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Evaluation of antitumor activity of xanthones conjugated with amino acids

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Abstract

Background: Cancer is a complex disease characterized by several alterations that confer on the cells, the capacity to proliferate uncontrollably and to resist cellular death. Multiresistance to conventional chemotherapy drugs is often the cause of treatment failure; thus, the search for natural products or their derivatives with therapeutic action is essential. Chiral derivatives of xanthones (CDXs) have shown potential inhibitory activity against the growth of some human tumor cell lines and the influence of the stereochemistry [1,2]. **Objective:** This study aimed to screen a library of previously synthesized CDXs in a panel of cancer cell lines to identify the most promising compounds for further study as possible chemotherapy drugs, as well as to analyze their effect on several parameters of cancer cells and verify whether the compounds under study were substrates of P-glycoprotein (P-gp), one of the main mechanisms of resistance in cancer therapy. **Methods:** In this study, cell viability assays were performed on three tumor cell lines: MCF-7, NCI-H460, and A375-C5 using a library of previously synthesized CDXs. CDXs' effect was analysed based on several parameters of cancer cells, like extracellular levels of glucose and lactate, the mechanism of cell death, and it was also verified whether these compounds were substrates of P-gp. **Results:** The cytotoxic activity of forty-six CDXs was evaluated, and an enantiomeric pair was considered as lead compounds and selected for other studies since they presented GI_{50} values lower than 15 µM for all cell lines. The selectivity index higher than 1 against cancer cells was found for both enantiomers, indicating that these compounds are considerably more specific to cancer cells, which is desirable. No significant changes were identified in the metabolic parameters analysed and it was not possible to determine whether the compounds are P-gp substrates. The main mechanism of death triggered by these compounds was apoptosis. **Conclusions:** These results show that some CDXs present promising antitumor activity, but other mechanisms besides metabolism, should be triggered by these compounds. Evidence of enantioselectivity was found being the D enantiomer more cytotoxic, compared to L.

Keywords: derivatives of xanthones; cancer; P-glycoprotein; multidrug resistance

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