Drug Design Teaching

Answers to Exercise 7 and to questions of Session3 (Ligand-based Virtual Screening)

Exercise 7. Enrichment of anti-inflammatory molecules in FDA-approved drugs.

This exercise aims at realizing the fact that virtual screening is an enrichment procedure. The procedure allows not to test an entire chemical collection, but a reduced selection of molecules. Instead of random picking, virtual screening helps choosing the most interesting ones. In the given example at the beginning of Session 3, we rely on similarity of molecules in 3D, with the hypothesis that molecules similar in 3D-shape to Diclofenac have a higher probability to be also inhibitors of COX2 and having hence an anti-inflammatory effect.
To monitor whether your criteria of virtual screening makes sense, you will measure how many "known actives" are top-ranked. In the context of this exercise the known actives are known anti-inflammatory drugs.

In the virtual screening of similar FDA-approved drugs to Diclofenac according to Electroshape, in

- *Calculate the enrichment at 1.3% (= top 20)*
    - *How many of these COX inhibitors can you find in the top 20 molecules provided by Electroshape screening* (#$COX_{screening}$)*?*

In the virtual screening of similar FDA-approved drugs to Diclofenac according to Electroshape, we look at the 20 first most similar molecules to Diclofenac in the result pages. Among these, 15 are known anti-inflammatory drugs (Diclofenac, Lumiracoxib, Bromfenac, Carprofen, Fenoprofen, Flurbiprofen, Etodolac, Naproxen, Suprofen, Meclofenamic acid, Ketoprofen, Flurbiprofen, Ketorolac, Mefenamic acid and Tiaprofenic acid).

    - *How many COX inhibitors are in total in the FDA library* (#$COX_{library}$)*?*

There are 39 COX inhibitors anti-inflammatory drugs in the FDA collection.

The enrichment is the ratio of anti-inflammatory drugs in the top-20 over the ratio of anti-inflammatory drugs in the whole database (formula in page 42).

Here:

$$\boldsymbol{Enrichment\ (at\ 1.3\%)} = \frac{\frac{15}{20}}{\frac{39}{1516}}$$ ***= 29.2%***

This virtual screening produced an enrichment of nearly 30% of anti-inflammatory drugs at 1.3% compare to random picking. This is huge compared to 'real-life' virtual screening enrichment.

Answers to questions along Session 3 (COX inhibitors).

When screening FDA with FP2, one can retrieve only 3 approved drugs, whose chemistry resembles very much to Dicofenac. When screening the same library but with ElectroShape, you look for 3D shape and hence different chemistry. You can retrieve so 98 molecules, which are marketed (and not all are anti-inflammatory drugs).

Answers to questions along Session 3 (EGFR inhibitors).

- With that results let's try to answer the following questions about compound CHEMBL461792:

  - *What is the similarity score and ranking of compound CHEMBL461792?*
    Score : 0.741
    Rank : #8

  - *What are the two structural differences between CHEMBL461792 and Erlotinib?*
    1. The cyano substituent of the aromatic of erlotinib is replaced by a chloro substituent in compound CHEMBL461792.
    2. The ether "side chains" of erlotinib are linked together by an additional bond in CHEMBL461792.

  - *Which of these chemical modifications makes CHEMBL461792 more rigid than Erlotinib?*
    The modification 2 rigidifies the long "side chains".

  - *Any clue about the potential benefit to test a more rigid ligand?*
    By limiting the flexibility of free parts of the ligand is one typical trick in drug design. If the geometry of the molecule is locked in its bioactive conformation (the geometry of the binding mode), the ligand doesn't need to freeze in the right geometry to complement the active side of the protein. This represents a gain of entropy, a component of the free energy of binding. The favorable impact on the free energy of binding is effective only if the rigid molecule has a geometry complementary with the binding site, not producing clashes nor unfavorable interactions with the atoms of the protein.
    Another effect is that very flexible molecules are less prone to pass through biological barrier (such as gastrointestinal wall for absorption, or blood brain barrier to access CNS).