Abstract

Urotensin II is a biological active peptide, which consists of 11 amino acid residues. It has been shown to be one of the most potent peptides involved in blood pressure regulation and is proposed to be of considerable interest for future drug development studies.

This thesis describes a structure activity relationship study based on the first reported urotensin II receptor agonists AC-7954. The optimised isochromanone based agonist 3-(3,4-dichlorophenyl)-6,7-dimethyl-3-(2-dimethylaminoethyl)isochroman-1-one HCl had a potency of 51 nM compared to 1 μM for AC-7954.

The first asymmetric synthesis of a 3,3-disubstituted isochromanone derivative is also described. In this method the chirality was introduced via a distant chiral auxiliary and transferred over a carbon-lithium bond. Advanced NMR spectroscopy gave indications that a defined dilithium complex was formed in solution which could react with high stereoselectivity with electrophiles. DFT calculations assisted in the prediction of the absolute configuration of the product.

To further expand the scope of urotensin II receptor agonists non-heterocyclic derivatives were also discovered and explored, leading to four different classes of active compounds, esters, amides, carbamates and ureas. The most active compound in this series was *N*-[3-dimethylamino-1-(2-naphthyl)propyl]-4-(4-chlorophenyl)benzamide HCl having a potency of 23 nM. In addition, the most active conformation was found to have the (*S*)-configuration using a X-ray crystallography and chemical correlation.

For the non-heterocyclic compounds, chemistry has been developed that is well suitable for combinatorial chemistry. The protocol resulted in high yields of pure products without complicated purification procedures. It was possible to use the same protocol also for reactions on 5 mg scale with retained yields and purities.

With the results from the different structure activity relationship studies we have proposed a pharmacophore model for urotensin II receptor agonists involving the centra of two aromatic rings and a basic amino function. The model differs from a published model for urotensin II receptor antagonists.

Keywords: Urotensin II, Structure activity relationship, parallel synthesis, isochromanone, R-SAT functional assay.

ISBN: 978-91-628-7019-5