Abstract

Chromones and flavones (2-phenyl-chromone) are naturally occurring compounds showing a wide range of biological activities which make them interesting as lead compounds in drug discovery and development. The thesis deals with different synthetic methods to obtain highly functionalized 2,3,6,8-tetrasubstituted chromone derivatives. An efficient synthetic approach to introduce a carbamate-protected primary aminomethyl group in the 3-position of a chromanone ring system is described. The method is based on first synthesizing the 3-methylene chromanone followed by an aza-Michel reaction Earlier approaches have only resulted in tertiary amines which prevents an easy use of the amine for further synthetic modifications.

The thesis also describes the use of different palladium-mediated coupling reactions (Heck, Stille, Sonogashira and Suzuki reactions) to incorporate a variety of substituents in different positions on the chromone scaffold. Using the differences in reactivity in the various positions and by careful choice of reaction conditions we have shown that it is possible to introduce substituents in high yields and with excellent regioselectivity. The substituents can contain functional groups such as ester or amino functions, or alkenes or alkynes which all can be transformed into other interesting functionalities.

Computational modelling studies have shown that our chromone structures are applicable as scaffolds in β-turn peptidomimetics. The synthesis of two examples of mimetics based on the Gly-Tyr-Phe-Gly and Phe-Tyr-Lys-Gly sequences is described. Also described are our attempts to synthesize a mimetic based on the Phe-Trp-Lys-Thr sequence of somatostatin, a peptide known to adopt a β-turn conformation.

The fluorescence properties of synthesized 3-hydroxychromone derivatives have also been studied. It was shown that the fluorescence is dependent on the substitution pattern of the chromanone system. One 3-hydroxychromone derivative was used for studies in living HeLa-cells using multiphoton fluorescence microscopy, it was shown that the compound rapidly entered the cells and accumulated in a specific region inside the cell.

Keywords: chromone, flavone, scaffold, Pd-catalyzed chemistry, Stille, Heck, Sonogashira, Suzuki, Mannich reaction, peptidomimetics, β-turn, fluorescence.

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