

Chem377: ChimeraX Pharmacophore Graphics Assignment

Report Format:

- Each student will provide a report on their individual protein target (assigned by the instructor)
- All pictures must be made by the student—**do NOT copy pictures from online and present them as your own work.**
- For full credit, please answer questions in the order they are provided.
 - An example complete assignment has been attached for reference.
- If the protein is a dimer, trimer, etc., please delete the extra protein chains. See the tutorial for instructions on how to do this.
- If you have questions, please ask! It's most helpful if you bring a computer to my office, or you email me a saved "session" file that I can open with you in my office.
- **Turn in the assignment by emailing me a PDF by the due date indicated on the syllabus. Late papers will have points deducted.**

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

[2]: What is the name and chemical structure of the co-crystallized ligand/drug? (ChemDraw is preferred, but other drawing programs are fine. No hand-drawn image). Include the PDB "abbreviation" for this ligand (2 pts.)

[3]: Briefly, what is the function of the enzyme? If the enzyme catalyzes a simple reaction (i.e. a substrate to a product) please indicate the simplified reaction. You do NOT need to show a full arrow-pushing mechanism, just the reactants and products (3 pts.)

- *For this part, it's recommended that you search for the information and/or read the reference for the crystal structure. Be sure to provide references if you use outside resources like this! I don't expect most of you know what a particular protein does off the top of your head, so I expect most people will have a reference here or there.*

[4] Attach three (3) different views using different parameters of the protein-ligand complex generated using ChimeraX. By "different parameters" I mean you need to vary the types of surfaces/ribbons you use to represent the molecule and/or protein to give different insight. Do not take the same picture and just rotate it. Also, **DO NOT just give me a series of "Preset" options.** I want to see your work—not the work of the programmers. It is fine to start with a Preset and modify from there, of course (6 pts.).

- *Note that a protein can have several cofactors bound to it in addition to the ligand. You only need to develop a pharmacophore for the inhibitor/ligand, NOT cofactors! The ligand is usually the synthesized organic substrate. If you're unsure which molecule is the ligand, just ask. If a metal is present and binding the ligand, please show it. Common cofactors which you can ignore include ATP, Orotic acid, flavins, hemes, NAD, NADP, FAD, SAH, SAM, sugars and vitamins.*

[5] Attach two (2) pictures of the binding interactions between the drug/inhibitor and any interacting protein side chains (polar and non-polar). Also, show one with a ribbon backbone (no surface), and the other with some kind of surface (can still have a ribbon). Include labels on the residues, and show the H-bonds and non-polar contacts with their default colors. You may need to show the two pictures at different angles to see everything (7 pts.).

- *Since drugs are carbon chains, there will always be vdW interactions. If ChimeraX is not detecting vdW interactions, then it's likely you are not entering in the command correctly. This is a complex command, so check it carefully! If you need help, please let me know!*
- *It is possible that your molecule has no H-bonding interactions to the protein, although this is uncommon.*
- *If your molecule is buried deep, it's okay to provide more than just 2 pictures, or to provide some with certain residues removed for clarity. As long as I can see all interactions across the set of pictures you provide, it's fine.*
- *Note that some drugs will form interactions with the peptide backbone. You need to include these!*

[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 (6 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).*

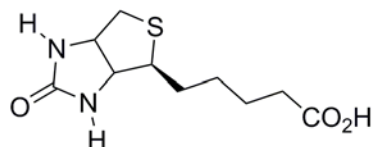
[7] Add references at the end if you used any. Most people will reference the original paper or a database like Wikipedia (or both).

