

## Chem377: Webina Docking Assignment

### Report Format:

- Each student will provide a report detailing their design of a modified drug candidate with a predicted improved binding ability.
- All pictures must be made by the student—**do NOT present work from others as your own.**
- For full credit, please answer questions in the order they are provided.
  - An example completed assignment has been attached for reference.
- Your PDBQT file for your protein can be downloaded from the course Canvas page.
- If you have questions, please ask!
- **Turn in the assignment by uploading a single PDF file to Canvas by the due date indicated on the syllabus. Note for problem #7 you must also upload 2 other files along with your PDF to Canvas. Late papers will have points deducted.**
  - If you have trouble uploading to Canvas, you may email your files directly to me.

### Questions:

[1]: Please list the following: (1 pt.)

- (a) The PDB code
- (b) The literature citation for this structure
- (c) The name of the enzyme
- (d) The organism from which the protein was obtained
- (e) The structure of the original co-crystallized ligand/drug

[2]: Show a 2D pharmacophore of the original ligand/drug, and indicate binding residues/areas that you are attempting to interact with. Use chemical drawing software to do this--no hand-drawn images please. You are more than welcome to use your 2D pharmacophore from the last assignment as a starting point. (4 pts.)

- *I'm looking for your thought process here. You need to identify areas that can make additional contacts with your molecule, then make candidates based on that plan. For instance, if you see a set of greasy residues near your molecule and there is space, then it would make sense to add greasy residues to your molecule pointing toward that area in an attempt to make new vdW interactions. Don't just randomly slap functional groups on your molecule.*
- *Consult the [Webina Docking Drug Design Example PDF](#) on Canvas for a walkthrough on this process.*

[3]: Show the structure of the derivatives of your original ligand/drug that you have designed. You must design a minimum of 10 molecules, and these molecules must contain the following: (4 pts.)

- A. Identical or nearly identical scaffold (don't mess with the core unless you're swapping heteroatoms)
- B. Some kind of name or identifier under each structure (just numbers or short names are fine)
- C. Only 1 addition/modification to the core for each molecule (in other words, don't add 2 groups at once)
- D. Added 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 functional groups are fair game, don't add known toxicophores.
  - c. It's fine to have multiple related additions, like a methyl/ethyl/propyl series of derivatives.
- E. You are welcome to design more than 10 molecules, but it is not required for full credit.

[4] Dock your molecules with Webina and identify the best inhibitor among your molecules that binds with a similar orientation as the original ligand (it can't be spun around or anything like that). When you run Vina, be sure to also dock the original ligand/drug as a positive control! If you have a tie between two or more of your molecules (same energy scores), just pick one. Use ChimeraX to show a 3D surface representation of your best drug bound while also showing the original ligand (by "original ligand" I mean the one in the PDB crystal structure). Be sure to label your picture so I can tell what I'm looking at! (4 pts.)

- *The calculated binding energy can be found in the output text file from Webina*
- *It doesn't matter what kind of a surface you use when showing the bound ligand, as long as I can see the pocket and both of your molecules (the original ligand plus your best drug candidate)*
- *Using different colors for your molecules (original ligand vs. your compound) is a good idea*
- *While it's nice if your best designed molecule has a higher calculated binding score than the original ligand/drug, this is not required for full credit. Remember, you can always dock more than 10 molecules in an attempt to find something that improves your binding score if you want to challenge yourself.*
- *If your molecule has assumed a very different binding pose (like spun 180° in the pocket), this is an indication that your protein will probably not be able to make the conformational changes required to fit your drug, even if the calculated energy value looks good. If this has happened, then choose the next best inhibitor you designed. These different poses often occur if you put too large a group on a molecule, forcing it to find a new conformation. See the report below for an example of this.*

[5] Show a 3D ribbon representation of your best docked drug and mark all polar & non-polar contacts. Do not show the original ligand in this picture. (4 pts.)

[6] Develop a 2D model of the binding interactions from the previous question using ChemDraw (or similar chemical drawing program). Indicate the bonding interactions and the residues. (5 pts.)

