

# Example Drug Design from a Docking Model

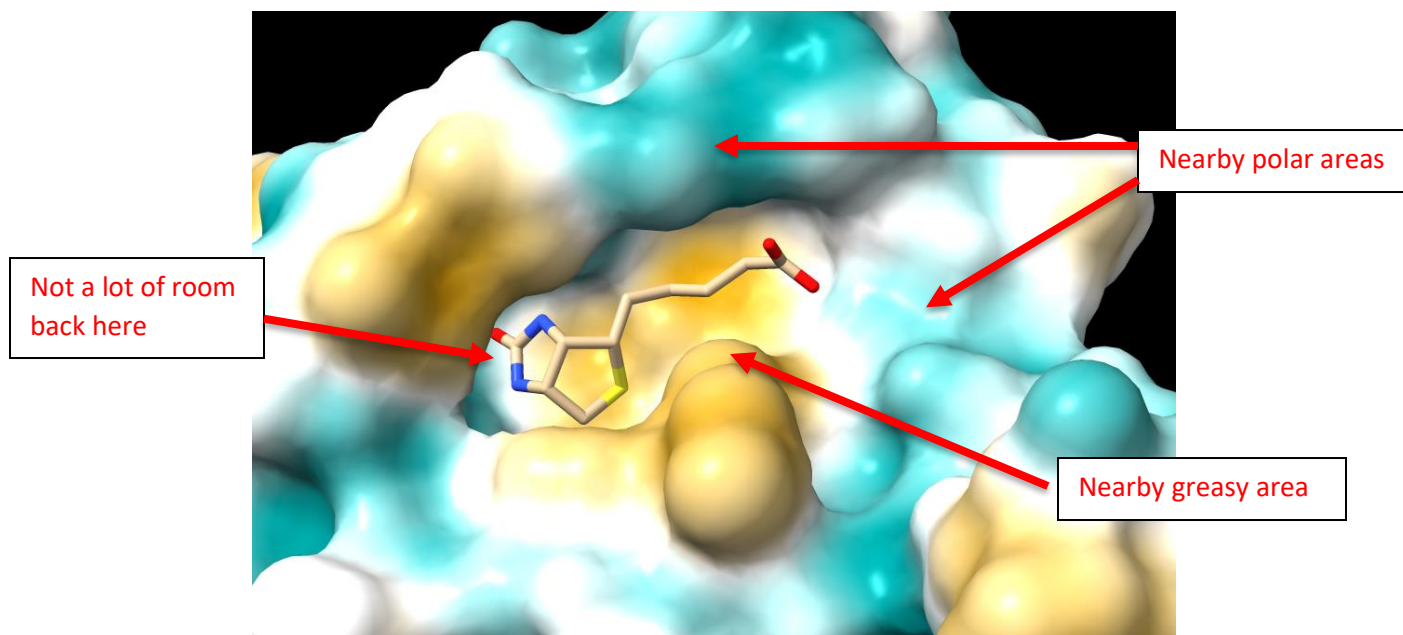
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**Note:** We're going to use protein structure 1stp (streptavidin) bound to biotin that we've used for all of our tutorials here, but the process is the same for any drug target.

## Visualizing the Pocket

While you can envision a large number of synthetic variations to any molecule, we first need to figure out where we have "space" in the pocket to accommodate changes. It doesn't make any sense to slap a functional group on a molecule if there is no room for the binding pocket to accommodate your changes.

A good place to start is to use the "mlp" surface which visualizes both space and polarity. Looking at biotin in the 1stp crystal, we have something like this:



