In Silico Screening of Xenobiotic Compounds for Inhibition of Cytochrome P450 19A1

Introduction

Cytochrome P450 19A1 (CYP19A1) is an enzyme involved in estrogen synthesis. It catalyses the conversion of androstenedione to estrone (E1), and of testosterone to estradiol (E2).[1] E1 can in turn also be converted to E2 by other enzymes. E2 is of key importance for proper sexual development and pregnancy. However, elevated levels of E2 can promote hormone-related cancers and endometriosis. This makes CYP19A1 an interesting therapeutic target, as its inhibition can reduce E2 concentration.[2] Conversely, unintended interaction of compounds, such as pesticides, with CYP19A1 can disrupt its activity and the hormonal balance. To understand and prevent such disruptions, it is important to identify inhibitors of CYP19A1. In addition, a study of inhibitors can aid in developing save therapeutic agents targeting CYP19A1, to control E2 levels.

1) J.I. Seo *et al. Chem. Biol. Interact.* **2024**, *392*, 110927. DOI: 10.1016/j.cbi.2024.110927
2) Eissa, A.G. *et al. RSC Med. Chem.*, **2023**, *14*, 356–366. DOI: 10.1039/d2md00352j

Aims of the project

The goal of this project is to screen *in silico* for potential inhibitors of CYP19A1. Specifically, the screening will focus on xenobiotic and non-drug like compounds. To this end, the student will:

- Prepare a protein model of CYP19A1
- Validate the protein model with a ligand ensemble of known CYP19A1 inhibitors
- Use the model to screen for new inhibitors
- Study interactions between CYP19A1 and potential inhibitors

Techniques and programming language

- Protein preparation using Schrödinger
- Ligand clustering (RDKit)
- Ligand docking (Glide, Smina, Gnina, …)
- Molecular Dynamics
- Development of quantitative structure-activity relationships QSAR model(s)
- Linux terminal syntax, data analysis with Python

Timescale of the project

The schedule below is an estimation and can be tailored depending on the requirements for the internship. During the research, there could be deviations from the schedule in consultation with the supervisor.

Month	Activity
1	Literature research, getting familiarized with the techniques
2	Preparing protein ensemble and ligand validation ensemble
3	Validation of model with prepared ligands
4 + 5	Preparation of ligand test set and using model to screen for new inhibitors
6 + 7	Additional analysis of potential hits: SAR, binding free energy calculation, …
8	Finishing up last experiments, data analysis, writing report and preparing final presentation

Requirements

- Open to Chemistry, Drug Sciences, and Pharmacy students. External students are also welcome to reach out.
- Strong interest in proteins, chemical interactions, and modelling
- Willingness to learn the basics of Linux terminal syntax and programming

Contact

Daily supervision will be performed by Rianne van Diest MSc (PhD candidate). Overall responsible will be Prof. Dr. Martin Smieško. Please apply with a short motivation letter to Rianne van Diest (rianneelaine.vandiest@unibas.ch).