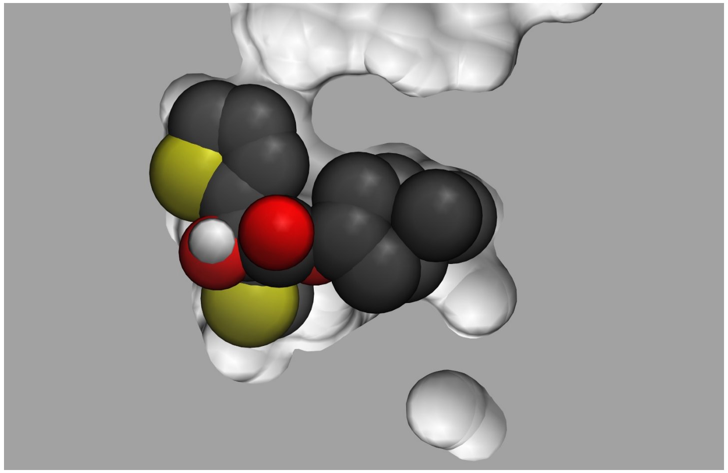
Week 6 problem solving
+ equations, + applications

structural views
of intermolecular forces
that enable drug-target binding

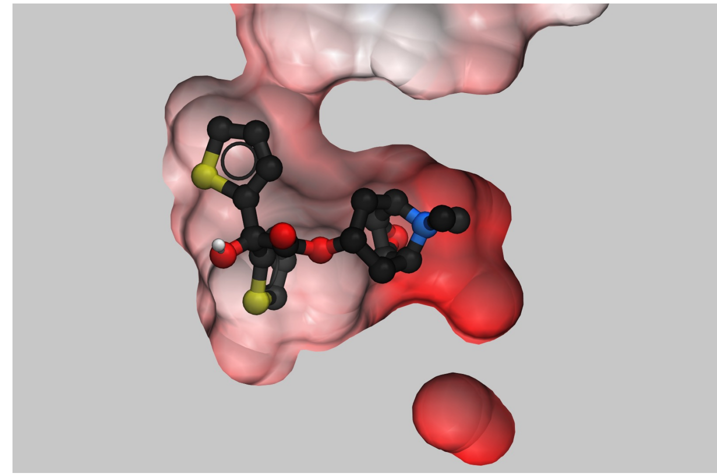
Muscarinic acetylcholine receptor 3 (ACM3) in complex with Tiotropium, PDB 4u15

close-up view of the binding site, alternative visualizations

"front view"

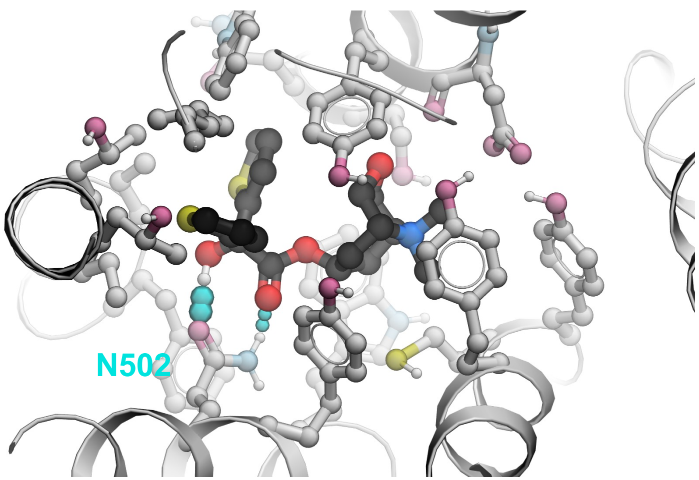


Drug binding pocket inside the target protein; shape complementarity and **Van der Waals interactions** are obvious. Also think **hydrophobic effect**.

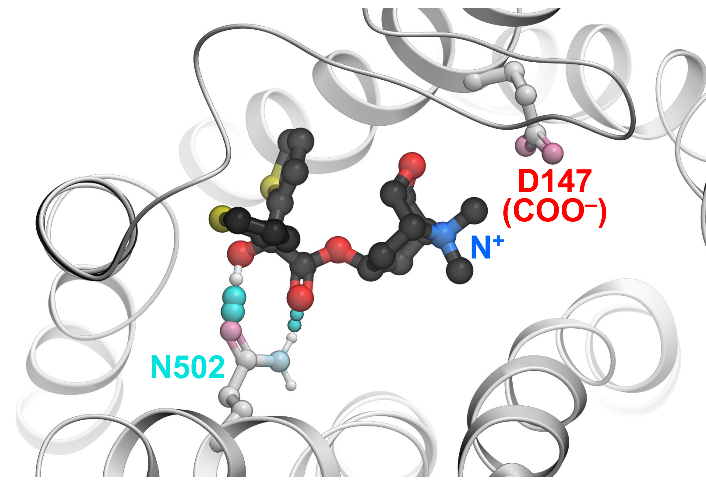


View highlights the **ionic interaction** between the negatively charged right side of the pocket (**red**) and the positively charged quaternary nitrogen in the drug (**blue**)

"top view"



Amino acid residues in the binding pocket are shown as sticks, two intermolecular **hydrogen bonds** with N502 in cyan



Same as left but simplified, only the hydrogen bonds and the ionic bond are shown

Electrostatic interaction energy

- ***Problem***: The electrostatic interaction energy of *two charges inside the protein* (assume dielectric constant of $\varepsilon = 10$) is **X**. What is the electrostatic interaction energy of the same charges at the same distance, but in water (assume $\varepsilon = 80$)?
  A. same
  B. 0.125X
  C. 8X
  D. 12.5X
  E. 64X
- ***Solution***:

  The interaction energy is inversely proportional to the dielectric constant of medium.