The Next Page Shows an Example Report Based on the Tutorial

Pharmacophore Graphics Assignment

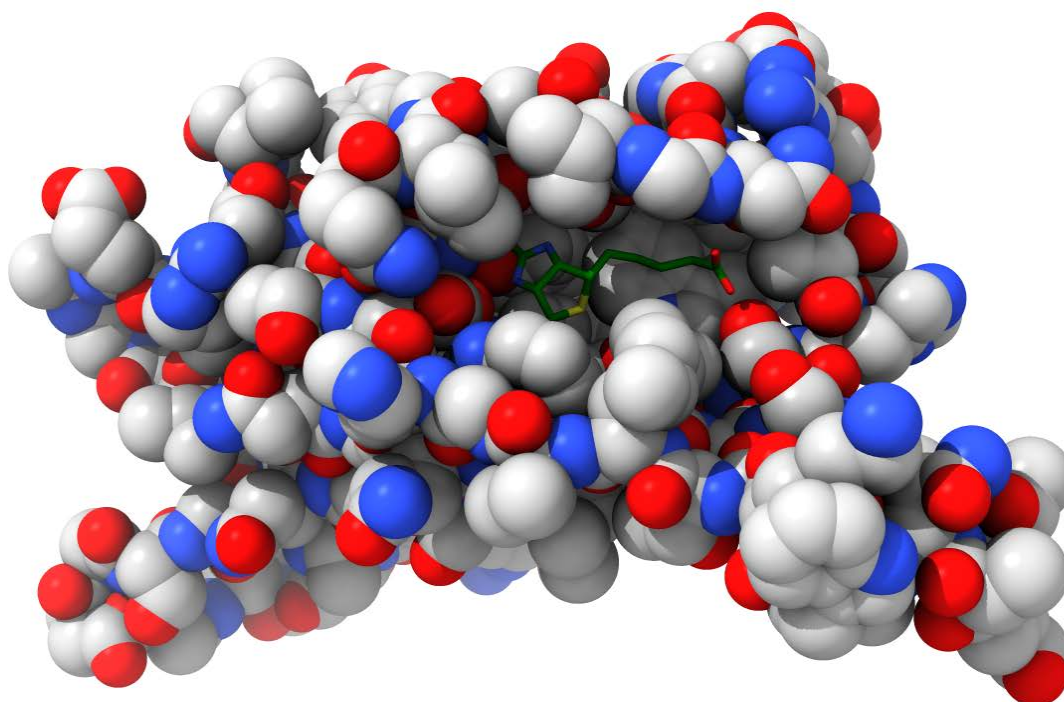
- [1] (a) 1STP
(b) Weber, P. C.; Ohlendorf, D. H.; Wendoloski, J. L.; Salemme, F. R. "Structural origins of high-affinity biotin binding to streptavidin." *Science*, **1989**, *243*, 85-88.
(c) Streptavidin
(d) *Streptomyces avidinii*

