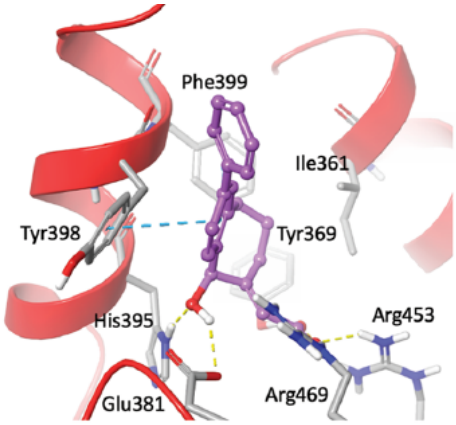
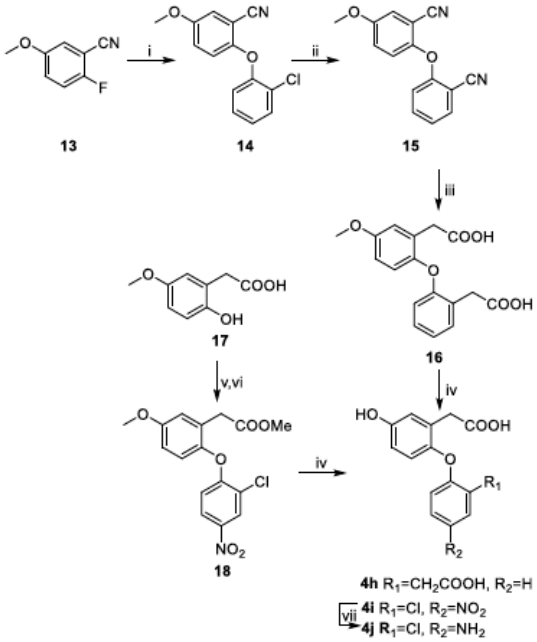
Development of molecular probes for CaMKII, a brain-relevant kinase

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a crucial brain-relevant protein kinase, which is intimately associated with synaptic plasticity and long-term potentiation (LTP) and modulates brain functions such as learning and memory.
CaMKII protein family consists of four isoforms – CaMKIIα, β, δ and γ, showing distinct spatiotemporal distribution, ontogenesis, and physiological functions in the brain. CaMKII is a major player in the regulation of neuronal signaling *via* phosphorylation of downstream ion channels and neurotransmitter receptors. This makes CaMKII subtypes interesting pharmacological proteins and emerging drug targets, however, so far, largely under-explored owing to the lack of subtype-selective ligands.
Through work on the neuronal subtype CaMKIIα, we have discovered a completely novel mechanism to achieve neuroprotection by allosteric modulation of CaMKIIα via a novel binding site, representing the high-affinity binding site for γ-hydroxybutyric acid (GHB). We are aiming for translating these findings to the highly homologous CaMKII subtypes to achieve similar protective effects in the respective areas of presence.

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 individual CaMKII subtypes, with potential therapeutic relevance.

Based on recent reported Cryo-EM structures the project will cover design and synthesis of potential selective ligands to be used for exploring the identified binding site. The ligands will cover ligands for structure-activity studies but also labeling ligands, such as fluorescent and photoaffinity. These studies are done in close collaboration with colleagues mastering molecular modelling and molecular pharmacology at The Department of Drug Design and Pharmacology.





Ref:

Leurs, U. et al, *PNAS*, **2021**, 118 (31) e2108079118, Tian et al, *J.Med.Chem*., **2022**, *65*, 15066–15084. Tian et al, *J.Med.Chem.* **2022,** *65* 6656–6676.

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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