Design and Synthesis of Chalcone and Chromone Derivatives as Novel Anticancer Agents

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Abstract

This thesis comprises the design and synthesis of chalcone and chromone derivatives and their use in various biological applications, particularly as anticancer agents (targeting proteins associated with cancer pathogenesis) and as potential fluorophores for live-cell imaging. Conveniently, all structures presented were synthesized from commercially available 2´-hydroxyacetophenones. Different synthetic strategies were used to obtain an easily accessible chromone scaffold with appropriate handles that allows regioselective introduction of various substituents. Structural diversity was accomplished by using palladium-mediated reactions for the incorporation of suitable substituents for the generation of chromone derivatives that possess different biological activities.

Challenging synthesis provided a series of fluorescent 2,6,8-trisubstituted 3-hydroxychromone derivatives with high quantum yields and molar extinction coefficients. Two of these derivatives were studied as fluorophores in live-cell imaging and showed rapid absorption, non-cytotoxic profiles and excellent fluorescent properties in a cellular environment.

Synthetic chromone precursors, i.e. chalcones, and related dienones were evaluated as antiproliferative agents that interfere with the tubulin-microtubule equilibrium, crucial for cellular mitosis. It was shown that several of the synthesized compounds destabilize tubulin assembly. However, one of the compounds was instead found to stabilize tubulin to the same extent as the known anticancer drug docetaxel, thus representing the first chalcone with microtubule stabilizing activity. Molecular docking was used in order to theoretically investigate the interactions of the chalcones with β-tubulin mainly focusing on binding modes, potential interactions and specific binding sites.

Structural-based design and extensive synthesis provided chromone-based derivatives that target two different MAP kinases (p38α and MEK1), involved in essential cellular signal transduction pathways. The study resulted in a series of highly selective ATP-competitive chromone-based p38α inhibitors with IC_{50} values in the nanomolar range. Among those, two derivatives also showed inhibition of p38 signaling in human breast cancer cells. Furthermore, molecular docking was used to study potential structural modifications on the chromone structure in order to obtain highly potent derivatives that selectively target the allosteric pocket on MEK1. Initial studies provided a first generation of non-ATP-competitive chromone derivatives that prevents the activation of MEK1 with micromolar activities.

Keywords: Chalcones, Chromones, Fluorescence, Fluorophore, Cellular imaging, Anticancer, Tubulin, Microtubule, Kinase inhibitors, p38, MEK1, Palladium-mediated reactions, Molecular modeling, Structure-Activity Relationships.