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Abstract - Master Thesis Project, the Pharmacy Programme

Synthesis of a chromone-based p38 MAP Kinase Inhibitor

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More than 500 of our genes encode a group of enzymes called protein kinases. These enzymes act on and modify the activity of specific proteins by the transfer of phosphate groups from ATP to the target substrates. The MAP kinases are a group of kinases that respond to extracellular stimuli and regulate various cellular activities such as growth, differentiation and proliferation. The p38 α is a subfamily of MAP kinases involved in the biosynthesis of the proinflammatory mediators IL-1 and TNF α , which play a key role in the pathogenesis of many chronic inflammatory and rheumatic diseases such as rheumatoid arthritis and Crohn's disease. Blocking of these inflammatory mediators by inhibition of p38 with small organic molecules is therefore an attractive therapeutic strategy for the treatment of the diseases and major efforts have been made in order to synthesize and evaluate different inhibitors. By computer-based design, chromone derivatives were identified as potential scaffolds for the development of novel p38 inhibitors. Therefore the 3-(4-fluorophenyl)-2-(4-pyridinyl)-chromone was synthesized in four steps and its biological effect on p38 was evaluated. The target compound was synthesized *via* esterification of 2'-hydroxyacetophenone followed by a Baker-Venkataraman rearrangement and cyclization. The 4-fluorophenyl group was introduced in 3-position *via* halogenation followed by a Suzuki cross-coupling reaction. The biological test showed that the target compound has inhibitory activity towards p38 α with an IC₅₀-value of 813 nM. The chromone derivative is thereby possible to use in the ongoing search for new potent p38 inhibitors.