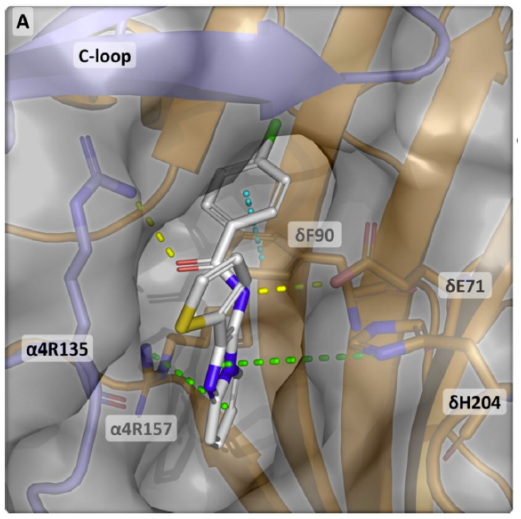
Development of molecular tools for studying the GABA$_A$ receptors

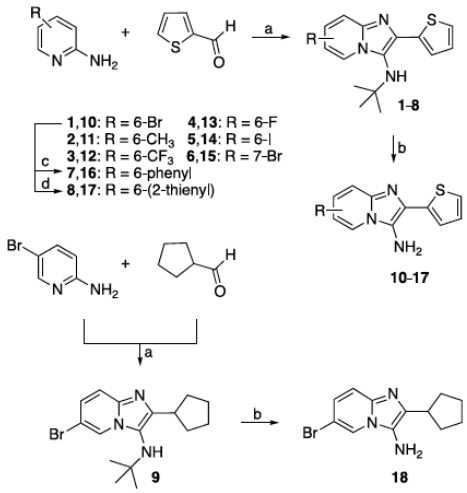
The GABA$_A$ receptors are important drug targets in a number of neurological and psychiatric disorders such as Alzheimer's Disease, Parkinson's Disease, epilepsy, schizophrenia and depression.

The aim of the overall project is to design and synthesize selective ligands that can be used for studying the architecture, localization and function of the GABA$_A$ receptors, with potential therapeutic relevance.

There exist a number of subtypes within the receptor differentiating in amino acid sequence, regional location and function. This opens for subtype selective targeting, and thereby development of ligands with potential optimized and specific therapeutic properties. Our studies are based on available structural insight and structure-activity studies of known ligands mainly developed in our group at The Department of Drug Design and Pharmacology.

The project will cover design and synthesis of potential subtype selective ligands to be used for exploring the binding pockets of the receptors, in search for the structural basis for subtype selective targeting. The ligands could include labeling ligands, such as fluorescent, photoaffinity and radioligands but also ligands for rewiring protein signaling. These studies are done in close collaboration with colleagues mastering molecular modelling and molecular pharmacology at The Department of Drug Design and Pharmacology.





[a]Reagents and conditions: (a) *tert*-butyl isocyanide, NH_4Cl, toluene, and reflux; (b) 5 M HBr and 110 °C. (c) $Pd(PPh_3)_4$, Na_2CO_3, $PhB(OH)_2$, DME/H_2O, and reflux. (d) $Pd(PPh_3)_4$, Na_2CO_3, 2-thienylB$(OH)_2$, DME/H_2O, and reflux.

Ref: ex. Rostrup et al, *J. Med.Chem.*, **2021**, 64, Falk-Petersen, C.B. et al, *Mol. Pharmacol.*, **2021**-000266; Giraudo et al, *J. Med.Chem.*, **2019**, 62, 5797-5809, L'Estrade et al, *ACSOMEGA*, **2019**, 4, 8846-8851.

As a MSc. student you will be part of the ongoing research at the actual stage for the start of the master project, guided by a post doc or PhD student involved in the project. For the student the present project will involve literature study, experimental organic synthesis, spectroscopic characterization and structure-activity studies. Furthermore, the molecular pharmacology and computer modelling relevant for the project can be followed.

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