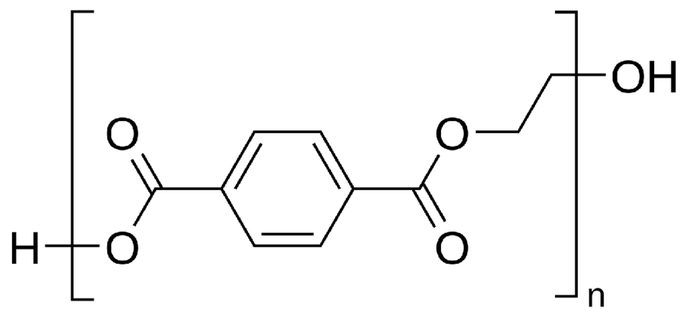
Module 1.1.1 Biological Macromolecules

- This mini-lecture will be about how biological macromolecules
  - are heteropolymers
  - are folded
  - have noncovalent interactions with many drugs
- At the end of this mini-lecture, you should be able to, at least at a very basic level, answer the following questions:
  - What are biological macromolecules made of?
  - What does it mean for a biological macromolecule to be folded?
  - How do most drugs interact with their targets?

- TODO: Introduce
  - energy landscape concepts
  - hydrophobicity as a driving force for folding
- TODO: Describe levels of protein stucture

Biological macromolecules are heteropolymers

- Polymers - made of smaller building blocks - monomers - that are covalently joined together
  - Homopolymers - monomers repeat, e.g. in a plastic
  - Heteropolymers - monomers do not exactly repeat
- Different types of macromolecules are made of different types of building blocks

