Design, Synthesis, and Evaluation of Functionalized Chroman-4-one and Chromone Derivatives

Somatostatin receptor agonists and Sirt2 inhibitors

Maria Fridén-Saxin
Institutionen för kemi och molekylärbiologi
Naturvetenskapliga fakulteten

GÖTEBORGS UNIVERSITET

Akademisk avhandling för filosofie doktorsexamen i kemi, inriktning läkemedelskemi, som med tillstånd från Naturvetenskapliga fakulteten kommer att offentligt försvaras torsdagen den 1 november, 2012, kl. 9:00, i KC-salen, Institutionen för kemi och molekylärbiologi, Kemigården 4, Göteborg.

ISBN: 978-91-628-8548-9

Abstract

Peptides are involved in many physiological processes such as regulation of blood-pressure, food intake, pain transmission and blood-glucose levels. They consist of amino acids that are connected through amide bonds which make peptides hydrophilic and conformationally flexible. Peptides generally make poor oral drugs as amide bonds are easily cleaved by endogenous enzymes. One way to overcome the structural problems with peptides is to develop stabilized mimetics, so called peptidomimetics, via a scaffold approach. The amino acid side chains needed for activity are attached as substituents to the scaffold.

In this thesis, chroman-4-ones and chromones have been used as scaffolds for the development of peptidomimetics. These frameworks are naturally occurring derivatives containing an oxa-pyran ring. Depending of the substitution pattern they show different biological effects. Synthetic modifications in the 2-, 3-, 6-, and 8-positions of chromones and chroman-4-ones have been conducted. This work has included the development of an efficient synthetic route to obtain 2-alkyl chroman-4-one derivatives. Via bromination in the 3-position of chroman-4-one, various substituents (NH_2, Br, OAc, CN, CH_2NHCbz) have been introduced either through substitution reactions or via a Sm-mediated Reformatsky reaction. By incorporation of the appropriate substituents on the chromone-4-one and the chromone scaffolds, the biological applications have included the development of β-turn mimetics of the peptide hormone somatostatin. This has resulted in two compounds with agonistic properties for two subtypes of somatostatin receptors.

In addition, functionalized 2-alkyl substituted chroman-4-one and chromone derivatives were developed as selective inhibitors of the Silent information type 2 (Sirt2) enzyme. Sirt2 functions as a deacetylating enzyme using both histones and non-histone proteins (e.g. α-tubulin) as substrates. Sirt2 is located in the cytosol but enters the nucleus during mitosis. Evaluation of a number of chroman-4-one and chromone derivatives resulted in the identification of a series of novel Sirt2-selective inhibitors with IC_{50} values in the low μM range. Two chroman-4-one derivatives with 2-pyridylethyl substituents in the 2-position of the chroman-4-one showed significant reduction of the proliferation of breast and lung cancer cells using a fluorescent based assay. These results indicate that the synthesized chroman-4-one based Sirt2-selective inhibitors can be valuable in more detailed studies of the function of Sirt2 in cancer.

Keywords: Chroman-4-ones, Chromones, Inhibitors, Molecular Modeling, Peptidomimetic, Samarium, Sirtuin, Sirt2, Somatostatin, Structure-Activity Relationships, Tubulin, β-Turn.