Postdoctoral fellowship in Molecular Modeling/ Computer Aided Drug Design

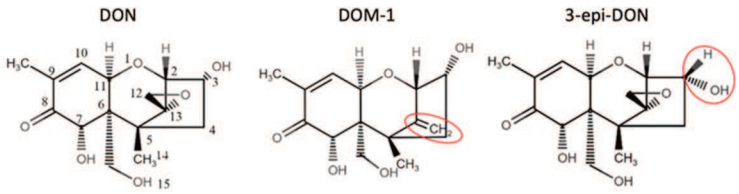
Laboratoire de Chimie de Coordination - CNRS UPR 8241
205 route de Narbonne, 31077 TOULOUSE Cedex 4 - France

Type of offer: Post-doctoral fellow 14 months
Financing: ANR
Salary: from 2805 and 3600 € (before taxes) according to experience
Starting February 2023
Deadline for application is December 30th 2022.

Key-words:
Drug Design, Pharmacophoric models, Molecular docking, Virtual Screening, S.A.R.

Context:
Food contaminants are substances of various kinds that are present in food. The presence of these substances may represent a risk to public health. Mycotoxins, which represent a large family of metabolites, are the most common naturally occurring food contaminants[1]. Deoxynivalenol (DON), which is a mycotoxin produced by fungi of the genus Fusarium, is the most widespread in Europe. Human exposure to DON is associated with numerous adverse effects[2] and chronic exposure may be associated with an increased risk of developing cancer. DON's toxicity arises from its ability to bind and to inhibit the peptidyl transferase site of the 60S subunit of the ribosome[3], thereby triggering mitochondrial dysfunction and oxidative stress.

Crystallographic studies demonstrated that DON binds the A-site of peptidyl-transferase of the large 60S eukaryotic ribosomal subunit, inhibiting polypeptide chain initiation and elongation[4]. Recent results showed that the metabolites of Dom: DOM-1 and epi-3-DON lost their toxicity, but can still fit into the pockets of A-site of the ribosome[3]. Other chemically diverse eukaryotic ribosome inhibitors share a mode of binding within the A-pocket similar to DON[4].



By comparing the DON non-ribotoxic metabolites with other A-pocket ligands, we plan to establish pharmacophoric models in order to identify the motifs allowing the ligands to bind into the A-site, but without interfering with ribosomal function. We will then use these pharmacophores to perform a virtual screening of commercial molecular databases to retrieve the structures with the required patterns and identify pharmacological antagonists of DON.

Missions:
The post-doctoral fellow work will be devoted to Molecular Modelling studies with the main objectives:

1. Construction of the pharmacophores hypotheses on the basis of DON non-ribotoxic metabolites and other known ribosome inhibitors of the A-pocket,
2. Use of these pharmacophores as templates to perform a virtual screening of commercial molecular databases (Zinc, DrugBank…) or the French "Chimiotheque Nationale". The selected molecules will then be subjected to quantitative structure activity relationship (QSAR) studies to refine the results.
3. A new screening will be performed by molecular docking with the compounds retained in step 2. This strategy will allow to take into account the shape compatibilities and the physical interactions between the ligands and the receptor.
4. To reduce the number of molecules that will emerge from step 3 to a few compounds, the interaction energy of the remaining compounds will be evaluated using classical molecular dynamics on global molecular systems. Quantum mechanical density-functional theory (DFT) and QM/MM approaches will eventually be used for a better evaluation of non-bonded interactions. Lastly, the most promising compounds will be proposed to the biologists for in vitro essays.

To achieve these goals, the post-doctoral fellow will have at its disposal the BIOVIA Discovery Studio software suite (Dassault Systemes), the Quantum mechanical Gaussian software and the computer facilities of the "mesocentre CALMIP"

Candidate profile:

The candidate should hold a Ph.D in computational chemistry, biomolecular modeling or a related discipline. He should have a research experience in small-molecule drug discovery and in simulations of protein/ligand interactions (molecular docking, molecular dynamics…)

Familiarity with the use of standard software packages (e.g. Discovery Studio, PipelinePilot, Maestro, MOE) would be desirable.

To candidate, connect to the employment portal of the CNRS by following the link below:
https://emploi.cnrs.fr/Offres/CDD/UPR8241-JEASTI-001/Default.aspx

Please provide :

- A cover letter demonstrating the adequacy to the scientific project
- a CV with a full list of publications and communications
- at least one recommendation letter from a previous supervisor

1. Bennett JW, Klich M (2003) Mycotoxins. Clin Microbiol Rev 16:497–516. *DOI: 10.1128/CMR.16.3.497-516.2003*
2. Pinton P, Oswald IP (2014) Effect of deoxynivalenol and other Type B trichothecenes on the intestine: a review. Toxins 6:1615–1643. *DOI: 10.3390/toxins6051615*
3. Pierron A, Mimoun S, Murate LS, et al (2016) Microbial biotransformation of DON: molecular basis for reduced toxicity. Sci Rep 6:29105. *DOI: 10.1038/srep29105*
4. Garreau de Loubresse N, Prokhorova I, Holtkamp W, et al (2014) Structural basis for the inhibition of the eukaryotic ribosome. Nature 513:517–522. *DOI: 10.1038/nature13737*