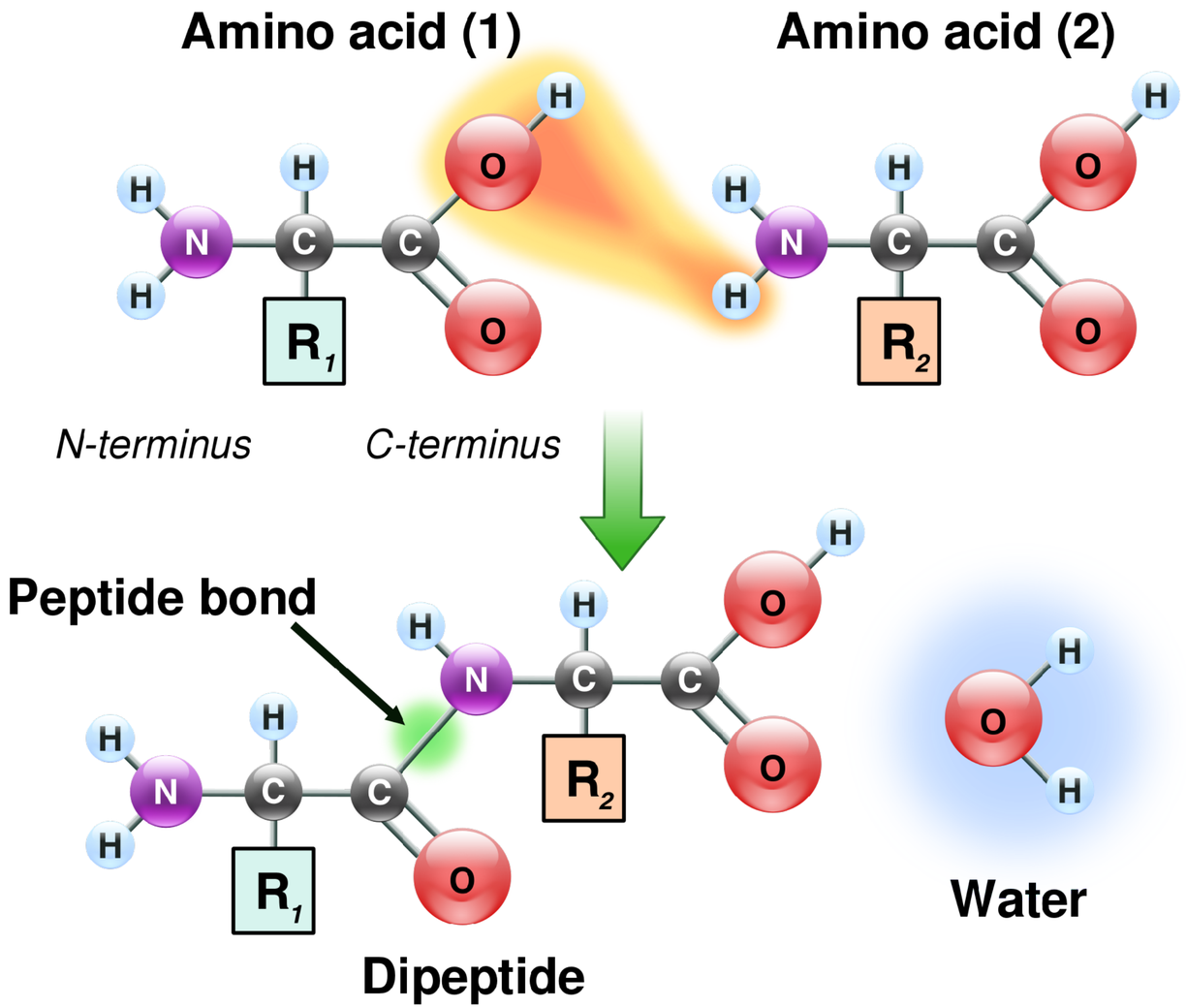


Polyethylene terephthalate, a homopolymer

https://commons.wikimedia.org/wiki/File:Polyethyleneterephthalate.svg

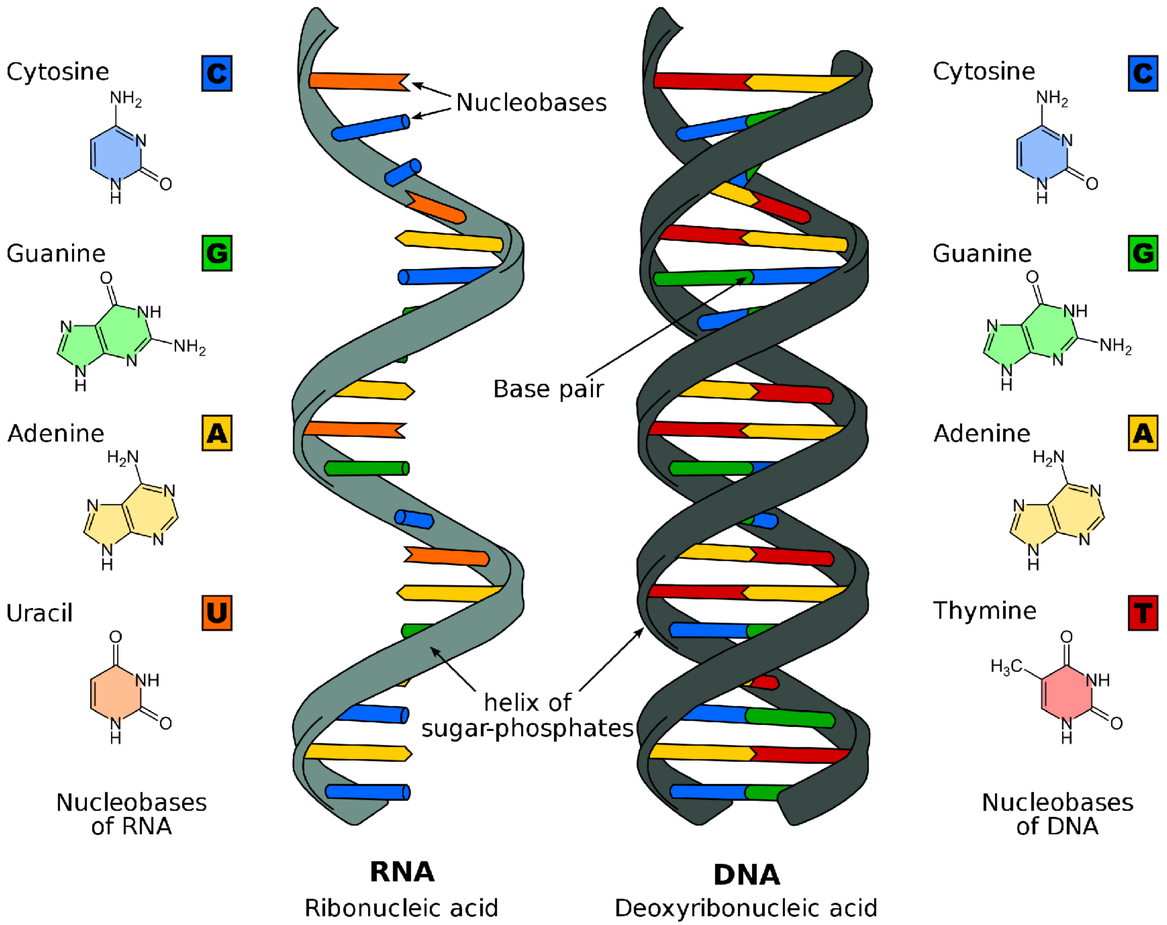
The monomers are small organic molecules

