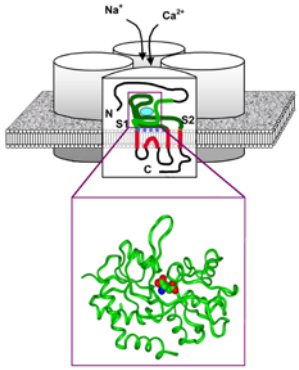
Structure-based medicinal chemistry towards subtype-selective kainate receptor ligands

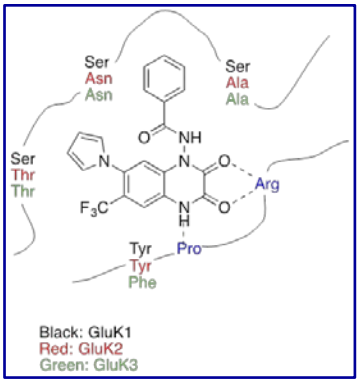
Tommy N. Johansen

Medicinal Chemistry Research

Why?

The GluK2 and GluK3 kainate-type subunits are two out of more than ten ionotropic glutamate receptor subunits present in the brain. It is well known that glutamate receptors play an important physiological role and also are implicated in a long list of neurological diseases currently without optimal treatment. But not much is known about the physiological functions and the therapeutic potential of GluK2- and GluK3-containing receptors. In order to study the function of such receptors there is a need for compounds selectively blocking GluK2- and GluK3-containing receptors. **This is what we would like to come up with. Would you like to be a part in this?**





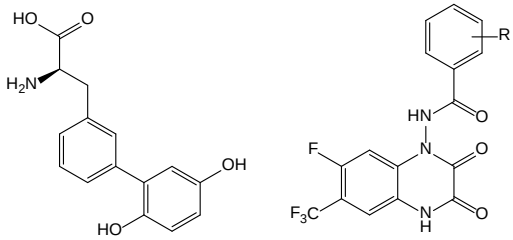
Structure-based design

When we decide which target compounds would be interesting/relevant to synthesize in your project, we combine 1) structural information, such as X-ray structures of the agonist binding site of a glutamate receptors co-crystallized with an antagonist (see the above model), 2) molecular modelling studies and 3) available structure-affinity relationships (SAR). Depending on your background and interest it might be relevant for you to carry out the design yourself. **Design your target compounds on a rational basis?**

Organic synthesis

Selected target compounds will be synthesized. We aim for simple and convergent retrosynthesis strategies that allows us to easily introduce different substitutents late in the syntheses. **Would you like to spend time in the lab trying to make the syntheses work? And to purify and characterize the isolated products using NMR- and MS-techniques?**

Examples of lead structures

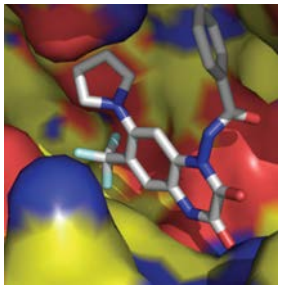


R	Native AMPA*	GluK1 *	GluK2 §	GluK3 *
H	0.95	0.15	-	0.33
o-OH	0.96	0.62	-	0.09
m-OH	0.72	0.52	-	0.10
p-OH	2.1	2.1	-	0.56

Pharmacology and structure-activity relationship

When the target compounds are synthesized they will be evaluated pharmacologically in house and by our collaborators. **Your contribution will expand the SAR and hopefully disclose how subunit selectivity can be controlled.**

- *: K_i values in µM obtained in receptor binding studies
- §: not yet tested



Type of projects available

It will be possible to set up exciting Master thesis projects as well as projects for bachelor students or international exchange students.

For more information about the project etc., please contact Tommy N. Johansen (tnj@sund.ku.dk)