- *Remember that the protein crystal shows no hydrogen atoms, so you won't see them. Thus, you need to add them in. Be sure to remember that this is at physiological pH and also be sure to indicate all formal charges (if they exist).*
- *If your molecule makes contact with the backbone of the protein, don't forget to show this in your 2D representation! The ChimeraX tutorial PDF shows how to do this. For full credit, you must show the correct atom-to-atom interactions!*
- *It's perfectly fine if your docked drug didn't make the contacts you were expecting it to. This is pretty common. In fact, it happens in the example report below!*

[7] In addition to this report, **please also upload the following files to Canvas:** (3 pts)

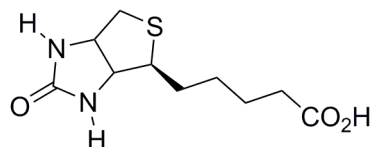
1. The text file of your best molecule that contains the calculated energy values
2. Your best molecule output file in PDB format

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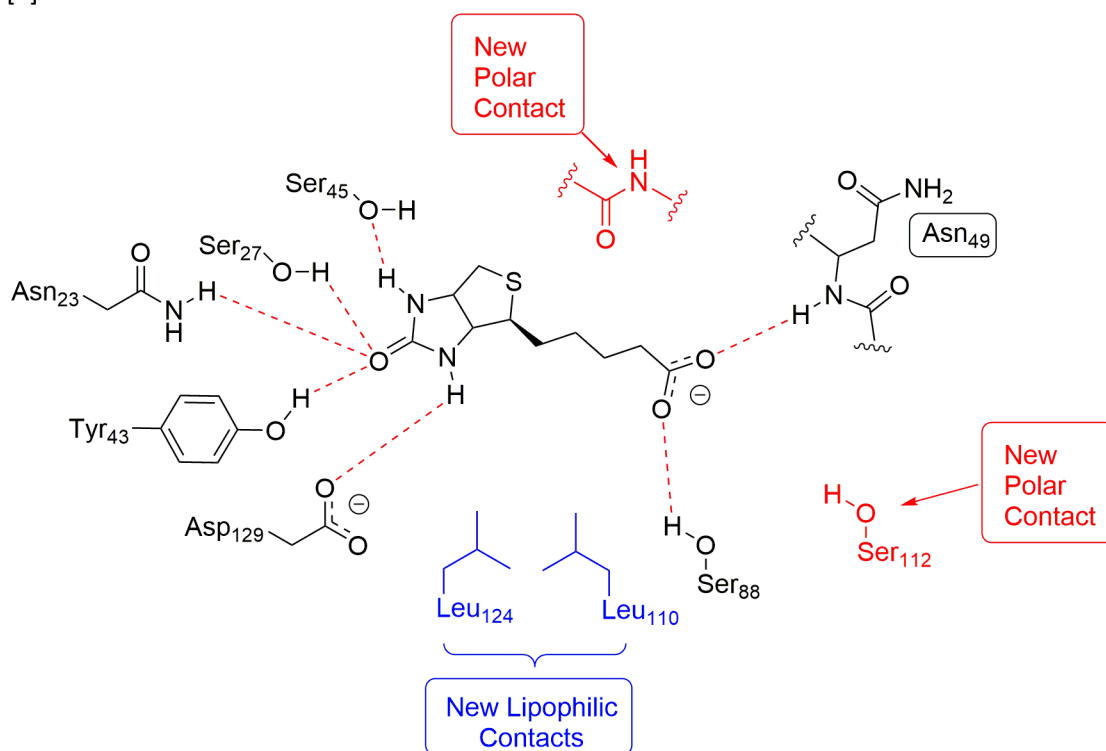
**The Next Page Shows an Example Report Based on the Tutorial Structure (1stp)**

