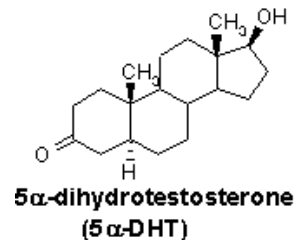
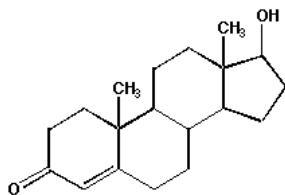


Problem Set 6: Cell Communication

Due Wed Nov 9th in class

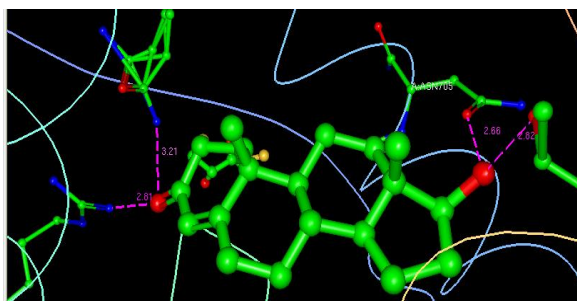
I. STEROID HORMONES: Review the hormone tutorial on the protein data bank on anabolic steroids: http://pd-beta.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb92_1.html and answer the following questions:

- What are two main functions of anabolic steroids? *Anabolic steroid are **androgenic**-directing the development of secondary sexual characteristics in men by raising the level of testosterone and **anabolic**, which means they build up muscle, increase the production of red blood cells by increasing protein synthesis.*
- Trace the path of testosterone from its synthesis to one of its many target sites. *Testosterone is produced in the testes and travels through the blood in carrier proteins such as serum albumin or sex hormone binding globulin. It passively diffuses through the cell membranes of target cells.*
- How does testosterone enter the cell? *Because it is hydrophobic, testosterone diffuses through the cell membrane.*
- What is testosterone's action once it enters the cell? *Testosterone finds its way to an androgen receptor protein which dimerizes and enters the nucleus where it binds to DNA and initiates transcription.*
- Draw the chemical structure of testosterone and the more active form of testosterone that is made in some cells. *Testosterone is on the left. DHT has two more H atoms in ring A, note double bond in the ring is gone.*

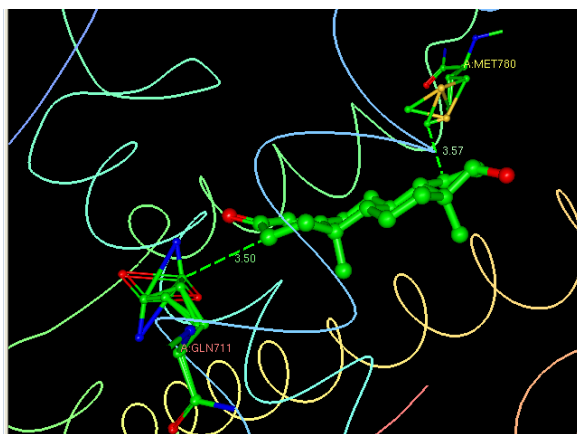


- Why can't you just take testosterone orally to build up muscles? *Oral steroid can be broken down in the digestive system and are not well absorbed by the gut.*
- What are designer steroids? *Designer steroid are anabolic steroids or compounds that can be turned into steroids by the body that are taken orally to build up muscle mass in the body. They are banned by most athletic organizations in the world.*
- How do certain "dietary supplements" provide a way around the bans on steroid use? *Dietary supplements like 17 β hydroxyl steroid dehydrogenase, are enzymes that lie along the biochemical pathway of testosterone biosynthesis and are used by some athletes as supplements to improve athletic performance.*

- i. The hormone binding domain of the testosterone receptor protein is shown in pdb structure (PDB entry [2am9](#)). Access this entry, and scroll down towards the bottom of the page where you will see a table of ligand chemical components. The last entry is testosterone (TES) and you will have the option of selecting a new program "ligand explorer". Select this program, and download the Java program onto your computer so that you can look at the ligand interactions. Then use the program to describe the four hydrogen bonds (include the atom on the testosterone, the amino acid number and atom, and the distances) and the two hydrophobic interactions that occur at less than 3.6 Å (you may need to change the cut-off distance for hydrophobic interactions to limit them to two).

