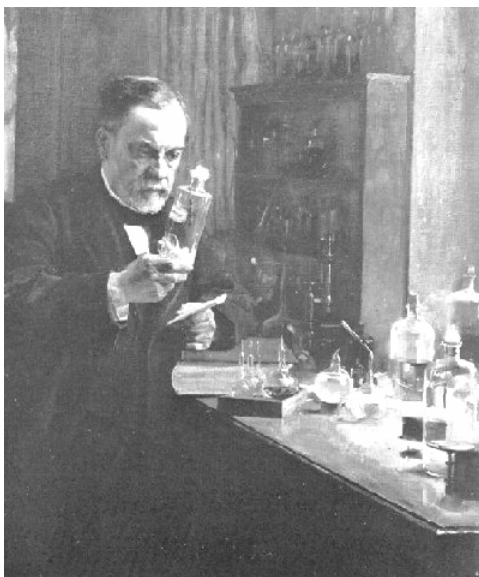


Ligand Optimization and *de novo* design



Purpose:

Identifying a molecule that binds to a given target is often not so difficult today, with the use of sensitive high-throughput screens, combinatorial chemistry and abundant structural data. However, finding a specific, high-affinity, deliverable small molecule remains very challenging (and rewarding).

In this lab you will use structure-based design tools to optimize a weak-binding lead molecule, hopefully generating drug-like candidates with better binding affinity.

Assumptions:

This lab assumes you are familiar with Mac OS and SYBYL. You should be comfortable with the concepts of conformational sampling and scoring, protein structure visualization, and ligand sketching and minimization.

Lab outline:

- 0) Listen to 10 minute intro on drug design and optimization.
- 1) Launch SYBYL, set up your RACHEL demo environment.
- 2) Do the RACHEL tutorials.
- 3) Use RACHEL to optimize the drug captopril in the pocket of ACE.
- 4) Answer the questions at the end.

0. Listen to intro on ligand optimization

(optional) Dr. Chris Ho, the author of RACHEL, maintains a web page with a good discussion of receptor-based design technology. If you want more info, or if you are unclear on the terms and technologies in these tutorials, go to: <http://www.newdrugdesign.com/Technology.html>.

1. Launch SYBYL, set up your RACHEL demo environment

i) Open a Terminal shell, it will become your SYBYL terminal. To launch SYBYL:
(create a new directory for this project, and navigate there)

```
trigo -shell sybyl8.1  
sybyl
```

ii) You need to setup the files required for RACHEL. In the SYBYL shell:

```
sh cp -r $TA_DEMO/rachel . (include the space and period)  
sh chmod -R +w rachel  
sh cp -R rachel/DBASE /tmp/
```

2. Do the RACHEL tutorials.

Tripos Bookshelf > RACHEL (middle left) > RACHEL Tutorials

You should do all four sub-tutorials:

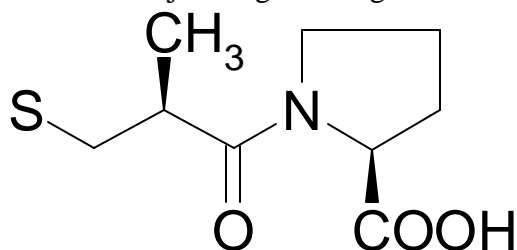
RACHEL:

- Create a RACHEL Project
- RACHEL scoring functions
- Run a RACHEL Combinatorial Search
- Using Chemical Templates and Descriptors

(You don't need to do the CHARLIE or Component Creation tutorials today).

3. Use RACHEL to optimize the drug captopril.

In the Conformational Search and QSAR lab, you operated on a series of drugs that target the protein ACE (Angiotensin-Converting Enzyme). The first major drug that targeted ACE was captopril, shown below:



What can you do to optimize captopril into a better ligand/drug?

What makes a good drug?

- (i) Systems biology: drug binding to the target has a large and desirable effect on the disease state
- (ii) High affinity: drug binds tightly to its target
- (iii) High specificity: high ratio of binding to desired target vs. non-specific targets
- (iv) Minimal side effects: off-target binding or systems biology effects are rare or mild
- (v) ADMET: Absorption/Distribution/Metabolism/Excretion/Toxicity
- (vi) PK/PD: Pharmacokinetics / Pharmacodynamics
- (vii) Synthesizable / purifiable: How many chiral centers? How many synthetic steps?
- (viii) Cost-effective and patentable: Easily made on kilogram scale? Novel scaffold?

Lipinski's rule of 5

Poor ADME is likely when any of the rules are violated:

- more than 5 H-bond donors
- more than 10 H-bond acceptors
- molecular weight > 500
- calculated log P (ClogP) > 5, or MlogP > 4.15
- if target = transporter, then ligand is an exception to rule of 5

Captopril properties:

- (i) target = ACE; complex but well-known system of renin-aldosterone-angiotensin
- (ii) $IC_{50} \sim 2.3 \times 10^{-8} \text{ M} = 23 \text{ nM}$
- (iii) May interfere with bradykinin. Known to specifically reverse angiotensin I effects.
- (iv) 7% (rash), 4% (loss of taste), 2% (cough)
- (v) 30% of dose binds blood plasma proteins. Major elimination via kidneys. No significant toxicity.
- (vi) (PK) Orally delivered captopril is rapidly absorbed, in less than one hour. Over 95% of the oral dosage secreted in urine within 24 h. Half-life for circulating active captopril is estimated < 2 h.
(PD) Blood pressure reduction follows 60-90 minutes after oral administration of captopril.
- (vii) Two chiral centers, peptidomimetic configuration.
- (viii) Straightforward synthesis. Was novel first-in-class drug when introduced, now off-patent.

How do you change the structure of the ligand molecule to cause the above changes in function/chemical properties? Use RACHEL to do computational optimization of captopril subject to your constraints!

1. Try extracting everything from the PDB (re-center, add H's, verify captopril chemistry, check atom types)
PDB id: **IUZF**, access via <http://www.rcsb.org/pdb>
2. If you can't get that working, I've prepared ligand (captopril.mol2) and receptor (ace.mol2) structures
<http://ccb.wustl.edu/~djkueter/ace.mol2>
<http://ccb.wustl.edu/~djkueter/captopril.mol2>

4. Questions

4.1 Your boss asks you to screen a library of ligands against a known pharmacophore to find candidate lead ligands. You end up with several thousand hits--far too many to look through individually. How can you improve the search process to prioritize useful structures?

4.2 You find a bunch of virtual screening hits that look promising, and you take them to your talented medicinal chemist friend for her advice on synthesizing them. She takes a quick look and says they will never work. She mutters something about Lipinski's rules on her way out...what is she talking about? How would you use Lipinski's rules to improve your virtual screening efficiency?

4.3 In the conformational search lab, you saw that conformational sampling can be a killer problem. Here, you have used a conformational sampling engine in combination with a scoring function. When can you expect a scoring function to give reliable results? Why do scoring functions often have trouble predicting ligand-receptor binding?

4.4 Bonus! Compare your results from the RACHEL optimization of captopril with Dan, to see if you have improved the binding affinity or specificity, or decreased the side effects.

You don't need to turn in anything for this lab, but make sure you understand the concepts. The next lab will integrate concepts, and you need to be comfortable with conformational search, scoring functions, protein modeling, ligand sketch and optimization and evaluation of ligand-receptor complexes.