## Vina Docking Assignment

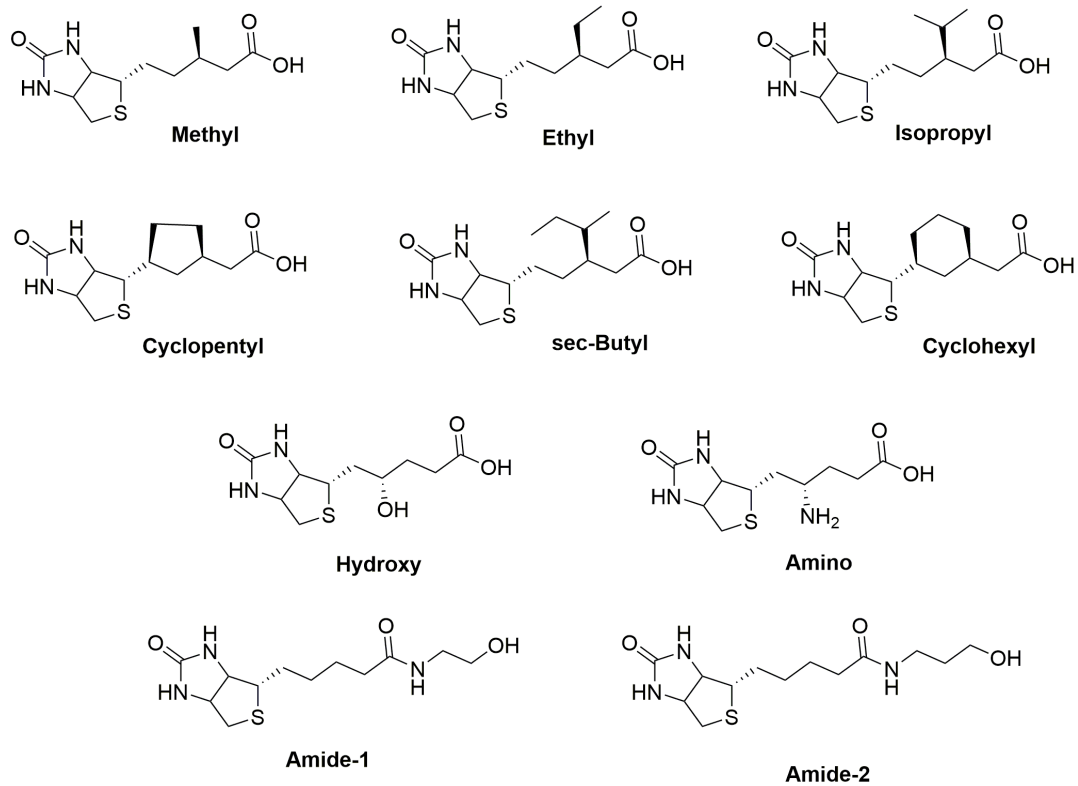
- [1] (a) 1STP  
(b) Weber, P. C.; Ohlendorf, D. H.; Wendoloski, J. L.; Salemme, F. R. "Structural origins of high-affinity biotin binding to streptavidin." *Science*, **1989**, *243*, 85-88.  
(c) Streptavidin  
(d) *Streptomyces avidinii*  
(e) Biotin (BTN)



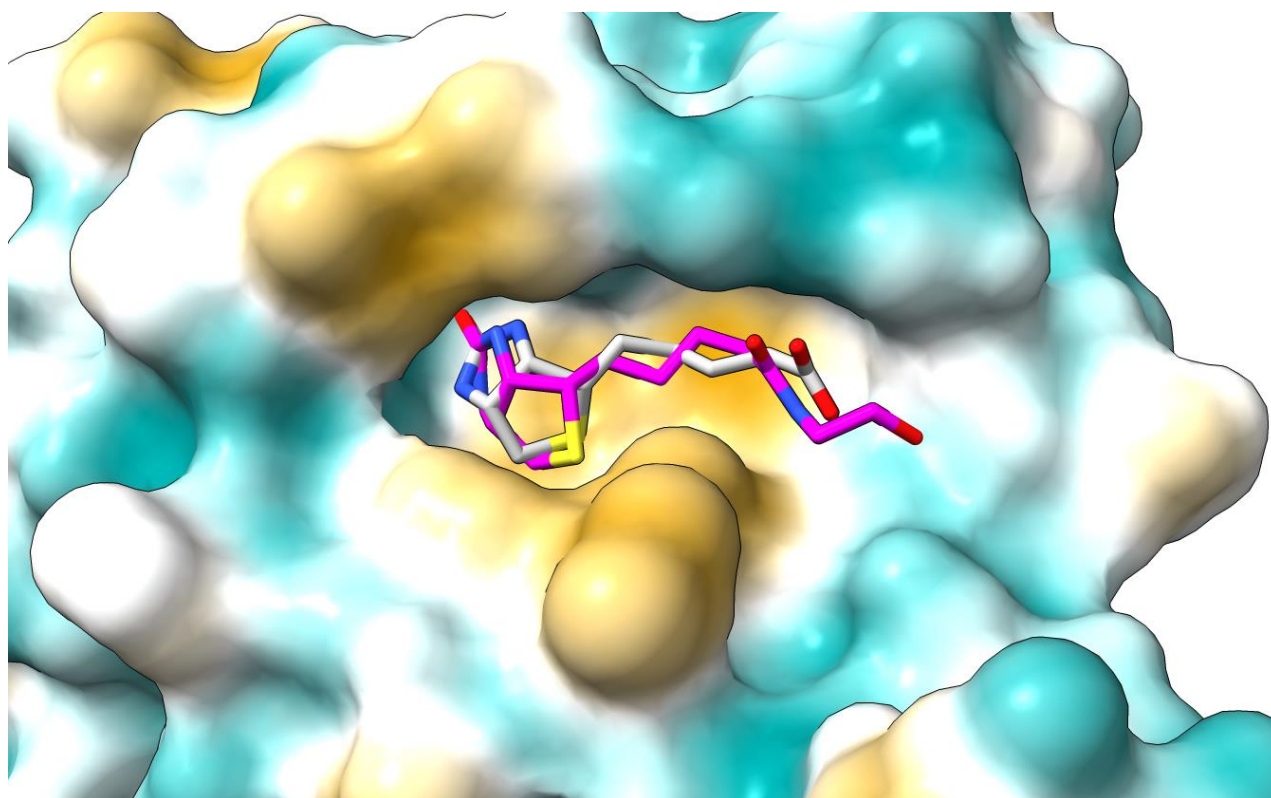
[2]