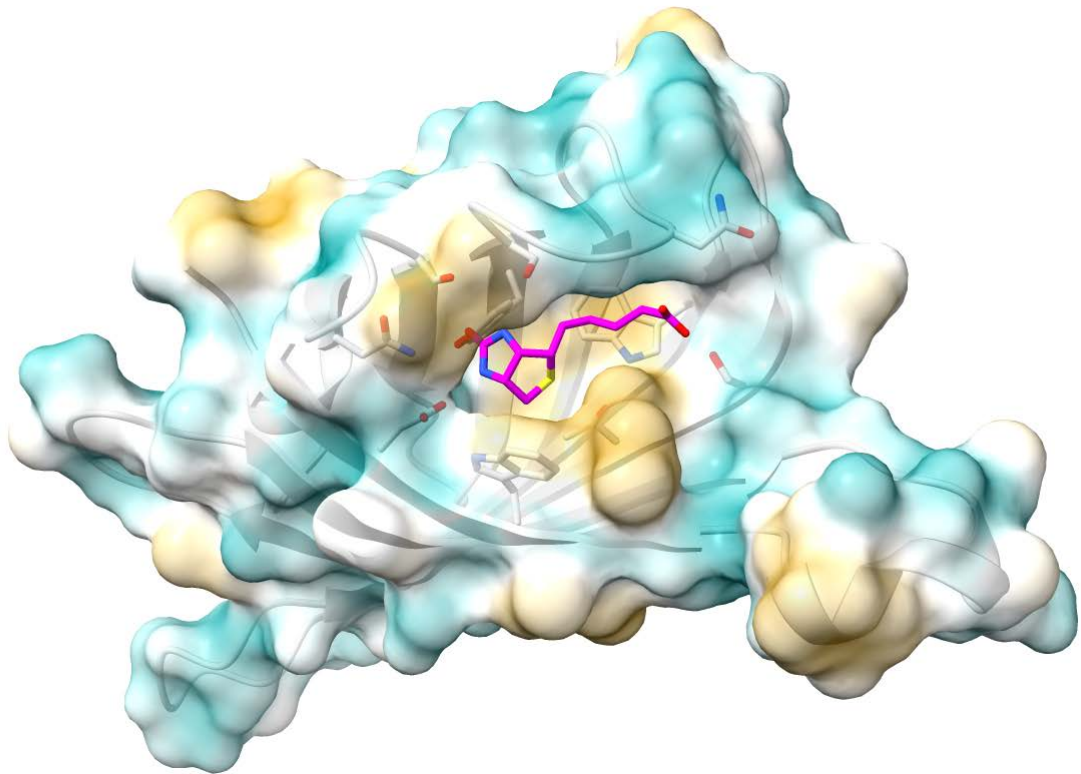
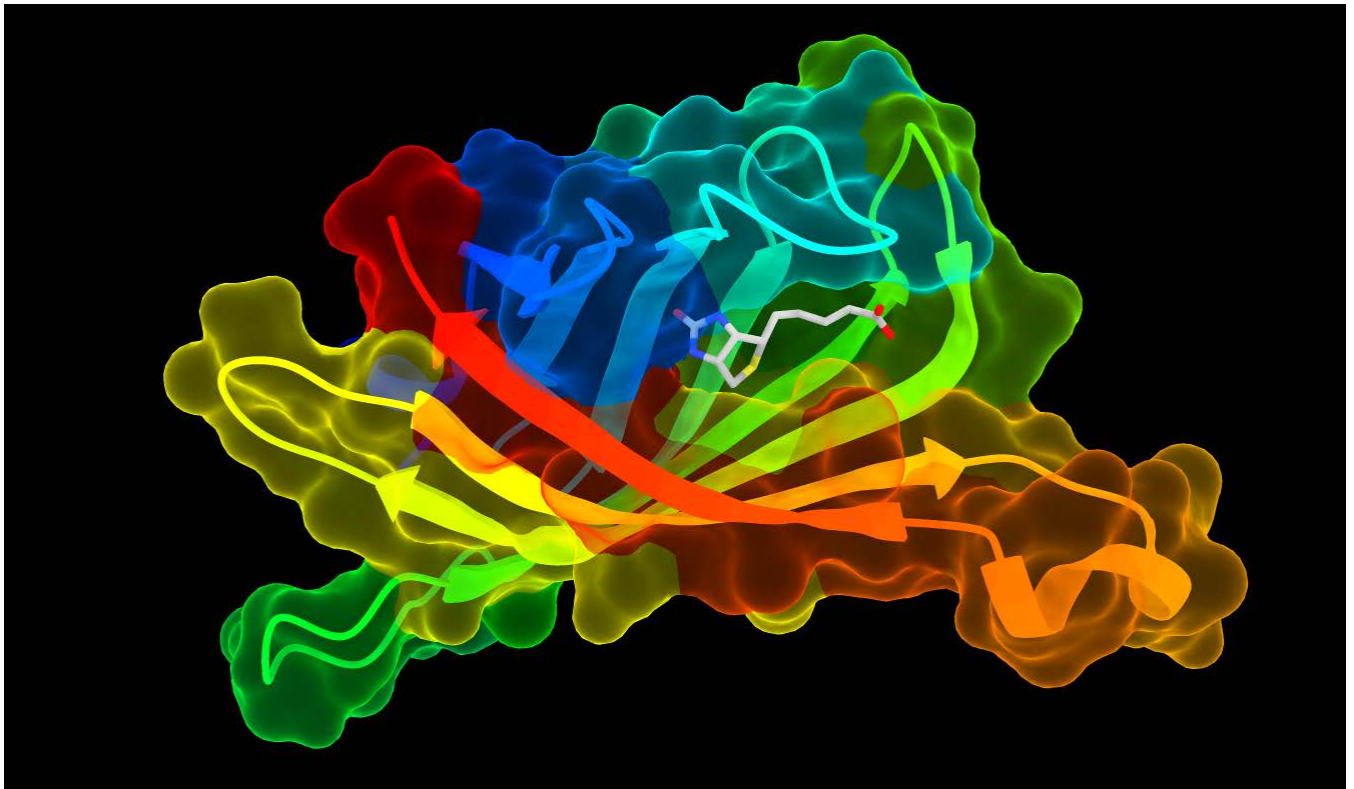
- [2] Biotin (BTN)