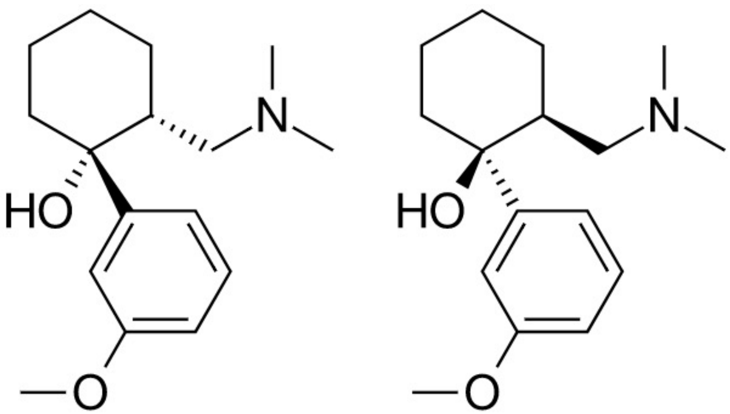
  8 times higher ε in water means 8 times weaker interaction energy

  The answer is **0.125X**, the 'absolute value' of interaction energy in water ,

  both attraction and rediction, is weaker because $U_{el} = C\, q_1\, q_2 /(\boldsymbol{\varepsilon}\, d)$

Electrostatic interaction energy

- ***Problem***: Tramadol, an opioid analgesic, has an amine group that is positively charged (**+1**) (at pH below 9.4). When tramadol is bound to its target μ-opioid receptor, this charged group is located within **3.5 Å** from the negatively charged carboxylate group of Asp147 side chain. Estimate the molar electrostatic energy between the amine and carboxylate assuming the dielectric constant of $\varepsilon = 15$ inside this protein.
  A. -6.3 kcal/mol
  B. 6.3 kcal/mol
  C. -174.3 kcal/mol
  D. 174.3 kcal/mol



(1*R*,2*R*)-tramadol (1*S*,2*S*)-tramadol

- ***Solution***:
  ❖ The amine and carboxylic acid carry charges of +1 and -1.
  ❖ Using Coulomb's formula, $E = 332\frac{(1)\times(-1)}{15\times 3.5}$ = -6.3 kcal/mol

Ion solvation energy, Born formula

- ***Problem***: Estimate the ion charge transfer energy when a mole of magnesium ions with formal charge of +2 and the Born radius of 1.73 Å is transferred *from water to a membrane* (dielectric constant of 2). C = 332 (kcal Å)/(mol eu^2).
  A. -187.1 kcal/mol
  B. -23.2 kcal/mol
  C. -470 cal/mol
  D. 23.2 kcal/mol
  E. 187.1 kcal/mol
  F. 470 cal/mol
- ***Solution***:
  - ❖ $E = C\frac{q^2}{2r_q} \times \left(\frac{1}{\varepsilon_{to}} - \frac{1}{\varepsilon_{from}}\right) = 332 \times \frac{2^2}{2 \times 1.73} \times \left(\frac{1}{2} - \frac{1}{80}\right)$
  - ❖ $E = 332 \times \frac{4}{3.46} \times 0.49$ = 187.1 kcal/mol, it is positive and unfavorable

Van der Waals interaction energy

- ***Problem***: Two cations with Van der Waals radii of 1.5 Å are placed next to each other so that the distance between their centers is 3.5 Å. Choose the most accurate statement:
  A. The electrostatic attraction energy exceeds the repulsion due to the Pauli exclusion principle
  B. The Van der Waals attraction energy exceeds electrostatic repulsion
  C. The repulsion due to the Pauli exclusion principle exceeds the electrostatic attraction energy
  D. The electrostatic repulsion energy exceeds the Van der Waals attraction

- ***Solution***:

  The VdW attraction energy does not exceed tens of cal/mol, $\approx -10 \div 50$ cal/mol

  The electrostatic repulsive energy depends on the dielectric constant ε…

  … but even assuming the strongest screening with $\varepsilon = 80$ (as in water):

  $E = 332\frac{(1)\times(1)}{80\times 3.5} =$ +1.18 kcal/mol = 1,180 cal/mol , therefore:

  The electrostatic repulsion energy far exceeds the Van der Waals attraction

Partial charges in peptides vs membrane crossing

Q: Can a cyclic amino acid peptide cross a membrane passively if it does not contain charged amino acids (no K,R,E, or D)?

A: No ; Yes ; Depends on residue composition, conformation, polar atom exposure, and LogP value

Answer: Even though the formal charges of the N- and C-termini are not present, the peptide still may contain many polar atoms in the peptide bonds and side chains of some amino acids, but they may be screened due to a conformation of the peptide. Therefore the 3rd answer is OK. 'No' is a simplified answer which is correct in most cases.