Drug Design Teaching

Answers to questions of Session5 and to Exercise 8 (ADME)

📣 With those results let's try to answer the following questions about the ADMET of those three molecules:

- *One of these compounds is predicted toxic, can you point out which one and the alert related to this prediction?*
  CHEMBL598797 shows 3 alerts according to Brenk definition of problematic fragments. One alert is for hydroxamic acid. This latter group is toxified by metabolism to nitrenium cation, a very reactive species.
- *Between both marketed drugs, which one of Sunitinib or Erlotinib is more prone to create drug-drug interactions linked with metabolism?*
  Erlotinib is predicted as inhibitor of all five major isoforms of cytochrome P450. Thus it is highly probable to hinder the proper metabolism of another drug taken at the same time.
- *Which of these molecules is the less druglike? What is the molecular property responsible for that?*
  CHEMBL598797 shows a violation of one druglikeness filter (Veber, more than 10 rotatable bonds). Hence the compound can be considered too flexible. This suboptimal property can be seen on the Bioavailability radar, as well (FLEX axis).
- *Are all three compounds predicted as well-absorbed by the gastrointestinal tract when administered orally?*
  Yes, because all three compounds as inside the BOILED-Egg. Please remember that the white and the yellow ellipses are not mutually exclusive.
- *Qualitatively, what is the propensity for each compound to passively cross the blood-brain barrier?*
  - Erlotinib and Sunitinib are located in the yolk of the BOILED-Egg and therefore predicted to permeate through the BBB. In contrast, CHEMBL598797 is predicted not to have the properties suitable to cross the BBB.
- *Which is the physicochemical property mostly explaining the difference in passive brain permeation behavior?*
  The apparent polarity, described by the topological solvent surface area (TSPA), on the X-axis of the BOILED-Egg. CHEMBL598797 is too polar to be predicted to access the CNS passively.
- *Which compound(s) is (are) predicted actively pumped out from the central nervous system? Why?*
  Sunitinib is predicted by the SVM classification model to be a substrate of the P-gp efflux pump (blue dot on the BOILED-Egg).
- *Finally, which compound has the highest probability to be in significant concentration in the brain?*
  Erlotinib because it shows properties to cross the BBB passively and is predicted as non-substrate of the P-gp.

Exercise 8. Pharmacokinetics optimization of EGFR inhibitor.

- Imagine that your endeavor consists in optimizing the properties of CHEMBL598797, which has to inhibit a kinase in the CNS. Have some tries of small chemical modifications (e.g. copy/paste SMILES in the sketcher, apply chemical modifications and transfer multiple entry lines to the SMILES list). You have so initiated an iterative optimization process. Once you are happy with the ADMET properties, click on the target icon to submit your optimized molecule to SwissTargetPrediction.
    - *Describe your optimization strategy.*

One has to reduce the apparent polarity of the molecule (lowering the TPSA), by i) shielding polar atoms with bulky groups at their vicinity; or ii) removing polar atoms (like oxygens or nitrogens).
The first strategy could increase the lipophilicity of the molecule too much with WLOGP values outside the optimal range. The second strategy can break the pharmacophore and so the designed molecule could lose too much potency to inhibit EGFR.

    - *What are your conclusions regarding pharmacokinetics and pharmacodynamics?*

Molecular design is an optimization procedure that has to follow many objectives. A lot of empirical (trial-and-error) cycles are needed to find a well-balanced molecule, with all properties suitable to reach all objectives (pharmacokinetics, pharmacodynamics, toxicity, just to cite a few). This is why multiple thousands of molecules are actually synthetized and tested; and tens, hundreds of thousands are design or screened virtually during a typical medicinal chemistry project.