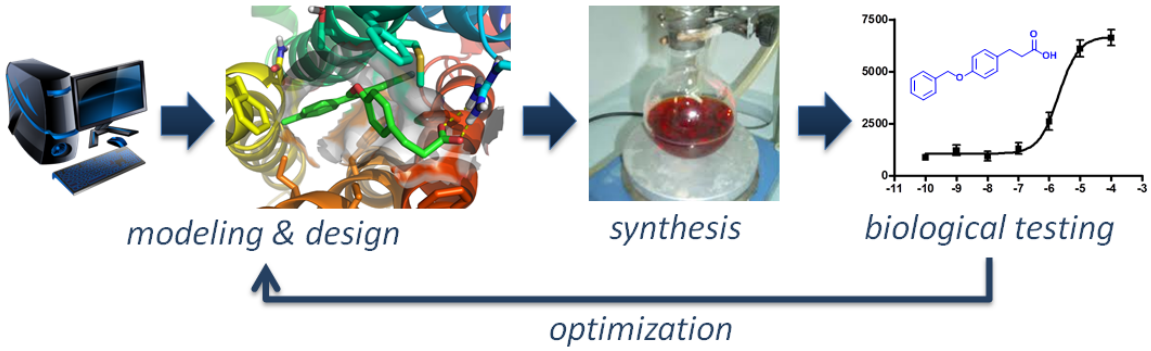
Master projects in medicinal chemistry - early drug discovery: Design and synthesis of free fatty acid receptor modulators

In the Ulven group we work to identify and improve novel tool compounds and potential drug candidates for G-protein coupled receptors (GPCRs), especially the free fatty acid receptors FFA1 (GPR40), FFA2 (GPR43), FFA3 (GPR41), FFA4 (GPR120) and GPR84.

The long-chain fatty acid receptor FFA1 is a target for treatment of type 2 diabetes that enhances insulin secretion at high but not low glucose levels and therefore without risk of hypoglycemia, a serious side effect of many current anti-diabetic drugs. FFA4 is a receptor of long-chain fatty acids that is found to act complementary by sensitizing the body to insulin. The short-chain fatty acid receptors FFA2 and FFA3 have anti-inflammatory effects and GPR84, activated by medium-chain fatty acids, has pro-inflammatory effects. The receptors are potential targets for serious diseases such as type 2 diabetes, arthritis, inflammatory bowel disease, asthma, inflammatory pain, and Alzheimer's disease, many of which currently lacks efficient drugs.

We offer projects on all these receptors involving diverse chemistry. In general, the projects start by designing the target compounds based on what we know, including other active compounds and the target structure. This is a challenging step and you will receive help and guidance, but you will also get the chance to test your own ideas. The next step is to synthesize the compounds. This usually takes the main part of the time and you will get the chance to test lots of different reactions. It is therefore important that you are interested in organic synthesis. The third step is to test the new compound on the target. In some projects we test the compounds in our own labs but in most cases we send the compounds to pharmacology collaborators who do the testing and send back results. The results are then fed back to the design and a new optimization cycle starts.



We usually have good models or crystal structures of our targets, and you can implement computational modeling into your project if you are interested in this. It is important not only to design compounds that are potent but also have desirable properties like solubility – high potency is not enough to give good tools or drug. It is therefore also relevant to determine solubility, lipophilicity, chemical or metabolic stability, and it is possible to implement this type of assays in your project. In some projects, it can also be possible that you are involved in testing your new compounds on the target.

Find out more at http://tugrp.dk or drop by for more specific information. We are always interested in talking with motivated and ambitious students.

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Sounds interesting? Background information and some ligand examples can be found here:

- Discovery of FFA1 agonists:
  - Christiansen et al, *ACS Med. Chem. Lett.* **2010**, *1*, 345-349
  - Christiansen et al, *J. Med. Chem.* **2013**, *56*, 982-992
- Discovery of FFA2 agonists:
  - Hansen, et al, *J. Med. Chem.* **2018**, doi: 10.1021/acs.jmedchem.8b00855
- Discovery of FFA4 agonists:
  - Shimpukade et al, *J. Med. Chem.* **2012**, *55*, 4511-4515
  - Azevedo et al, *J. Med. Chem.* **2016**, *59*, 8868-8878