ABSTRACT

Aiming for new compounds with antitumor activity, the synthesis of prenylated xanthones and prenylated and geranylated flavones was recently achieved on CEQOFFUP. In this work the potential antitumor activity of these compounds in three tumor cell lines, namely MCF-7 (human breast cancer cells expressing estrogen receptors (ER+)), MDA-MB-231 (human breast cancer cells non expressing estrogen receptors (ER-)) and NCI-H460 (non-small cell lung cancer) was evaluated. Structure-activity relationships were established highlighting the influence of prenylation and geranylation.

Concerning xanthones, prenylation of 3,4-dihydroxyxanthone **(XXIX)** furnished more potent and selective derivates for MCF-7 (ER+) cells than the original oxygenated xanthone. Xanthone derivate **XP13** showed the strongest inhibitory effect on the growth of breast adenocarcinoma cell line ER+, MCF-7 (GI_{50} = 5,3 μM). Thus, potential estrogenic/antiestrogenic properties were investigated for this compound. No proliferative effect at low concentrations was observed for **XP13** in experiments performed in steroid-free medium (RPMI-SFM). However, when high concentrations of **XP13** were used, this prenylated xanthone inhibit cancer cell growth in a dose-dependent manner, being more active on MCF-7 (ER+) cell line than on MDA-MB-231 (ER -) cell line. This antiproliferative effect was not influenced by the culture medium (steroid (RPMI) or steroid-free medium (RPMI-SFM)). From these results it can be inferred that **XP13** does not directly act on the estrogen receptor, suggesting that it could interfere with other signaling pathways. Moreover, **XP13** enhanced the growth inhibitory action of 4-hydroxytamoxifen (4-OHT, **XIV**), a partial antiestrogen in estrogen sensitive breast cancer cells.

Concerning flavone derivates, none of the six flavones investigated, that were resulted from prenylation and geranylation of baicalein (BAIC, **XIX**), presented a higher cytotoxic effect on all tumor cellular lines (MCF-7 (ER+), MDA-MB-231 (ER -) and NCI-H460) when compared to the original oxygenated flavone BAIC **(XIX)**. However, monoprenylation in C(7) conduced to a flavone **(FP2)** with a selective inhibitory effect on the growth of MCF-7 (ER+) cells. Possible estrogenic/antiestrogenic properties were investigated for this compound. It was verified that in steroid-free medium (RPMI-SFM) experiments, **FP2** presented a biphasic effect in vitro growth on the ER-positive MCF-7 cell line. Although at low concentrations this flavone has stimulated cell growth, at high concentrations a cell growth inhibition was observed. Then, the effect of **FP2** in combination with **E2** was examinated. Results showed that **FP2** suppressed at low concentrations, the mitogenic effect enhanced by estrogenic stimulation, suggesting a competition for ERs. Also, the **FP2** cancer cell growth inhibitory effect on MCF-7 (ER+) cells was stronger when assed in steroid free medium, i.e., in the absence of estrogenic stimulation. These results suggest a direct involvement of estrogen receptor in the proliferative/antiproliferative effect of flavone **FP2**. Moreover, **FP2** enhanced the growth inhibitory action of partial (4-OHT, **XIV**) and pure (ICI 182,780, **XII**) antiestrogens in estrogen sensitive breast cancer cells.

These results were consistent with previous reports of prenylated flavones and disclose for prenylated xanthones effects compatible with antiestrogenic activity. Thus, the present work represents a promising contribution for the prevention and treatment of hormone-dependent breast cancer.