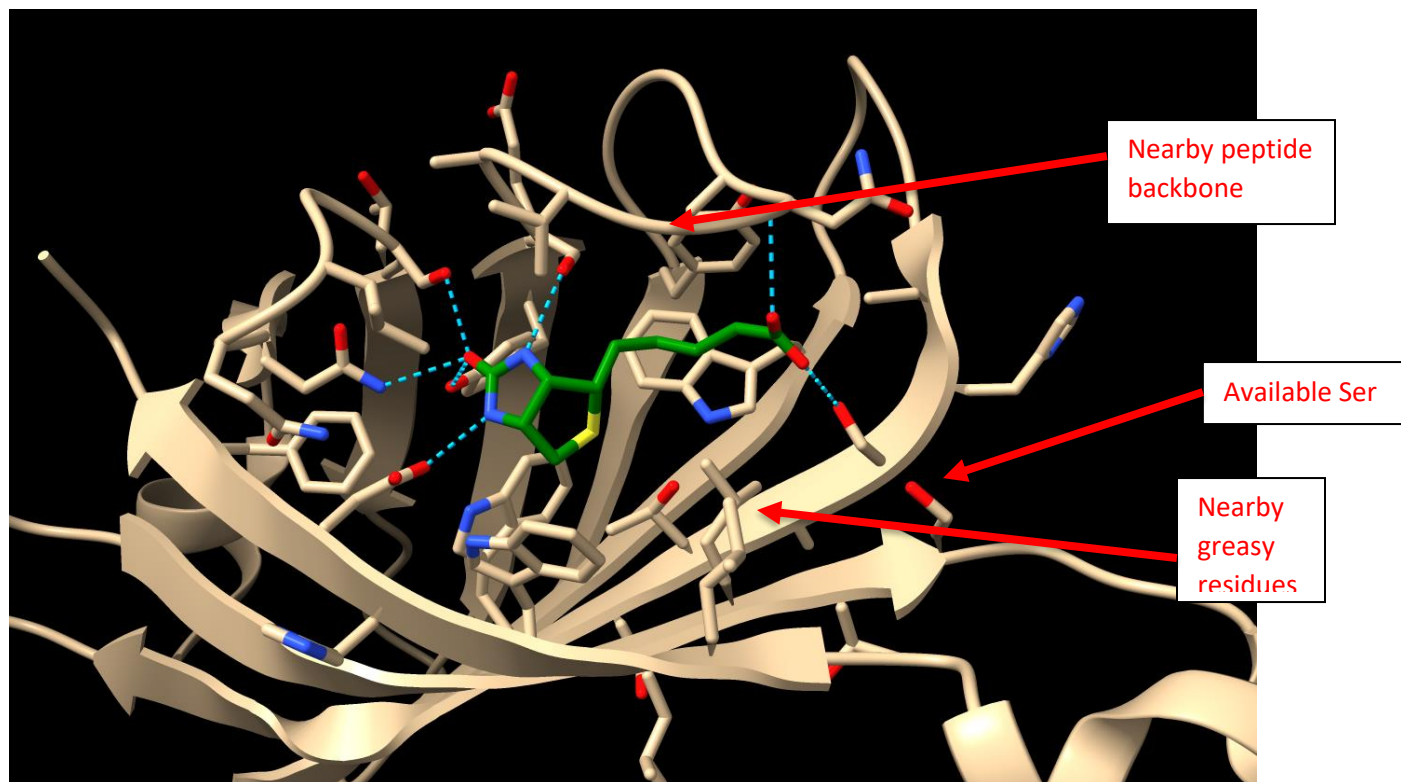
From this view, a few things should pop out:

1. There's not a lot of room to mess with the fused 5-member rings
2. The alkyl chain has a lot of open area that we could add some branches to
3. Past the carboxylic acid, there's a polar region would could potentially access
4. There's a polar region sitting above the carbon chain

## Identifying Nearby Residues

There are a couple of ways to show nearby residues. One way to do this is to first hide all the atoms, then show your ligand and everything within 7 Å or so, being sure to include what H-bonds already exist. Here's an example set of commands that you can use:

- \$ hide atoms
- \$ show :BTN :<7
- \$ color :BTN green; color :BTN byhetero
- hbonds :BTN

