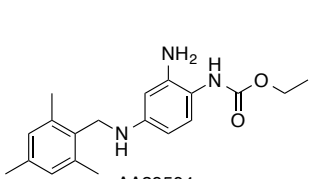
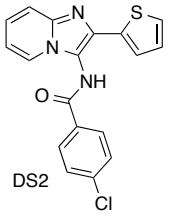
Abstract

γ-Aminobutyric acid (GABA) is the overall inhibitory neurotransmitter in the central nervous system (CNS) and is responsible for the overall balance between neuronal inhibition and excitation. Actions of GABA are partly exerted via a sustained tonic inhibition, which is mediated by extrasynaptically located $GABA_A$ receptors. GABA mediated tonic inhibition has been shown to be implicated in several neurological disorders, including epilepsy and stroke. Better understanding of the mechanisms affecting GABA mediated tonic inhibition is needed in order to understand its role in physiological and pathophysiological conditions. The work presented in this dissertation includes two projects aimed at the extrasynaptic $GABA_A$Rs and GABA transporters (GATs) as parts of the GABAergic system implicated in tonic inhibition.

Project 1

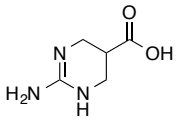


AA29504



DS2

Project 2



ATCPA

Firstly, structure-activity relationship (SAR) studies were performed on the two δ-preferring $GABA_A$R positive allosteric modulators (PAMs), AA29504 and DS2. Aminopyridine analogues of AA29504 were identified as positive allosteric modulators of the $\alpha_4\beta_1\delta$ receptors, with no or negligible effect on the binary $\alpha_4\beta_1$ receptors. However, the compounds need to be further investigated with respect to δ-selectivity. A series of DS2 analogues was made in collaboration with the University of Mainz. The study revealed potent analogues of the α_6-$GABA_A$Rs and identified an analogue suitable for a radioactive tracer. Based on this scaffold and previously performed PET chemistry, a [^{3}H]-labelled DS2 analogue was synthesized. However, the compound needs to be further evaluated for its use as a pharmacological tool compound.

Secondly, the BGT1 preferring substrate inhibitor, ATPCA was investigated. A [^{3}H]-labelled analogue of ATPCA was synthesized with the use of $^3H_2$ over Pd/C in DMF and was shown to be useful as a pharmacological tool compound in GABA uptake studies. A SAR study was conducted to investigate the selective inhibition of ATPCA at BGT1. Combining the SAR-study with computational docking and mutagenesis studies, specific interactions in the orthosteric binding site of BGT1 were shown to be determining for BGT1 selectivity of the synthesized analogues.

Conclusively, this PhD has resulted in new pharmacological tool compounds, important for the future investigation of GABA mediated tonic inhibition in the CNS.