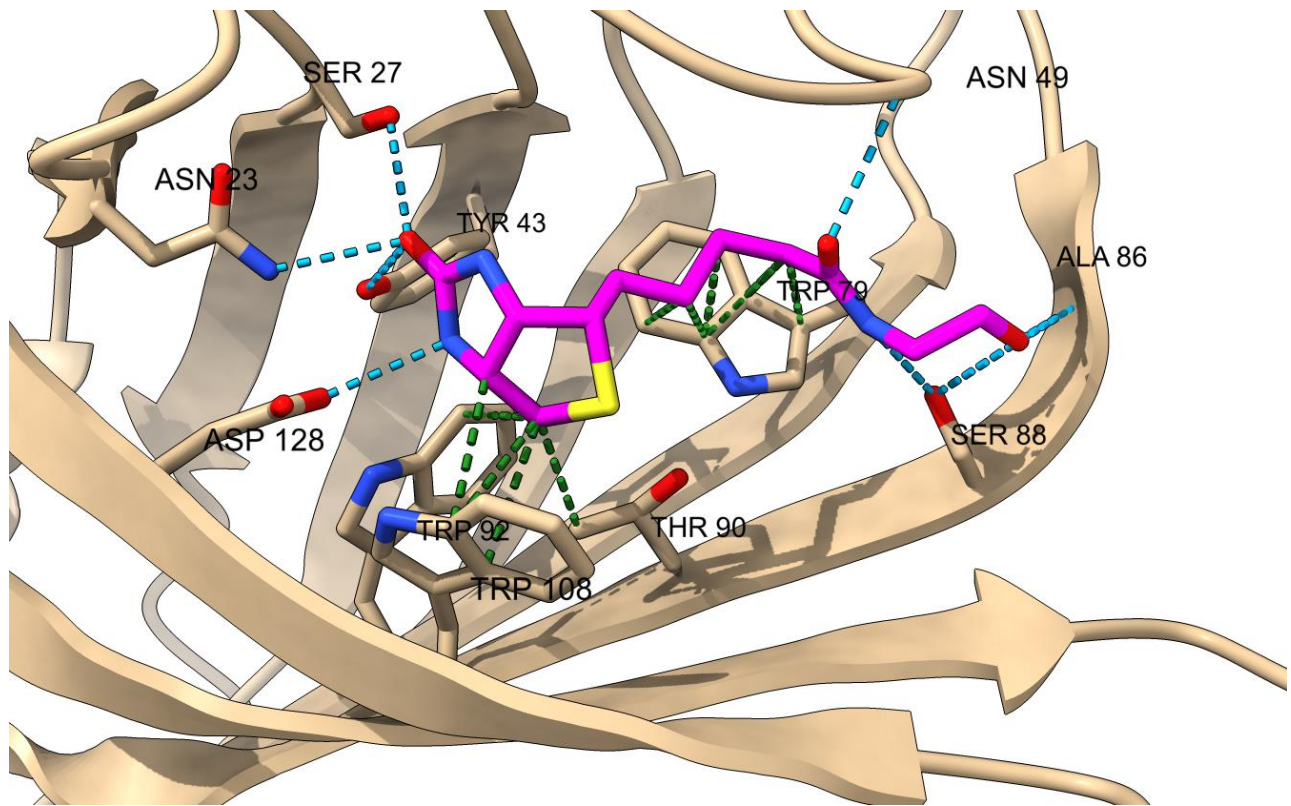
[3]



