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Enantioselectivity in antitumor activity of flavone derivatives

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Abstract

Background: Nature represents a rich source of bioactive compounds, with flavones standing out as privileged scaffolds owing to their multiple biological activities [1]. Their potential as antitumor agents arises from their ability to act on multiple cellular pathways implicated in cancer progression and to attenuate multidrug resistance (MDR) [2]. However, to overcome inherent pharmacokinetic drawbacks and target selectivity, flavones are commonly subjected to structural modifications [3]. The incorporation of chiral moieties, such as amino acids, is used to improve the pharmacokinetic parameters and selectivity [4]. **Objective:** This study screened a library of thirty-two new chiral flavone derivatives (CDFs) to identify promising chemotherapeutic candidates. Beyond cytotoxicity, their effects on tumor metabolism, cell death mechanisms, and their potential as P-glycoprotein (P-gp) inhibitors to overcome multidrug resistance were evaluated. **Methods:** Cell viability assays were performed against a panel of four human cancer cell lines: A375-C5 (melanoma), MCF-7 (breast), NCI-H460 (lung), and HCT-15 (colorectal). The most promising CDFs were further characterized with respect to their impact on metabolic profiles through the quantification of extracellular glucose and lactate levels. Additionally, apoptosis induction was evaluated by Annexin V/PI double staining and flow cytometry, while the Rhodamine 123 exclusion assay was conducted in HCT-15 cells to assess the compounds' potential as P-gp inhibitors. **Results:** Derivatives 6HF-DTrp and 7HF-DTrp were the most potent candidates (GI_{50} < 25 μM), with 7HF-DTrp displaying high specificity (SI up to 7.94) across all tumor lines. While metabolic and apoptotic responses varied by cell type, both compounds were confirmed as P-gp inhibitors through *in vitro* and *in silico* assays. **Conclusions:** These findings identify 6HF-DTrp and 7HF-DTrp as potent, selective, and P-gp inhibitory leads, highlighting their potential as candidates for both monotherapy and combination strategies in cancer treatment.

Keywords: chiral flavones; antitumor activity; multidrug resistance

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