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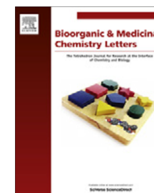

Antiproliferative and apoptotic effects of the oxidative dimerization product of methyl caffeate on human breast cancer cells

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A B S T R A C T

Caffeic acid derivatives are increasingly regarded as potential oncoprotective that could inhibit both the initiation and progression of cancer. Here we have synthesized seven 1-arylnaphthalene lignans and related compounds and tested their impact on breast cancer cell growth in tissue culture. The product of the oxidative dimerization of methyl caffeate, 1-phenylnaphthalene lignan, was found to induce a strong decrease in breast cancer cell number (IC_{50} ~1 μM) and was selected for further investigation. Flow cytometry analysis revealed a decrease in cell proliferation and an increase in apoptosis in both MCF-7 and MDA-MB-231 breast cancer cell lines that are representative of the two main categories of breast tumors. The 3,4-dihydroxyphenyl group probably induced the biological activity, as the control compounds lacking it had no effect on breast cancer cells. Together, our data indicate that the oxidative dimerization product of methyl caffeate can inhibit breast cancer cell growth at a concentration adequate for pharmacological use.

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Food derived polyphenol anti-oxidants have been shown to have an oncoprotective effect.[1,2] This is particularly well illustrated with propolis that was used for the treatment of tumors in traditional oriental medicine, and has been shown to have the ability to inhibit breast cancer cell growth.[3,4] Several studies[5–10] have reported the antiproliferative effect of caffeic acid derivatives (including caffeic acid phenylethyl ester (CAPE), a beehive propolis component) on human breast cancer cells. Caffeic acid itself has been found to exert an antiproliferative and anti-apoptotic activity at low concentrations on some breast cancer cell lines such as T47D, whereas others such as MCF-7, MDA-MB-231 and HS578T were insensitive.[3] Several synthetic caffeic acid esters were found to inhibit the growth of MCF-7 cells[5,8,9] and the reduction of the double bond improved this antiproliferative activity.[5] In addition, CAPE induced apoptosis of MCF-7 cells by inhibiting NF-κB and activating Fas.[7]

Lignans are formed in nature by the oxidative dimerization of C_6C_3 phenols and are defined as those compounds in which the two C_6C_3 units are linked by a bond connecting the central carbon atom of each side chain. Many lignans, such as podophylotoxin or enterolactone, exhibit important antitumor activities[11] and are regarded as phytoestrogens.[12] The 1-phenylnaphthalene lignan **1** (Chart 1), obtained by oxidative dimerization of methyl caffeate by iron(III) chloride, was previously tested as topoisomerase inhibitor.[13] It presented a 100% topoisomerase II inhibition at 50 μM.

In the present study, we explored the effect on breast cancer cells of a series of 1-phenylnaphthalenes issued from the oxidative dimerization of methyl caffeate and ferulate by iron trichloride[14–18] or by a procedure described by Yvon et al.[19] Amongst a series of seven selected compounds that have been tested, the best tumor cell growth inhibitory effect was obtained with compound **1**. Subsequently, the antiproliferative and apoptotic activity of **1** was evaluated on MCF-7 and MDA-MD-231 cells.[20–22]

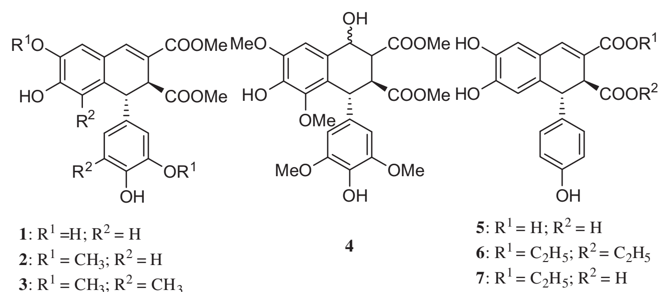

Chart 1.

