Chemoinformatics Virtual Screening using ChemProt

In this exercise you will get hands-on training on our new web-server, ChemProt. ChemProt is a resource of annotated and predicted chemical-protein interactions that have been compiled from over 1 100 000 unique chemicals with biological activity for more than 15000 proteins.

ChemProt can assist in the *in silico* evaluation of small molecules (drugs, environmental chemicals and natural products) with the integration of molecular, cellular and disease-associated proteins complexes. It suggests diseases and side effects associated with protein targets, and provides biological information for a protein when it is part of a disease complex.

0) Warming-up with ChemProt


Go to the ChemProt server:

http://www.cbs.dtu.dk/services/ChemProt-2.0/

and read the “Instructions” section.

i) If you type a compound name, what is the default search that ChemProt will do for this compound?

ii) How can you import compounds that you have in a .smi format, .sdf format, or as a list of InChiKeys? *(The last one is a bit tricky and needs some extra imagination.)*

1) Searching for similar, bioactive compounds

Search for compounds that are 90% similar to Citalopram based on the MACCS fingerprints and answer the following questions:

a) For how many targets are there experimental activity data for Citalopram?

b) Which resource provides the most data points?
c) How many similar compounds do you find?

d) What is the main difference in the structure of Citalopram and its most similar compound? How does this difference affect the pharmacokinetic properties of the two compounds? (*Hint: Hover your mouse over the ID of each compound.*)

e) Which is the target where the majority of the similar compounds have measured activity?

2) Evaluating the polypharmacology profile of a compound

On the Display Settings click on Values: All, and on the Activity values click on IC50 and Ki.

* IC50 stands for the half maximal inhibitory concentration and is a measure of the effectiveness of a compound in inhibiting a biological or a biochemical function. It indicates how much of a particular compound is needed to inhibit a given biological process.

** Ki is the inhibition constant of a compound. It refers to the concentration of a compound, which would occupy 50% of the receptors in competitive binding experiment.

f) For which target(s) is Citalopram most effective as an inhibitor, based on the IC50 and Ki values that are available?

According to Drugbank, Citalopram is a selective serotonin-reuptake inhibitor (SSI) and P31645 (sodium-dependend serotonin transporter) is its primary target ([http://www.drugbank.ca/drugs/DB00215](http://www.drugbank.ca/drugs/DB00215)).

g) Do you agree with Drugbank's description in the light of the data that you retrieved from ChemProt?

h) Drugbank mentions also a number of off-label indications of Citalopram (Unlabeled indications include mild dementia-associated agitation in nonpsychotic patients, smoking cessation, ethanol abuse, obsessive-compulsive disorder (OCD) in children, and diabetic neuropathy.) Can you identify the targets on the heatmap that could be responsible for some of these indications? (*Hint: Go the right side of the heatmap (Disease Categories) and hover over the red circles.*)
3) Predicting potential side effects

Citalopram, as well as other anti-depressants, have been associated with increased appetite and increased weight as possible side effects ([http://sideeffects.embl.de/drugs/2771/](http://sideeffects.embl.de/drugs/2771/)).

i) Can you identify the targets that could be responsible for these side effects?