Abstract in English

G Protein-Coupled Receptors (GPCRs) represent the largest class of drug targets. It is estimated that 30-50% of marketed drugs act by modulating GPCRs. Despite the importance of GPCRs we still have a poor understanding of GPCR structure, function and signalling. The aim of the present PhD was to develop peptidomimetics that can modulate GPCRs in novel ways and be used as pharmacological tool compounds in order to gain new knowledge about this important class of receptors. The β_2 adrenergic receptor (β_2AR) is one of the best characterised members of the GPCR family and as X-ray crystal structures of β_2AR alone and in complex with the intracellular G_s protein subunit $G\alpha_s$ are available, β_2AR was selected as model system for the present project.

This PhD thesis describes the development of peptidomimetics, mimicking the crucial protein-protein interaction (PPI) observed between the α-helical C-terminal of the $G\alpha_s$ subunit and the intracellular binding site of β_2AR. A series of 15-mer peptidomimetics were designed and synthesised. Un-natural acetylene and azido derivatised amino acid residues were incorporated into the peptide sequences in an *i*, *i*+4 approach and cyclised to a triazole-based staple by the copper-catalysed azide alkyne cycloaddition (CuAAC). The position of the staple was systematically varied and both linear and stapled peptidomimetics were structurally analysed by circular dichroism (CD) and pharmacologically characterised in a membrane-based cAMP assay and in a bimane fluorescence assay.

Several of the peptidomimetic were able to inhibit agonist induced cAMP formation by lowering the maximal efficacy of the agonist isoproterenol (ISO), the most potent peptidomimetic lowered the maximal efficacy to 61%. However, none of the peptidomimetics were able to stabilise an active conformation of β_2AR in the bimane fluorescence assay. Overall, the results imply that the peptidomimetics may be able to compete with $G\alpha_s$ for the binding to the intracellular binding site, but are unable to stabilise the receptor in an active-like state. Future studies of the intracellular binding site of GPCR interacting proteins (GIPs) in β_2AR would hopefully lead to a complete understanding of the different conformations of β_2AR and provide novel compounds that may function as allosteric modulators.