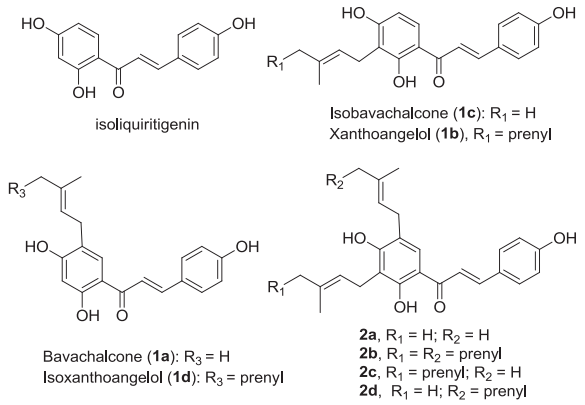


Fig. 1. The structures of chalcone natural products and their derivatives.

introduce the prenyl or geranyl groups. However, poor regioselectivity of the rearrangement limited their further use. Recently, McGlinchey applied iodination and Stille coupling to the synthesis of isobavachalocone. But the overall efficiency was low due to poor regiochemical control for the iodination as well as the low yield for the Stille coupling [15]. The 3′, 5′-diprenylated chalcone Medicagenin (**2a**) was isolated from the roots of *Crotalaria medicagenia* DC [16] and synthesized later by Narender [17] with a poor regioselectivity. However, no work has been reported on the synthesis and biological activity evaluation of other digeranylated chalcones, including **2b** and analogs **2c** and **2d**.

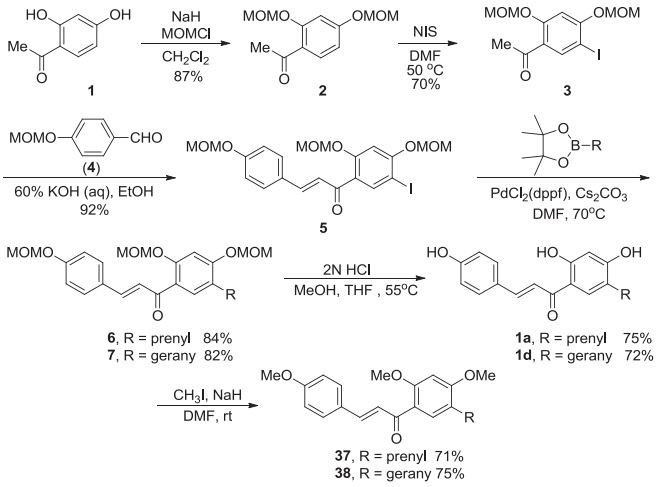
As part of our ongoing program on the synthesis of flavonoid and chalcone natural products, we have recently reported a regioselective iodination of flavonoids by NIS under neutral conditions [18], regioselective iodinations of chalcone derivatives using this protocol and the total synthesis of the aforementioned chalcone natural products by Suzuki coupling of the iodinated intermediates as the key step [19,20]. In this paper, we would like to report in details the synthesis and anticancer activity evaluation of the 3′ and/or 5′ prenylated/geranylated chalcone natural products (**1a**–**d**, **2a**) and their derivatives (**2b**–**d**, **33**–**40**) as well as the likely molecular mechanism of their cytotoxic activity.

2. Chemistry

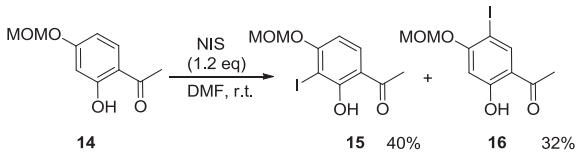
As shown in Scheme 1, iodide **3** was readily synthesized from the bis-MOM intermediate **2** by iodination of **1** with NIS in DMF [16]. Base promoted condensation of **3** with aldehyde **4** afforded the iodo precursor **5** which was converted into **6** and **7** by $PdCl_2$(dppf) catalyzed and microwave-assisted coupling reaction with the corresponding boronic acid pinacol esters in good yields. Removal of the MOM protecting groups finished the first total synthesis of isoxanthoangelol (**1d**) in 36% overall yield and the improved preparation of Bavachalcone (**1a**) in 35% overall yield respectively. The corresponding 2′, 4′, 4-trimethoxy derivatives **37** and **38** were obtained when **1a** and **1d** were treated with iodomethane and NaH in dry DMF in excellent yield.

The synthesis of isobavachalocone (**1c**) and xanthoganelol (**1b**) necessitates a 2-iodo-4-acetylresorcinol derivative such as **15** (Scheme 2). Unfortunately, iodination of the mono-MOM protected substrate **14** led to the formation of **15** along with a significant amount of its regioisomer **16**. However, utilization of an alternative iodination system (I_2/KIO_3) [21] provided a much cleaner access to the analogous iodide **8** directly from **1** (Scheme 3).

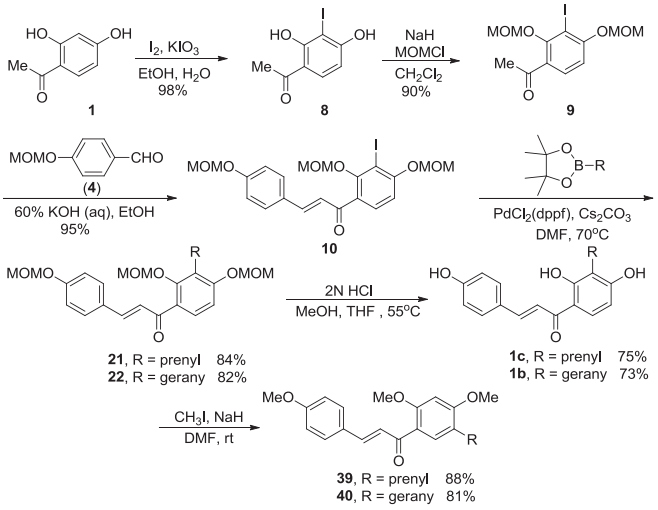
With compound **8** in hands, the total synthesis of both xanthoganelol **(1b)** and isobavachalocone **(1c)** was achieved uneventfully under similar conditions with an overall yield of 53% and 50%



Scheme 1. Synthetic route for target compounds **1a**, **1d**, **37** and **38**.



Scheme 2. Iodination of compound **14**.



Scheme 3. Synthetic route for target compounds **1b**, **1c**, **39** and **40**.

respectively, from the commercial material 4-acetylresorcinol (**1**). Compound **39** and **40** were prepared from **1b** and **1c** by methylation with MeI in 88% and 81% yield, respectively.

To synthesize the 3′, 5′-disubstituted chalcones Medicagenin (**2a**) and **2d**, we initially planned to employ the Pd-catalyzed coupling reaction to install the second prenyl/geranyl side-chain. This route required a 5′-iodo-3′- prenylated intermediate such as **23** (Scheme 4). Unfortunately, when using a protocol for the regieoselective iodination developed for the flavonoid substrates [18], the desired iodination product **23** was not formed. Therefore we decided to utilize the combination of Pd-catalyzed coupling reaction (for 5′-substitution) and O-alkylation/Claisen rearrangement (for 3′-substitution) to prepare the target compounds.

As shown in Scheme 5, compounds **6** and **7** were selectively deprotected with 1 M HCl at 0 °C to give the compounds **11a** and