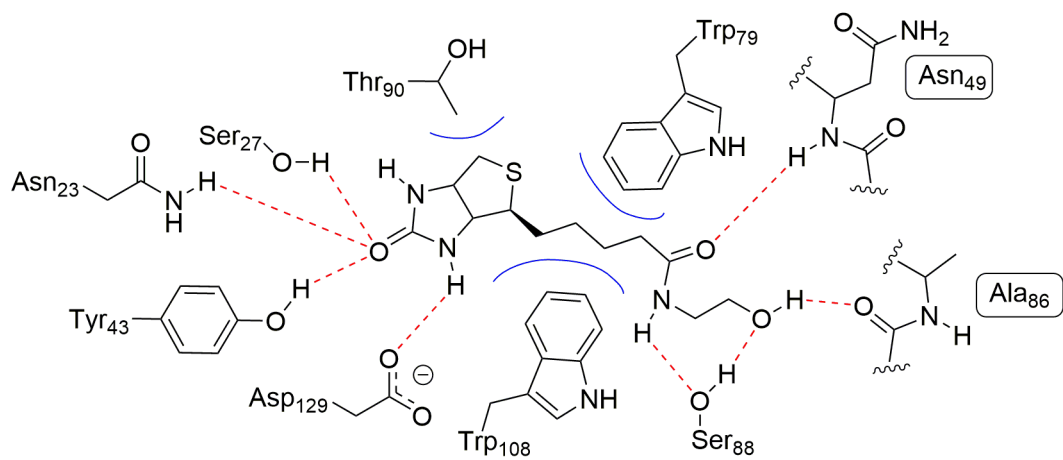
[4] Amide-1 bound to 1stp. Original ligand is shown with a silver backbone, while Amide-1 is shown with a magenta backbone.



[5]



[6]

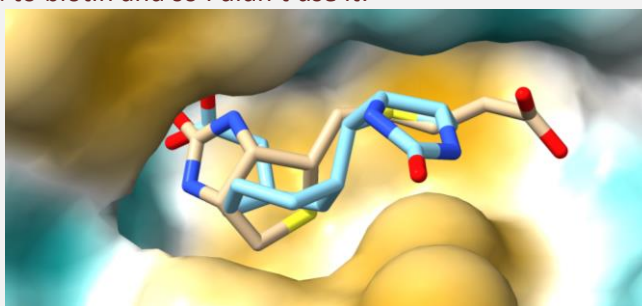


Polar interactions are shown with dotted red lines. Non-polar interactions are shown with solid blue lines.

**Note:** For this example report, I got the following energy results which I put into a text file:

ligand_Cyclohexyl.pdbqt.txt	-7.4
ligand_Amide-1.pdbqt.txt	-7.3
ligand_biotin.pdbqt.txt	-7.1
ligand_sec-Butyl.pdbqt.txt	-7.1
ligand_Amino.pdbqt.txt	-7.0
ligand_Cyclopentyl.pdbqt.txt	-7.0
ligand_Isopropyl.pdbqt.txt	-7.0
ligand_Methyl.pdbqt.txt	-7.0
ligand_Hydroxy.pdbqt.txt	-6.9
ligand_Amide-2.pdbqt.txt	-6.6
ligand_Ethyl.pdbqt.txt	-6.5

You can see that my top score was actually the cyclohexyl compound, but the docked conformation was flipped around compared to biotin and so I didn't use it:



You'll also notice that most of my docked compounds were scored lower than the original biotin ligand. This is not uncommon. Remember, things have to bind fairly tightly to a protein in order to get a crystal structure, so a lot of what you try may not score as well.

If you really want to improve your binding score, it's not a bad idea to pick your best compound and then make derivatives of that one (what we would call a 2<sup>nd</sup> generation library). This is often how we do it in the lab--multiple generations all building off of the best compound from the previous generation. Again, this isn't necessary for the assignment, but something you can play with if you want to challenge yourself.

**Another Note:**

Sometimes ChimeraX will show strange bonds connecting distal atoms when you view a PDB of a molecule you design. This doesn't affect your docking results, but it does make the molecule look weird. This is pretty rare, however, so most people won't see it. If have this issue, you can delete the bond holding CTL and double clicking to bring up a menu where you can select "delete bond." An example is shown below:

