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Original article

Prenylflavonoids and prenyl/alkyl-phloroacetophenones: Synthesis and antitumour biological evaluation☆

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ABSTRACT

Several prenylflavonoids have been synthesised and tested against human tumour cell lines. The prenyl unit has been geranyl or a labdane diterpene. These labdane-flavonoids have been synthesised for the first time. The antitumour activity increase with the prenylation at C-8 position. Twenty-three *C* and *O*-prenylated acylphloroglucinols have been synthesised as well. In this case the C-alkylation products have resulted, in general, more active.

1. Introduction

Nature is always an innovative laboratory. The combination of two or more types of natural products leading to hybrid compounds is not unusual [1]. This concept applied to chemical synthesis is a promising approach in the development of novel compounds either in medicine or in agrochemistry [2].

Many terpenoids are known to be biologically active [3,4], for instance their anti-inflammatory properties [5–7] have been well proven. Likewise, a wide range of bioactivities are described for flavonoids [8–12]. As a result, the combination of these two types of compounds could lead to more active hybrid compounds, or even with new biological properties.

In this work we aimed the synthesis and biological evaluation as antitumour agents of several terpenoid–flavonoid hybrid compounds.

The pharmacological activity of several prenylated flavonoids has been reviewed by Botta [13]. Other previous studies by Barron et al. [14,15] have shown that *C*-prenylated flavonoids are interesting synthetic targets due to their biological activities. Many of these compounds show affinity to *P*-glycoprotein and constitute promising potential modulators of multidrug resistance. Another series of *C*-isoprenylflavonoids show antiproliferative activity against HT-29 human colonic cell line.

Several phloroacetophenone analogues, intermediates in the synthetic pathway of flavonoids, have been reported from natural sources [16]. Several of these compounds, such as thouvenol A and thouvenol B (Fig. 1), isolated from *Protorhus thouvenotii* [17], showed *in vitro* cytotoxicity against A2780 ovarian cancer cell lines.

Acylphloroglucinols present interesting biological properties and they are both synthetically and biosynthetically related to flavonoid. These facts motivated us to accomplish the synthesis of an acyl phloroglucinol library with either a prenyl or alkyl moiety. Besides, the evaluation of their biological activity as potential antitumor agents is our final aim.

2. Results and discussion

To start with, we studied Barron et al. conditions [14] in order to optimize the alkylation of flavonols. Our fist attempt was the C-prenylation of chrysin.

In addition to the C-alkylation products described by Barron et al (**5** and **6**), compounds of C and O-alkylation **2**, **3** and **4** were also

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☆ In memoriam of Prof. J. M. Concellón.

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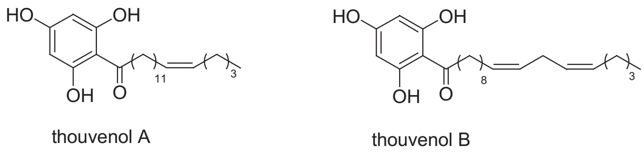
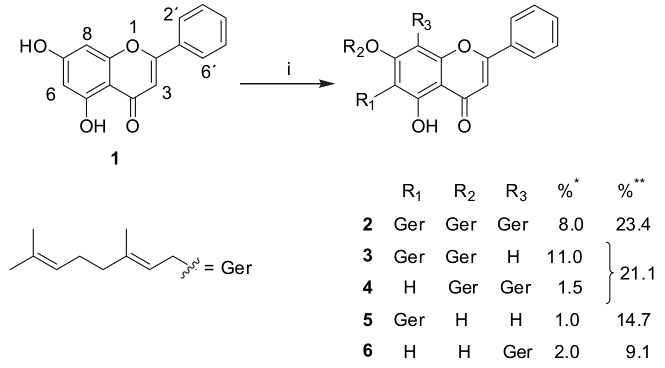


Fig. 1.



	R_1	R_2	R_3	%*	%**
2	Ger	Ger	Ger	8.0	23.4
3	Ger	Ger	H	11.0	21.1
4	H	Ger	Ger	1.5	
5	Ger	H	H	1.0	14.7
6	H	H	Ger	2.0	9.1

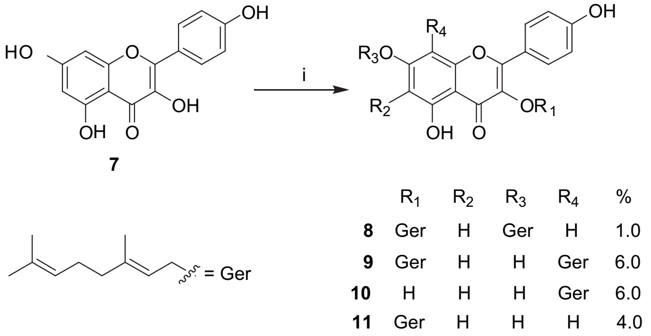
Scheme 1. *i) Me_4NOH 10% aq. (10 equiv.), Et_4NI (1 equiv.), MeOH, 6 times of 45 s each, MW (160 W), geranyl bromide (1 equiv.); **i) Me_4NOH 10% aq. (10 equiv.), Et_4NI (1 equiv.), MeOH, 6 times of 30 s each, MW (90 W), geranyl bromide (1 equiv.).

obtained. These molecules are interesting to develop SAR studies in tumour cell lines.

The reaction mixtures were submitted to several chromatographic stages yielding pure alkylated chrysin derivatives. The compounds were identified on the basis of their spectroscopic data. The alkylation position was determined by $^1H-^{13}C$ heteronuclear long-range correlations.

Once we had the pure alkylated chrysin derivatives on hand, they were used for the HPLC analysis of the several reaction mixtures obtained after varying reaction conditions. In our hands the best conditions to achieve the C-alkylation products of chrysin with geranyl bromide were 10 equiv. of base and 6 successive 30-s microwave irradiations at 90 W Scheme 1 summarizes the results obtained, recovering a 29.0% of unreacted chrysin.

The same reaction conditions for the C-alkylation of chrysin with geranyl bromide (90 W, base 10 equiv.) were used with kaempherol **7**. In this case, as it is a flavonol, opening products were obtained in a big ratio. Therefore, it was necessary to reduce the quantity of base to three equivalents. As shown in Scheme 2, 20% of unreacted kaempherol and opening products were obtained. The reaction mixture was purified as before and the products were identified by spectroscopic methods. The spectroscopic data of **10** are identical to the natural compound isomacarangin, isolated from *Macaranga Schweinfurthii* [18].



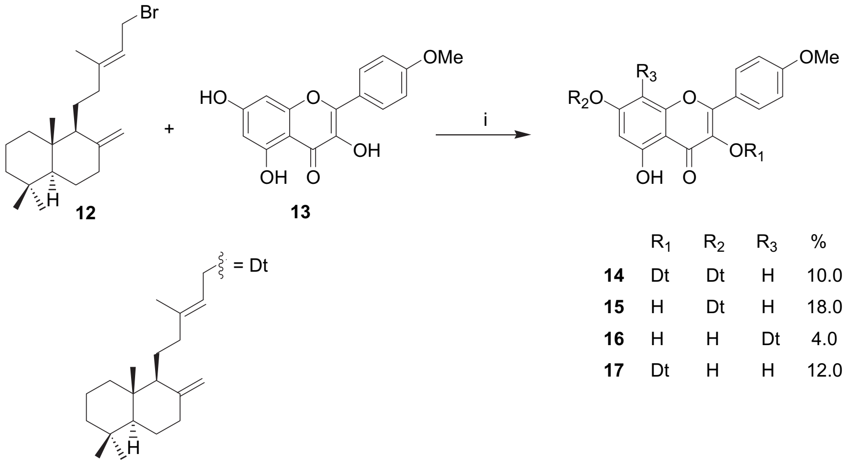
	R_1	R_2	R_3	R_4	%
8	Ger	H	Ger	H	1.0
9	Ger	H	H	Ger	6.0
10	H	H	H	Ger	6.0
11	Ger	H	H	H	4.0

Scheme 2. i) Me_4NOH 10% aq. (3 equiv.), Et_4NI (1 equiv.), MeOH, 7 times of15 s each, MW (90 W), geranyl bromide (10 equiv.).

In order to achieve molecules with the prenyl group as a diterpenoid, the alkylation of kaempheride, **13**, was tested with **12**, a diterpene bromide obtained from sclareol [19]. In this case, the microwave irradiation produced the decomposition of the diterpene moiety, so it was necessary to carry out the alkylation by refluxing kaempheride with 0.80 equiv. of the diterpene bromide **12** in acetone and K_2CO_3 (0.30 equiv.) over 3 h [20]. The results are presented in Scheme 3.

The reactions conditions established with kaempheride (Scheme 3) were used in the case of kaempherol, obtaining compounds of *C* and O-alkylation, as depicted in Scheme 4.

Either in the case of kaempheride, **13**, or kaempherol, **7**, it was not possible to isolate any C-alkylation product at C-6. Therefore, in order to obtain macarangin, **23**, isolated from *Macaranga denticulate* [21] and *Macaranga vedeliana* [22] and denticulaflavonol, **24**, isolated from *M. denticulate* [21] as well, the total synthesis is required. Denticulaflavonol is the first natural compound hybrid of a diterpene and a flavonol. So as to achieve the synthesis of this compound, firstly it was necessary to obtain ω-benzoyloxyphloroacetophenone **22**, Scheme 5.



	R_1	R_2	R_3	%
14	Dt	Dt	H	10.0
15	H	Dt	H	18.0
16	H	H	Dt	4.0
17	Dt	H	H	12.0

Scheme 3. i) K_2CO_3 (0.30 equiv.), **12** (0.8 equiv.), acetone, 74 °C, 3 h.