Master « Sciences, Technologie, Santé »
Mention « In Silico Drug Design »
Second Year

OFFER AN INTERNSHIP
Academic Year 2014 – 2015

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Specialty training: Research X☐ Professional ☐

A few key words to describe the subject of training:
The project is part of an intensive computational chemistry based approach to study the structure-activity relationships of cytochromes P450 at the Biostructural Research group (http://www.farma.ku.dk/br) at University of Copenhagen

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Title of internship:

New inhibitors for Cytochrome P450 17A1 – A Potential Anti-Cancer Target

This subject is a first step towards a thesis: Yes

The project is a research project and the candidate will be able to base his/her Master thesis on it.

Short text describing your project:

Cytochrome P450 17A1 (CYP17A1) is a target for anti-canter therapy. In 2011 FDA approved abiratone acetate (Zytica) for treatment of prostate cancer. Abiraterone is superior to previous drugs against this type of cancer, but still not impressive. In Phase III trials it extended survival from 11.2 months for placebo to 14.8 months.

Recently, the 3D structure of CYP17A1 in complex with abiraterone has been determined (PDB entry 3RUK). The steroid part binds in a narrow pocket and the O-atom forms a H-bond to the O-atom in the Asn202 side chain. The N-atom in heterocyclic ring forms a covalent bond to the Fe-atom in the HEM-group (2.0 Å). The 3D structure of a similar compound, galeterone, in complex with CYP17A1 is also reported revealing a similar binding mode (PDB entry 3SWZ). The steroid part of these two ligands resembles the classical steroids, e.g. estradiol.

There are many examples on estrogen receptor agonists and antagonists where the classical steroid moiety has been replaced by other moieties, e.g. in diethylstilbestrol (DES) and zindoxifene. Thus, it could be interesting to investigate, if other moieties could fit to the CYP17A1 active site. If they can, it would be interesting, if a specific HEM-binding group could be attached to these moieties, and yield potential CYP17A1 inhibitors with a non-steroid structure.

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