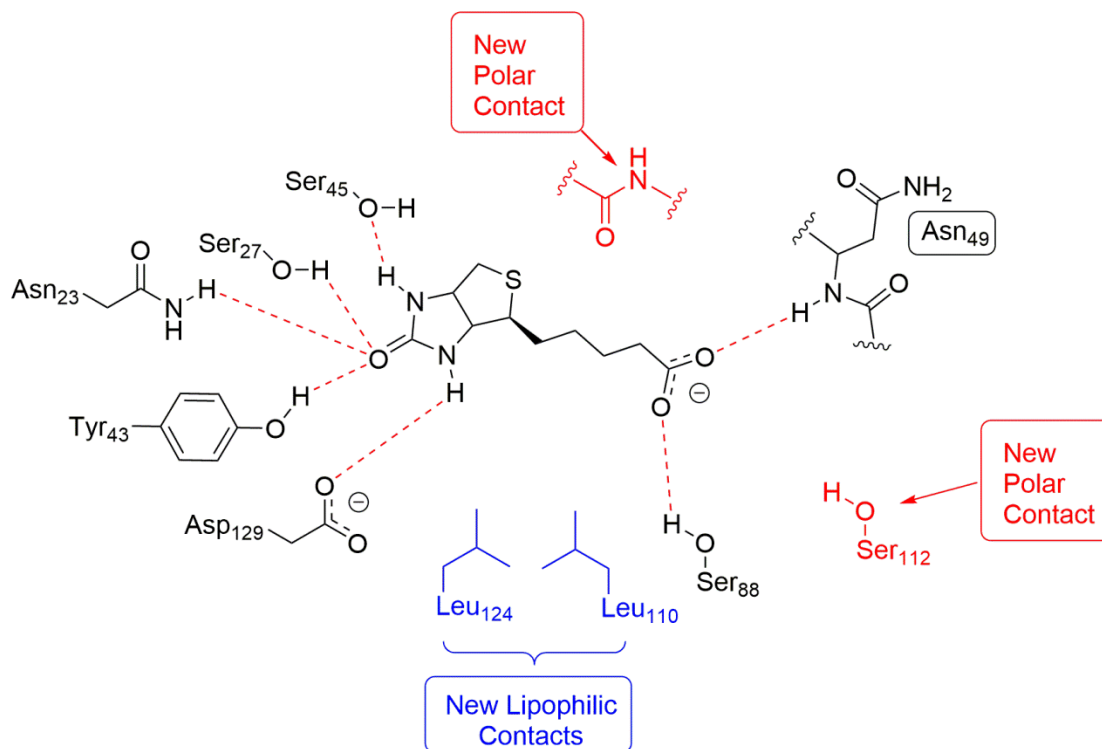


This view shows the relative position of the residues in our nearby open pocket. The polar area we saw on the surface view earlier is due to a nearby serine, while the greasy “bumps” are due to a couple of nearby leucine residues.

**Note:** Since H-bonds are very strong, we want to try and avoid breaking them when we make modifications. While it isn't forbidden, you're likely paying a pretty high price by breaking such an interaction, and it will probably give you a result that's not much better than what you started with. If you have no choice but to break an H-bond to add a group, try to keep a polar atom in the same or similar position.

## Drawing a Model Pharmacophore with Predicted Areas for Improvement

This is most easily accomplished by starting with your 2D pharmacophore you first developed for your original ligand, then adding in the additional nearby residues you identified above. Here's an example:



This model shows the nearby residue(s) that we're thinking about forming new interactions. It's pretty common to find only 2-3 areas that you access, and this is fine. You do NOT need to look for every possible pocket imaginable. As long as you present a logical model, you're fine. You'll also note that I have deleted some residues which were in the original 2D model in order to make room for the new residues I'm targeting here. This is fine, as long as you show the majority of the interactions.

Also note here that we're not making predictions about any specific interaction (H-bonding vs. ionic vs. dipole-dipole vs. vdW, etc). All you need to specify is polar vs. non-polar.

**Note:** The model I have above is NOT the only answer here. There are other additional areas we could have targeted. There is no "one model" that is correct here. Without experimental validation, there are many models that you could predict here. I'm only going to ask you for a minimum of 10 derivatives, so identifying 2-3 areas for additional contacts should be plenty.

## Designing Molecules to Reach your Targeted Residues

Before you design your molecules, remember that they must contain the following:

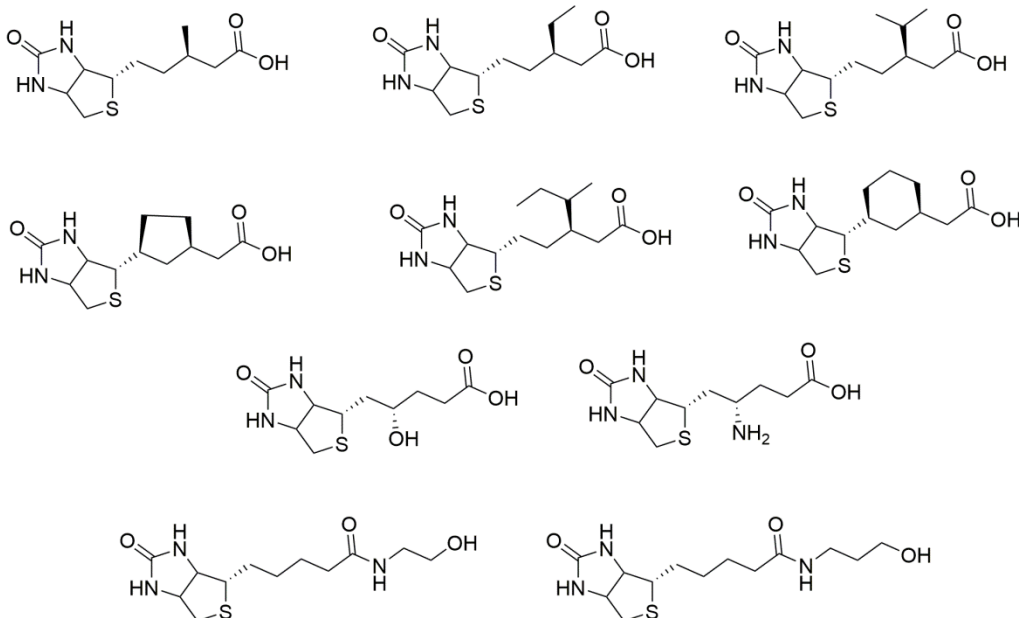
1. Identical or nearly identical scaffold (don't mess with the core)
2. Some kind of name under each structure (short names or just numbering them is fine)
3. Only 1 addition/modification to the core for each molecule (in other words, don't add 2 groups at once)
4. Added functional groups can have no more than 6 carbons and no more than 16 total atoms (including the carbons)
  - a. In other words, don't add anything bigger than a 6-carbon chain or a 6-membered ring.
  - b. While most function groups are fair game, avoid adding known toxicophores.
  - c. It's fine to have multiple similar additions, like a methyl/ethyl/propyl series of derivatives.