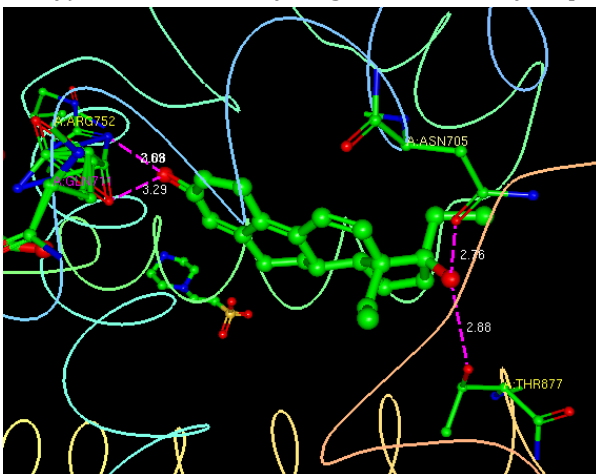


H: bonds. We can see the four H bonds, two between the ketone oxygen (acting as a H bond acceptor) in ring A to Arg 752 (2.81 Å) and Gln711 (3.21 Å), and two between the -OH on ring D of the hormone to Thr 877 (2.82 Å) and Asn 705 (2.66 Å).



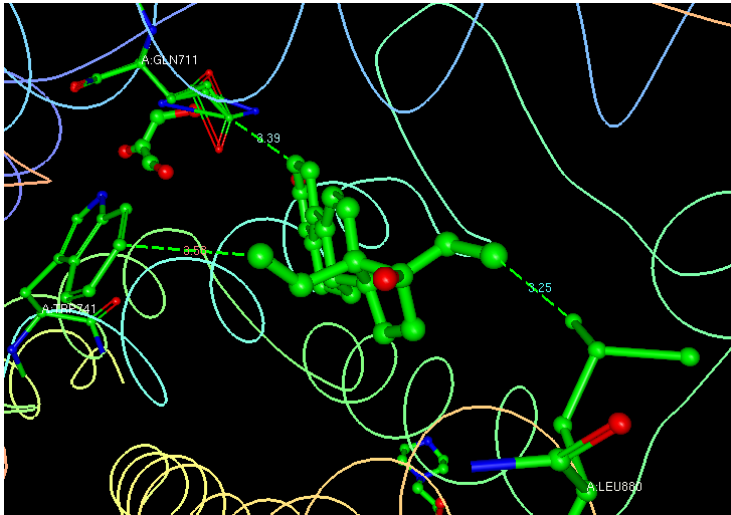
Two hydrophobic interactions are seen at less than 3.6 Å, once between -C atoms in ring A to -C atom on Gln 711 (3.5 Å) and another between -C atom in ring D and -C atom on Met 780 (3.57 Å)

- j. A synthetic designer steroid, tetrahydrogestrinone (THG) can also bind to this receptor (PDB entry [2amb](#)). THG is the "undetectable" anabolic steroid uncovered in the 2003 BALCO doping scandal. Does this molecule (named 17H in the pdb entry) make the same hydrogen bonds and hydrophobic interactions as TES?



both lengthen [Thr 877 (2.82 → 2.88 Å) and Asn 705 (2.66 → 2.76 Å)].

H bond interactions: Ketone O on ring A of the hormone makes a similar bond to Arg 752 but it is shorter (2.81 → 2.69 Å), meanwhile, another H bond from the same atom (ketone O on ring A) to the O on Gln711 lengthens a bit (3.21 → 3.29 Å) but since the Gln can rotate to also provide H bonding through N on Gln at 3.06 Å, Meanwhile, on the other side of the molecule the same two H bonds are made,



The same hydrophobic interaction is made from the C on ring A (Gln 771 at 3.5 \rightarrow 3.39 \AA), but we lose the hydrophobic interaction from the C on ring D and replace it with two new hydrophobic interactions, from the C atoms off the ring, one with Leu 880 at 3.25 \AA and the other with Trp 741 at 3.58 \AA .

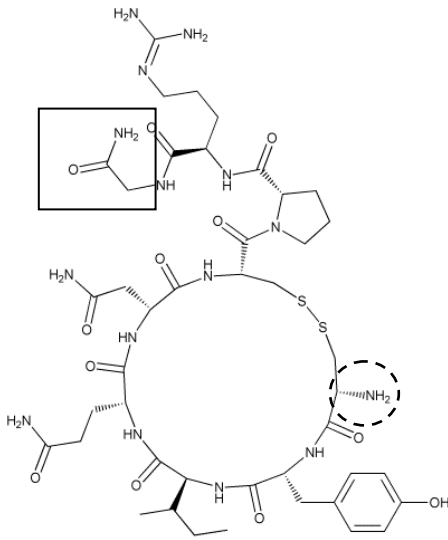
- k. Use your knowledge of the electronegativity of atoms to explain why you do not see H-bonds between carbons and hydrogens?

