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Synthesis and anti-proliferative activity of fluoro-substituted chalcones

Serdar Burmaoglu [a,c,*,†], Oztekin Algul [b,*,†], Derya Aktas Anıl [c], Arzu Gobek [c], Gulay Gulbol Duran [d], Ronak Haj Ersan [b], Nizami Duran [e]

[a] Tercan Vocational High School, Erzincan University, Erzincan 24800, Turkey
[b] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Mersin University, Mersin 33169, Turkey
[c] Department of Chemistry, Faculty of Science, Ataturk University, Erzurum 25240, Turkey
[d] Department of Medical Biology, Medical Faculty, Mustafa Kemal University, Antakya-Hatay 31100, Turkey
[e] Department of Medical Microbiology, Medical Faculty, Mustafa Kemal University, Antakya-Hatay 31100, Turkey

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ABSTRACT

A series of novel fluoro-substituted chalcone derivatives have been synthesized. All synthesized compounds were characterized by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and elemental analysis. Their anti-proliferative activities were evaluated against five cancer cells lines, namely, A549, A498, HeLa, A375, and HepG2 using the MTT method. Most of the compounds showed moderate to high activity with IC_{50} values in the range of 0.029–0.729 μM. Of all the synthesized compounds, **10** and **19** exhibited the most potent anti-proliferative activities against cancer cells, and **10** was identified as the most promising compound.

Fluorine-containing compounds have been widely researched in the literature for their use as drugs or drug candidates. Fluorine as a substituent affects the bonding interactions and metabolic stabilities of drugs and has an impact on their physical features and selective reactivities.[1] The introduction of fluorine or fluorine-containing group to a molecule significantly changes its features. There are no elements or groups that cause similar effects on molecules.[2] In general, the effects of the addition of a fluorine atom to a molecule can be divided into two categories: chemical or biological. Table 1 shows the features of organofluorine molecules.[2]

Chalcones, one of the major classes of natural products, are open-chain flavanoids in which two aromatic rings are linked by a three carbon α,β-unsaturated/saturated carbonyl system. In general, they include polyhydroxy groups in their aromatic rings. The free radical quenching properties of these phenolic groups increase the interest in the use of these compounds or chalcone-rich plant extracts as drugs or food preservatives.[3] In addition, chalcones show many biological activities such as anti-diabetic,[4] anti-neoplastic,[5] anti-hypertensive,[6] anti-retroviral,[7] anti-inflammatory,[8] anti-histaminic,[9] anti-oxidant,[10] anti-malarial[11] and anti-cancer[4] activities.

Recently, many studies have been conducted on the anti-cancer properties of chalcones. In the last 30 years, research on the effects of chalcones on different types of cancer has attracted significant interest despite the considerable increase in the number of studies on the subject. The anti-cancer properties of chalcones result from the different functional groups on both aromatic rings (Fig. 1).[4] Chalcone derivatives still attract much attention as drug candidates because of their wide-ranging biological activities as well as their accessibility from the appropriate benzaldehyde and acetophenone derivatives. Here, we report the syntheses and anti-cancer activities of ten chalcones with fluorine substituents on their B-rings and two non-substituted chalcones.

The condensation of trimethoxyacetophenone (**1**) with **2** in an aqueous solution of KOH afforded chalcone **3** in 90% yield through the adoption of a general synthesis protocol (Scheme 1).[12] Hydrogenation of compound **3** on Pd/C afforded **4** in 80% yield. After the successful synthesis of chalcone **4**, compounds **8**, **9**, and **10** were obtained from the reaction of **1** with fluoro-substituted benzaldehyde (**5**, **6**, **7**) in 80–95% yield by employing the developed procedure. Hydrogenation of chalcones **5**, **6**, and **7** on Pd/C afforded **11**, **12**, and **13** in excellent yields (70–90%) (Scheme 1).

* Corresponding authors. Tel.: +90 446 441 3627; fax: +90 446 441 3672 (S.B.); tel.: +90 324 341 2815; fax: +90 324 341 3022 (O.A.).
E-mail addresses: sburmaoglu@erzincan.edu.tr (S. Burmaoglu), oztekinalgul@mersin.edu.tr (O. Algul).
† These authors contributed equally.