Your derivatives will all be pretty similar, and this is by design. Remember that small additions (like just a methyl group) can have a huge impact, so you don't have to make large changes in size to increase the binding affinity. In fact, large additions often cause the molecules to pop out of the pocket. When you design your drugs, remember that there are a number of possible techniques you can use: substituent variation, structure extension, ring expansion/contraction, aromatic ring variation, & ring fusion.

Another thing to keep in mind while you're making your molecules is the relative distances involved. Use ChimeraX to get a sense of how far away things are and go from there. **Also, don't forget that protein pockets are chiral!** Be sure to pay attention to the chirality of your molecules. It helps if you start by orientating your molecule the same way it appears in your ChimeraX pocket.

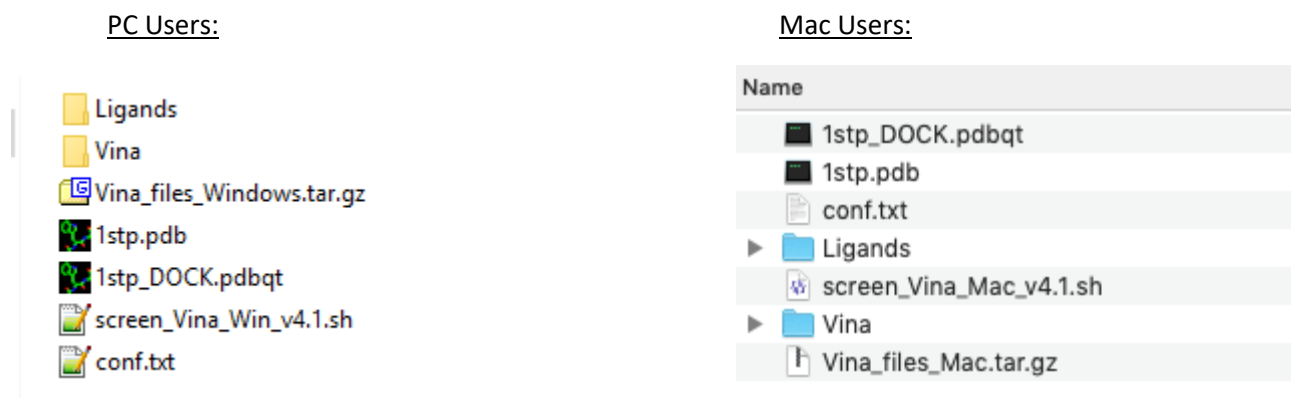
**Note:** We have no way of knowing beforehand how the molecule will wiggle into a pocket when we try to dock it. So, we can't assume that it will have a similar conformation as the original ligand/drug, nor can we know how it will change its conformation to fit. You just have to make your best guess and see what happens!

Based on the pharmacophore model from before, here are 10 example derivatives:



## **Running a Vina Docking Job with all of your Designed Molecules**

Running a Vina job with multiple ligands is almost identical to the way we ran it in the tutorial. You will set it up very similar to the way we did before. As a reminder, here's what it looked like with the biotin tutorial:



To run your own job, the differences would be as follows:

1. You need to have the PDBQT file for your target protein (instead of 1stp in the tutorial)
2. You need to have all of your ligands that you designed as PDBQT files in the **Ligands** folder.
  - a. You need to make the PDBQT files using the same online server we did for biotin. Be sure to use all of the same settings we used in the tutorial.
  - b. Don't forget that all of your ligands must be named starting with the word "ligand." Like ligand\_1.pdbqt, ligand\_2.pdbqt, etc. You can also use names like ligand\_amine.pdbqt, ligand\_alcohol.pdbqt, etc. As long as it starts with the word "ligand" and there are no spaces in the name.
3. You have to correctly set the parameters in the **conf.txt** file, like the protein name and the coordinates of the search space (see the tutorial for an example).

Once you've got everything set, just run the docking script! This will take several minutes, depending on your system and the settings in the **conf.txt** file.

If you run a screen, but then decide you want to add more ligands, the easiest way to do this is to delete the **Summary\_Final.txt** file and the **Results** folder, add your new ligands to the **Ligands** folder, then re-run the job. Keeping the old ligands in there will help you determine how the ligands rank relative to each other, as individual numbers will change from run to run (a normal variance is around  $\pm 0.5$  kcal/mol or so).