H bonds do not form between C and H because the electronegativities of those two atoms are too similar (2.5 and 2.1) so the electron pair bond will not be polarized enough to create an opportunity for H bonding with another atom.

- l. Use your knowledge of the structure of the atom to explain the origin of the hydrophobic interaction? (why does like dissolve like?)

The hydrophobic interaction exists between two neutral atoms with very similar or identical charge distributions and electronegativities. There is a small transient polarization of the electron cloud around one atom that arises from its closeness to the other atom. At distances of 3.5 \AA or greater this interaction is a favorable one that leads to very weak bonds between the two atoms (energies of less than 1 kcal). At shorter interactions, this can be repulsive.

II. Peptide Hormones. Shown below is a cyclic peptide.



- a. Circle the N- terminus. *done*
 b. Put a square around the C-terminus. *done*

c. What is unusual about the C-terminus? *It has an -NH₂ instead of -OH on the carbon of the carboxylic acid.*

d. How many amino acids does this peptide have? *nine*

e. A reaction between two amino acid side groups has created the ring. What are the amino acid side groups that reacted, and what is the new type of bond called?

Amino acids that reacted cysteine

Name of the new bond disulfide bond

- f. How many amino acids are in the ring? *Six*

g. How does this peptide differ from vasopressin? *Vasopressin has a Phe where this peptide hormone has a isoleu at position three*

h. How would this difference affect the binding of this peptide to receptors? *Since both amino acid side groups are quite hydrophobic, it wouldn't affect it too much. Phe is a bit larger than isoleu, but not by much*

- i. List the amino acids from N to C terminus.

Cys Tyr Ile Gln Asn Cys Pro Arg Gly

- j. It has been noted in class that the concentration of this hormone in blood is pg/mL. If the average molecular mass of an amino acid is 110 g/mole, calculate the molarity of this peptide in blood.

First thing to realize is that if each amino acid has an average mass of 110 g/mole, than the entire peptide has a molar mass of 9x110 g/mole or 990 g/mole.

$$1 \frac{\text{pg}}{\text{ml}} \times \frac{1 \times 10^{-12} \text{g}}{\text{pg}} \times \frac{1 \times 10^3 \text{ml}}{\text{l}} \times \frac{1 \text{ mole}}{990 \text{ g}} = 1 \times 10^{-12} \frac{\text{moles}}{\text{l}} = 1 \times 10^{-12} \text{ M} = 1 \text{ pM}$$

Nitric Oxide and Oxidation and Reduction

Nitric Oxide and Lewis Structures

Shown below are several complexes of nitrogen and oxygen. Draw the Lewis Structures for each and calculate the total number of valence electrons and the formal charge on each atom.

Molecule – Lewis Structure	Total Number of Valence Electrons	Formal Charges
O ₂ <i>Impossible to draw these in word, see separate structures</i>	2x6 = 12 electrons	FC each oxygen = $6 - (4 + \frac{1}{2}(4)) = 0$
N ₂	2x5 = 10 electrons	FC each nitrogen = $5 - (2 + \frac{1}{2}(6)) = 0$
NO	6+5 = 11 electrons	FC N = $5 - (3 + \frac{1}{2}(4)) = 0$ FC O = $6 - (4 + \frac{1}{2}(4)) = 0$
[NO ₃] ⁻¹	5 + 3(6) + 1 = 24 electrons	FC N = $5 - (0 + \frac{1}{2}(8)) = +1$ FC O(db) = $6 - (4 + \frac{1}{2}(4)) = 0$ FC O(sb) = $6 - (6 + \frac{1}{2}(2)) = -1$ Total charge is +1-1-1=-1
N ₂ O	5+5+6 = 16 electrons	FC N1 = $5 - (0 + \frac{1}{2}(8)) = +1$ FC N2 = $5 - (4 + \frac{1}{2}(4)) = 0$ FC O = $6 - (6 + \frac{1}{2}(2)) = -1$ Total charge is +1-1-1=-1
NO ₂	5+6+6=17 electrons	FC N = $5 - (1 + \frac{1}{2}(6)) = +1$ FC O(sb) = $6 - (6 + \frac{1}{2}(2)) = -1$ FC O(sb) = $6 - (4 + \frac{1}{2}(4)) = 0$ Total charge is +1-1+0=0