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Table 1
Properties of organofluorine compounds

Chemical	Biological
Small size	Electronegative effect of neighboring functionalities
Lipophilic	Strong C–F bonds resistant to metabolic processes
High electronegativity	Increases lipid solubility (bioavailability)
Low reactivity	Synthesis of isosteric analogues of drugs Useful for studying biochemical processes

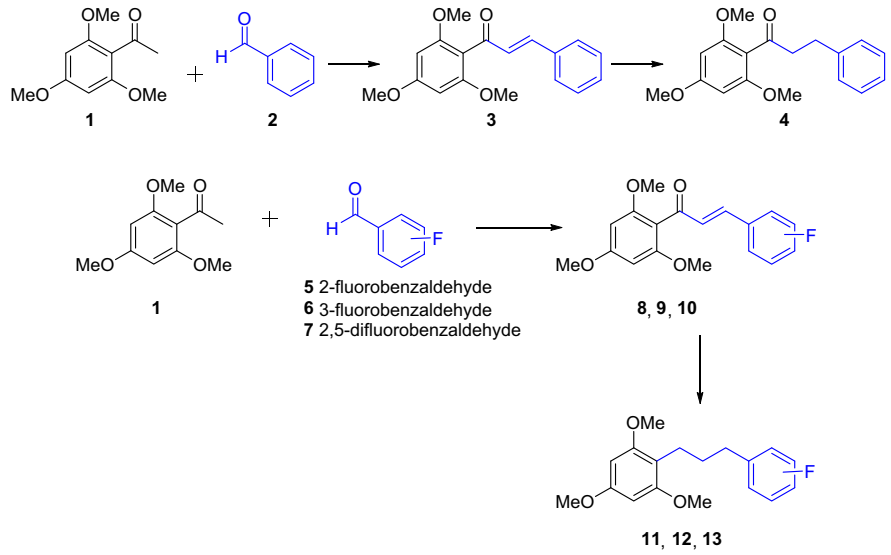
Having successfully synthesized the trimethoxychalcones, we turned our attention to trihydroxychalcones. Condensation of trihydroxyacetophenone (**14**) with fluoro-substituted benzaldehydes (**5** and **7**) did not afford compounds **16** and **17** and only the starting material was recovered. After this setback, we strategically decided to protect the hydroxyl groups with MOMCl, which is stable under basic conditions and can be deprotected easily under mild acidic conditions. The base-catalyzed reaction of **15** with both **5** and **7** afforded MOM-protected chalcones **16** and **17** in good yields. After the removal of MOM with HCl in MeOH, the α,β-unsaturated double bond of **18** and **19** was reduced to afford target compounds **20** and **21** in 80% and 85% yield, respectively (Scheme 2).

The structures of the molecules synthesized in this study are shown in Scheme 3. To the best of our knowledge, this is the first report on the preparation of compounds **8–13** and **19–21**, and of these compounds only **18** has been reported previously in the literature.[13] All the compounds were isolated as either solids or liquids and characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis (for detailed information see the supplementary data).

Several studies have been conducted on the anti-cancer properties of chalcones; however, only few studies on chalcones with fluoro groups in their B rings exist.[13,14] In a similar study, Padhye and co-workers[13] prepared 2′-hydroxychalcones with hydroxyl/fluoro groups in their B rings and evaluated their radical scavenging potential and anti-proliferative activities against human pancreatic and breast cancer cells. They found that the B ring fluoro-substituted chalcones exhibited superior anti-proliferative activities than their hydroxylated derivatives toward these cell lines.

In this study, the anti-proliferative activities of twelve chalcone derivatives (**3**, **4**, **8–13**, and **18–21**) were evaluated. The primary objective of the synthesis of the fluoro-substituted chalcone derivatives was to determine their potency and specificity against five different cancer cells compared with those of methotrexate (MTX). To assess the anti-proliferative properties, the synthesized compounds were grouped into two main groups (methoxy- or hydroxyl-substituted) and three subgroups (chalcone, semi-saturated, or saturated), and their effects on cancer cell proliferation were assessed in vitro using human lung adenocarcinoma epithelial cells (A549), human renal cancer cells (A498), human cervical cancer cells (HeLa), human skin malignant melanoma cells (A375), and human hepatocellular carcinoma cells (HepG2).

To assess the specificity of the compounds, their toxicity was tested against normal cells using human embryonic kidney cells (HEK 293). The specificity of the compounds was calculated as



Scheme 1. Preparation of non- and fluoro-substituted trimethoxychalcones.

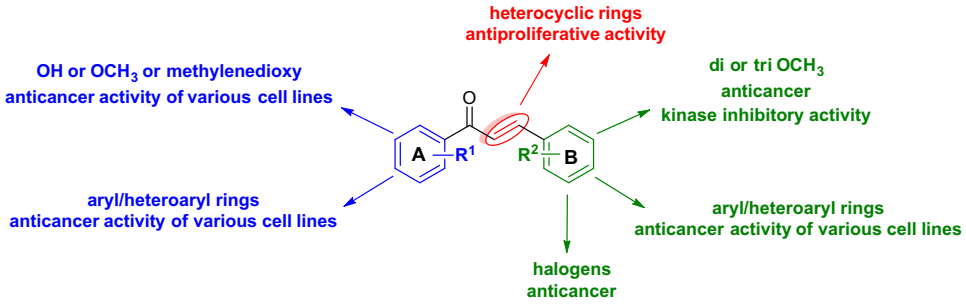


Figure 1. Anti-cancer activity properties of chalcones according to their different functional groups.