Gerit POTOTSCHNIG

Thesis Supervisor: Marko MIHOVILOVIC

Institute of Applied Synthetic Chemistry, Vienna University of Technology

MolTag 1st Funding Period.

Defensio: June 2016

Title: Scaffold optimization of the $GABA_A$ receptor ligand valerenic acid

The principal objective of the present thesis is the design and synthesis of valerenic acid analogs as $GABA_A$ receptor ligands. Via biological evaluation of these compounds, a better understanding of the interactions between the natural compound and the receptor can be gained contributing in the development of novel, potent and selective ligands as lead compounds for drug development.

Anxiety and panic disorders are amongst the most common mental diseases worldwide. Most effectively, these diseases are treated with benzodiazepines. However, these compounds are known to cause severe side effects like confusion, fatigue and drug addiction.

Valerenic acid, a sesquiterpenoidal compound isolated from roots of Valeriana officinalis, acts as subtype selective allosteric $GABA_A$ receptor modulator. The highly pronounced selectivity for β2/3 over β1 subunits allows for addressing anxiety rather than sedation in animal models. Therefore, valerenic acid could serve as alternative for benzodiazepines for the treatment of anxiety.

Based on the total synthesis of valerenic acid, a modified synthetic approach for the installation of bioisosteric modifications oft he carboxylic acid functionality was established. Via this synthetic route, sulfonamides have become available and their pharmacology profile has been investigated.

The natural compound's bicyclic core structure has been modified towards sterically more demanding derivatives. The cyclopentene ring in the original scaffold has been replaced by cyclohexene and cycloheptene. This replacement lead to the identification of a ligand with a novel subtype selectivity for $GABA_A$ receptors bearing β1 subunits.

The axial methyl substituent of valerenic acid has been replaced by a hydroxy group – a modification that required a more drastic adjustment of the published synthesis. Via an enantioselective epoxidation as key reaction, an alternative protocol could be established that allows for the preperation of an array of compounds with interesting modifications at this position.

One of the key elements of the literature-known approach is the definition of one stereocenter via a kinetic resolution of a secondary alcohol at a very early stage of the synthetic pathway. This enzymatic kinetic resolution is accompanied with the loss of a minimum of 50% of the matrial. Within this thesis, the enzymatic process was combined with an in situ racemization that renders the transformation dynamic. Thereby, the overall yield of this reaction step could be increased to 79%.

Several modifications and optimizations of the total synthesis of valerenic acid have been made that enabled the synthesis of new derivatives that will contribute to a more detailed understanding of its interaction with the $GABA_A$ receptor.