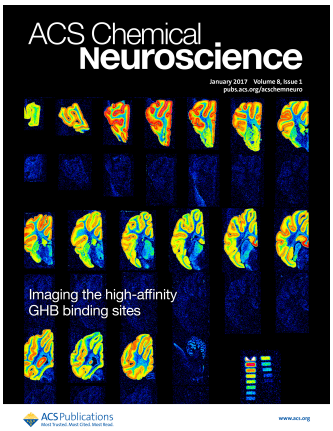
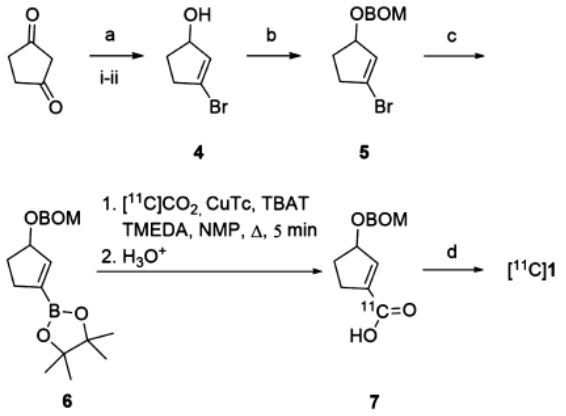
Unraveling the γ-hydroxybutyric acid (GHB) high affinity binding site: Is it just Fantasy….

γ-Hydroxybutyric acid (GHB) is a neuromodulator working alongside the main inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain. GHB is also a prescribed drug (Xyrem™) for treatment of narcolepsy and alcoholism (Alcover™). In yet another situation GHB is a drug of abuse known as a "date rape drug" or "Fantasy". In spite of GHB being a prescribed drug, the specific neuropharmacological actions remain to be elucidated. GHB have both low- and high-affinity binding sites and whereas the $GABA_B$ receptor, representing the low-affinity site, is well characterized for mediating several actions of GHB, major functional roles of GHB seem to be related to specific high-affinity sites. The molecular identities of the high-affinity sites have for long been under investigation without success. Recently a distinct protein has been identified as a high affinity target for GHB. These findings provide a unique base for further investigations and advancements in the GHB field.

The aim of the overall project is to understand in detail the architecture and mode of action of GHB at the relevant target, which could lead to the basis for potential GHB-antidotes and drugs.

The project will cover design and synthesis of potential selective ligands to be used for exploring the architecture and function of 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: Villumsen et al, 2011, Lægemiddelforskning, Vogensen et al, *J.Med.Chem.*, 2013, 56, 8201-8205, Bay et al, *Biochem. Pharmacol.* 2014, 220–228, Jensen et al, ACSChemNeuroSci, 2017, 22–27. *J.Med.Chem.,* **2017**, 60 (21), 9022–9039, Krall et al, . *J Med Chem* **2019,** 62, 2798-2813,

As a Master 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 characterisation and structure-activity studies. Furthermore, the molecular pharmacology and computer modelling relevant for the project can be followed.

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