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Compound **1** revealed an efficient inhibition of both proliferation and survival of breast cancer cells.

Compounds **1**,[14] **2**,[15,16] **3** and **4**,[17,18] (Chart 1) were synthesized according to known procedures using iron(III) chloride as oxidizing agent. The purity and spectral data of these derivatives were as reported in the literature.[14–18] Compounds **5**, **6** and **7** (Scheme 1) were obtained in the following four-step procedure. 3,4-Dimethoxybenzaldehyde was condensed on diethyl succinate in the presence of sodium *tert*-butoxide in *tert*-butyl alcohol to give ethyl (*E*)-2-[(3,4-dimethoxyphenyl)-methylene]succinic acid 1-methylester (**I**) in 56% yield. This monoester was esterified using thionyl chloride in ethanol to give **II**. A second Stobbe condensation was accomplished using 4-methoxybenzaldehyde in the presence of LDA in THF and the intramolecular cyclization was obtained in trifluoroacetic acid at room temperature yielding trans ethyl 1,2-dihydro-6,7-dimethoxy-1-(4′-methoxyphenyl)-naphthalene-2,3-dicarboxylate (**III**) in 40% yield. Finally, the total demethylation of the methoxy groups was accomplished using boron tribromide. Whatever the reaction conditions (temperature, equivalent number, time, temperature and time of hydrolysis) we always obtained a mixture of **5** and **7**. Under particular conditions, small amounts of **6** were also isolated. The best results were obtained when the reaction was conducted with 4 equivalents of boron tribromide in dichloromethane at room temperature during 30 min. With a 1 h hydrolysis at reflux, **5** and **7** were isolated in 54 and 18% yield, respectively. With a 30 min hydrolysis at room temperature, **7** was obtained in 28% yield and traces of **6** could be isolated.

The synthesized molecules **1–7** were first tested on the growth of MCF-7 breast cancer cells at the standard concentrations of 10 μM (Fig. 1). **1** was found to be the best compound of the series with 82% of inhibition.

Compounds **2** and **3** had no effect on breast cancer cell growth, indicating that the catechol moieties may support biological activity. The biological activities of compounds **5**, **6** and **7** show the relative impact of the two catechol moieties of **1** on the inhibition of the MCF-7 cell growth. The 3,4-dihydroxyphenyl group probably carried the biological properties of **1**. This result can be compared to the difference of activities of caffeic esters and dihydrocaffeic esters previously reported.[5] Dihydrocaffeic esters presented, in all cases, higher activities than their caffeic esters analogues. Compounds **4** and **5** presented moderate activities, but due to chemical instabilities (dehydration of **4** and decarboxylation of **5**) they were not selected for further investigation.

In order to characterize the growth inhibitory effect of **1** on breast cancer cells, we extended our study to MDA-MB-231 cells. We first tested compound **1** (0.05–10 μM) in the absence or presence of FCS. As depicted in Figure 2, compound **1** inhibited the growth of both cell lines. IC_{50} was not significantly different in presence or absence of FCS. It has been estimated to ~1 μM in MCF-7 and to ~5 μM in MDA-MB-231 cells.

