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In vitro antitumor activity of protoflavone-based hybrid compounds on human gynecological cancer cell lines

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Protoflavones are rare and unusual flavonoid derivatives having a non-aromatic B-ring; in nature, they can most typically be found in certain genera of fern species. Protoflavones are promising, natural anticancer agents, and their *in vitro* and in *vivo* activity inspired the synthesis of many semi- and total synthetic analogs [1]. In the current study, our aim was to evaluate the antitumor potential of a set of new hybrid compounds, each containing a protoflavone and a chalchone or ferrocene fragment.
Four new compounds were prepared and studied for their *in vitro* antitumor activity against four gynecological human cancer cell lines including HeLa and SiHa (cervical), and MCF-7 and MDA-MB-231 (breast) cancer cells, with cisplatin as a positive control. When testing by MTT assay, the compounds showed strong antiproliferative activities with IC_{50} values in the low-medium nanomolar range. To quantitatively evaluate pharmacological benefit gained by the coupling, bioactivity of each compound was further analyzed in a virtual combination study, i.e. considering it as an interaction of a 1:1 ratio mixture of the corresponding protoflavone and chalchone building block. The most potent compound demonstrated an IC_{50} value of 153 nM against SiHa cells, representing a combination index value of 0.10 (i.e. very strong synergism) for the two separate fragments. This compound was found to induce apoptosis in MDA-MB-231 and SiHa cells through the significant increase in the hypodiploid (sub G1) population as evidenced by cell cycle analysis and induced the activation of caspase-3.
Our study highlights the pharmacological potential of protoflavone-based hybrid compounds and demonstrates that these hybrids are much more than a simple addition of their chemical elements.

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Reference
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