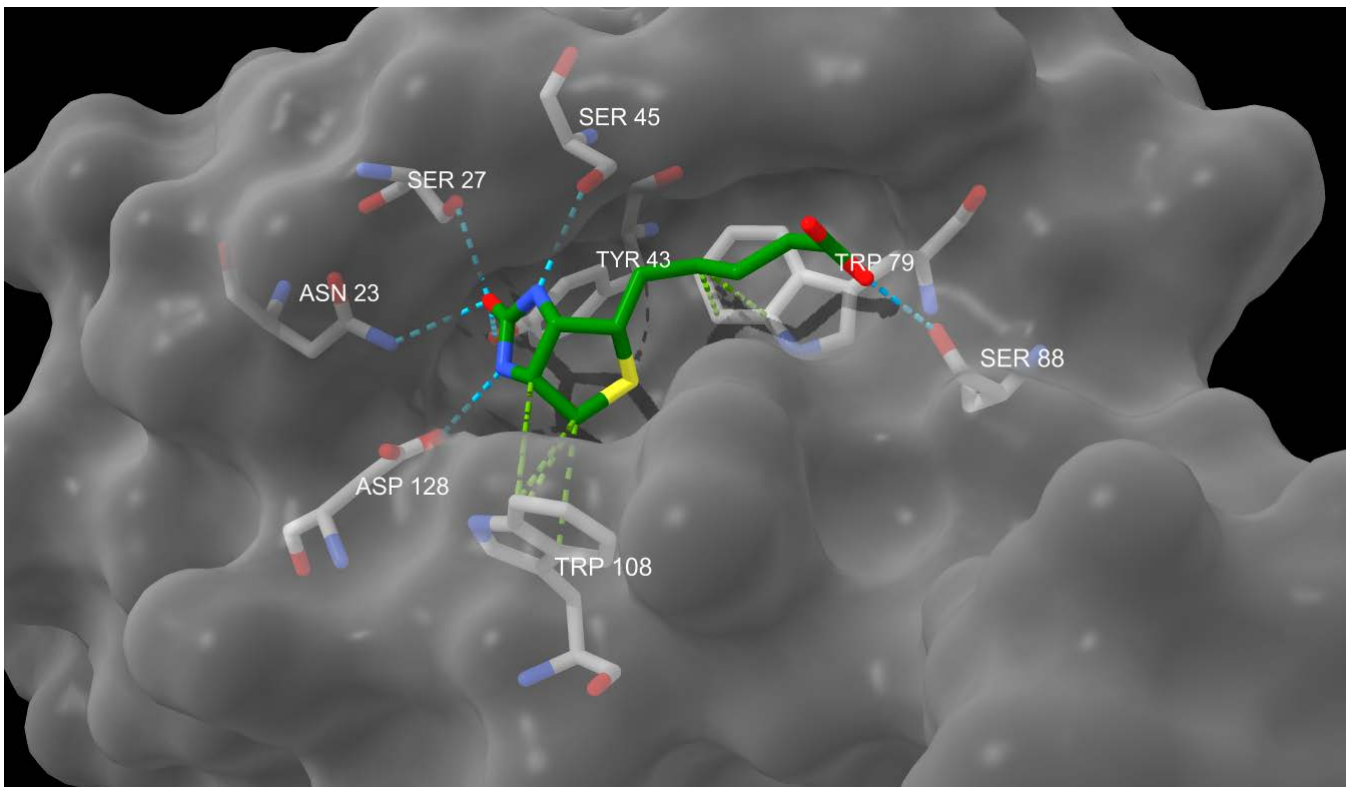
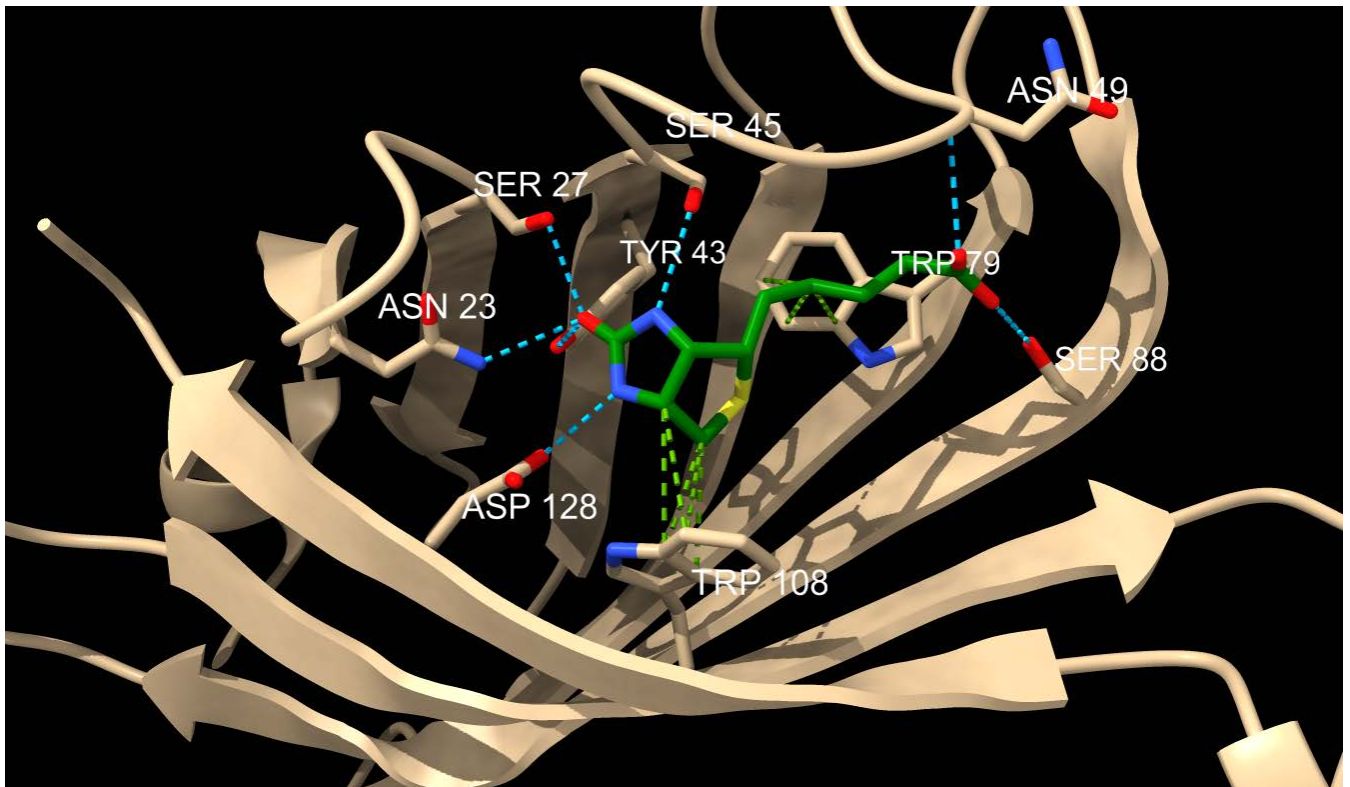
- [3] Streptavidin belongs to the avidin family of proteins and is used by *Streptomyces* bacteria to bind biotin, which is also known as vitamin B7. Streptavidin naturally occurs as a tetramer capable of binding two molecules of biotin. Streptavidin is notable as its disassociation constant is one of the smallest ever recorded for non-covalent interactions, on the order of 10^{-14} mol/L.¹