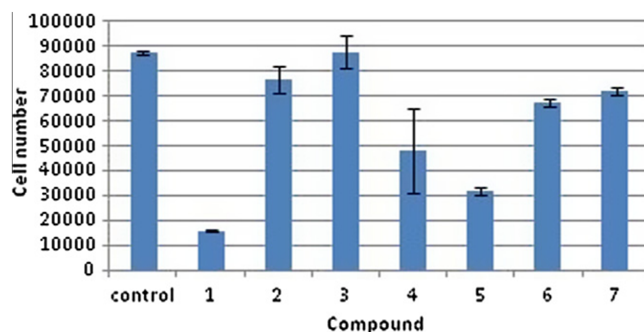
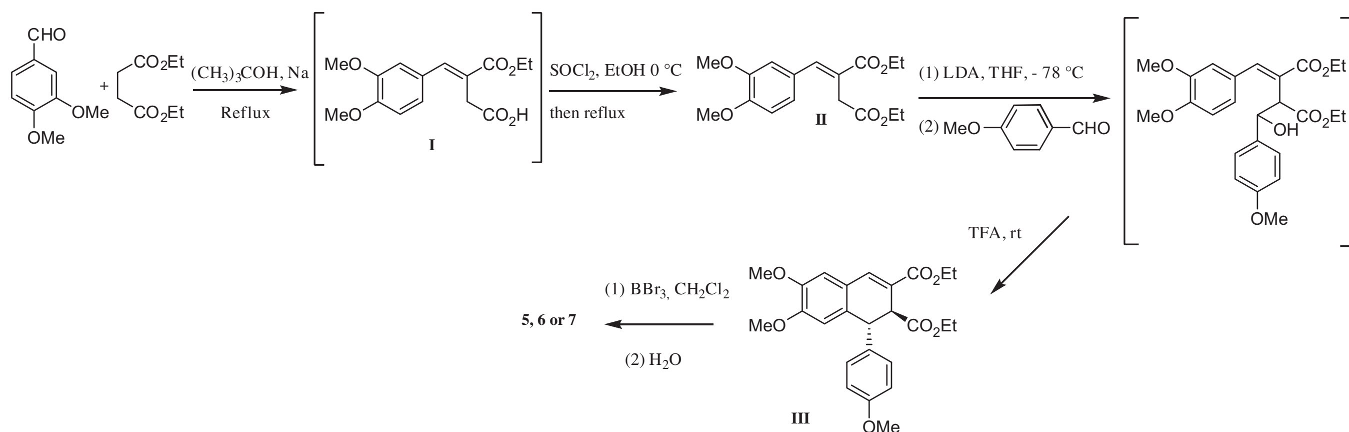


Figure 1. Effect of compounds **1–7** (10 μM) on the growth of MCF-7 cells in basal EMEM with 10% FCS.

As revealed by Hoechst staining, cancer cells entered apoptosis (Fig. 3A and B) when treated with compound **1**. In these experiments, apoptosis was found to be concentration-dependent and depended on the medium. When treated with 10 μM of **1** in the presence of FCS, percentage of apoptotic cells was 25% higher, independently of the breast cancer cell line.

The effect of compound **1** at 5 μM on breast cancer cell cycle was then evaluated. Typical feature of flow cytometry are shown in Figure 5A and B. Cell populations were reported on Figure 4A and B for MCF-7 and MDA-MB-231 cell line, respectively. The absence of FCS induced a G0/G1 phase cell arrest, as evidenced by accumulation in the G0/G1 phase, from 35.6% (MCF-7) and 31.7% (MDA-MB-231) with FCS to 70.9% (MCF-7) and 73.9% (MDA-MB-231) without FCS with a concomitant decrease in cell accumulation in the S and G2/M phases. In the presence of FCS, **1** induced different effects on cell cycle of MCF-7 and MDA-MB-231. Whereas **1** induced a slight decrease in MCF-7 cell accumulation in the G0/G1, S and G2/M phases (from 35.6% (without **1**) to 29.4% (**1** at 5 μM) for G0/G1 phase, from 46.6% to 34.7% for S phase and from 17.8% to 17.0% for S/G2 phase), **1** promoted a S-phase cell cycle arrest as evidenced by the accumulation of MDA-MB-231 cells in the S-phase (from 40.4% (without **1**) to 56.1% (**1** at 5 μM), with a concomitant decrease in cell accumulation in the G0/G1 and the G2/M phases.

As revealed by Propidium Iodide staining (PI staining), cell exhibited apoptosis when treated with compound **1**. MDA-MB-231 and MCF-7 cells treated with **1** at 5 μM exhibited a sub-G0 population. The sub-G0 peak corresponded to about 20% of total count whatever the cell lines or culture conditions.



Scheme 1. Synthesis of the target compounds **5–7**.

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