Department of Drug Design and Pharmacology, University of Copenhagen, 2020-21

Cytochrome P450 enzymes in Drug Metabolism and Cancer Therapy

Aim

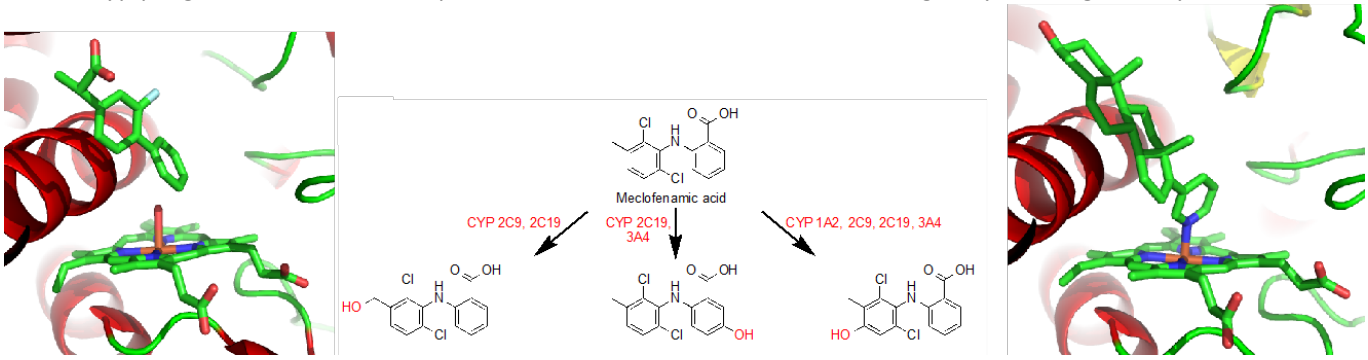
To study how drugs compounds are metabolized by or inhibit cytochromes P450 (CYP) enzymes.

Background

In humans, CYP enzymes are involved in several different transformations, e.g. the elimination of drug compounds and the synthesis of hormones. The main function of CYP enzymes is to oxidize compounds.

Oxidation of Drug Compounds

CYP mediated drug metabolism of a new compound is important to consider, e.g. to understand potential toxic effects or bioavailability. Thus, it is important to understand what metabolites that the CYP enzymes generate. It is very often difficult to predict what metabolites CYP generate (see figure, center, for an example). To help in this process we have developed the SMARTCyp program, which can predict the most likely CYP metabolites for a drug compound (you can try it on: smartcyp.sund.ku.dk). We work on implementing new features in the SMARTCyp program and extend our predictive methods to other metabolizing enzymes, e.g. aldehyde oxidase.



Left: Binding of ibuprofen analogue to CYP enzyme. **Center:** Metabolism of meclofenamic acid. **Right:** Binding of arbiraterone to CYP17A1.

Involvement in Cancer

Cytochrome P450 enzymes are involved in the formation of several hormones and is therefore a potential drug target in cancer. Arbiraterone is an example of a marketed drug compound that is used in the treatment of prostate cancer. We have over the past years gained expertise in the design of compounds that inhibit CYP enzymes and we have successfully designed a number of new inhibitors, but we would like to improve their selectivity.

MSc projects

The student will get the opportunity to work with the newest approaches in computational chemistry to rationalize ***how drug compounds are metabolized*** or to ***design new inhibitors for cancer treatment***. Below you find some examples on possible MSc projects. If you would like learning some ***Python programming***, we could easily design a MSc project for you. Examples on MSc projects are shown below.

CYP topic	Drug metabolism: Prediction of what metabolites are generated	Development of software for prediction of drug metabolism	Cancer treatment: Design of selective inhibitors of the CYP17A1
Methods	**Computational chemistry methods: Docking and molecular dynamics**	**Python programming, KNIME scripting and computational methods**	**Structure-based design and virtual screening. Synthesis in collaboration with Fredrik Björkling**

Contact

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