- [4]

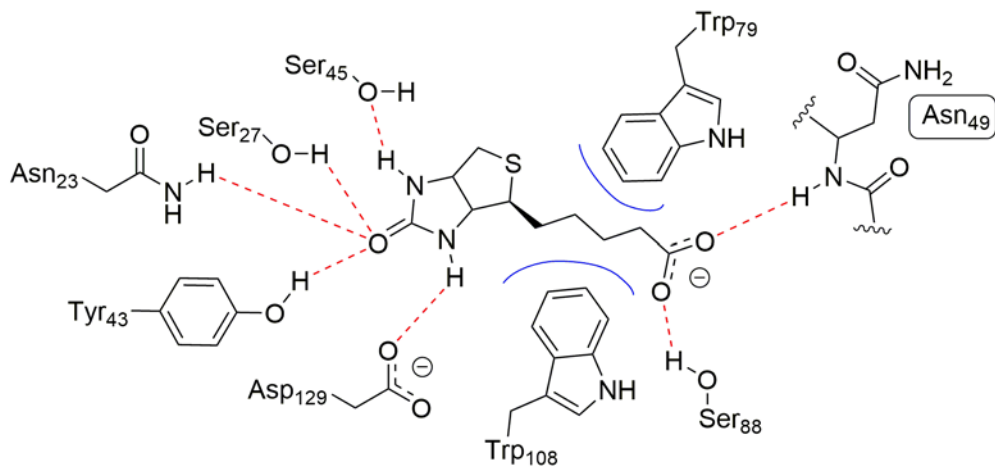




[5]



[6]



Polar interactions shown as dotted red lines

Non-polar interactions shown as blue lines

[7] References:

Green, N. M. "Avidin." *Adv. Prot. Chem.* **1975**, 29, 85-133.