- Proteins are made of
  - 20 standard amino acids
  - linked by peptide bonds
  - modifications, e.g.
    - post-translational modification
    - disulfide bonds
    - cofactors and prosthetic groups



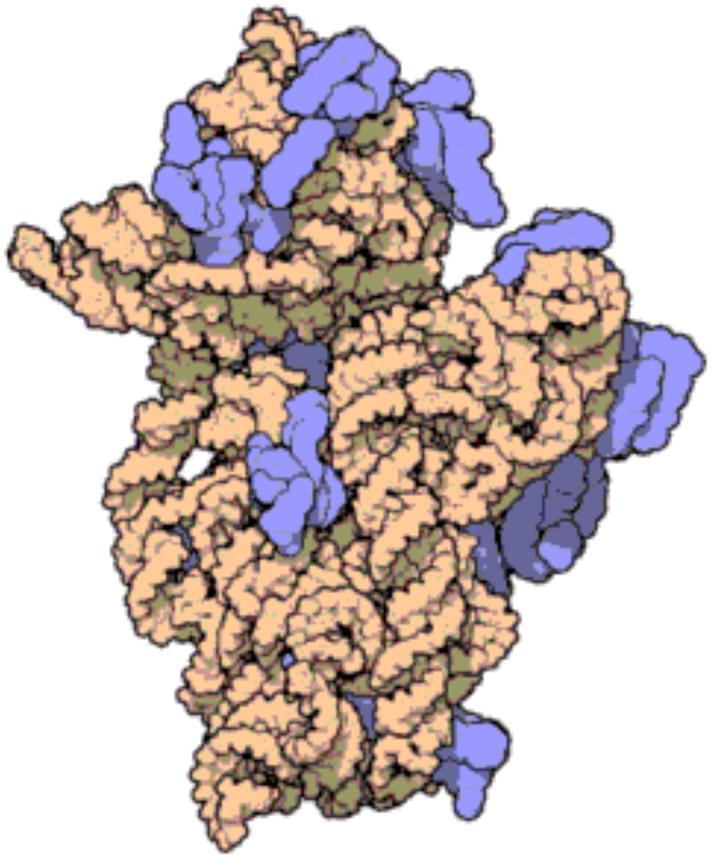
The monomers are small organic molecules

- DNA and RNA are made of nucleic acids
- DNA usually forms a double helix
- RNA is more flexible and can have complex structure



https://en.wikipedia.org/wiki/Nucleic_acid#/media/File:Difference_DNA_RNA-EN.svg

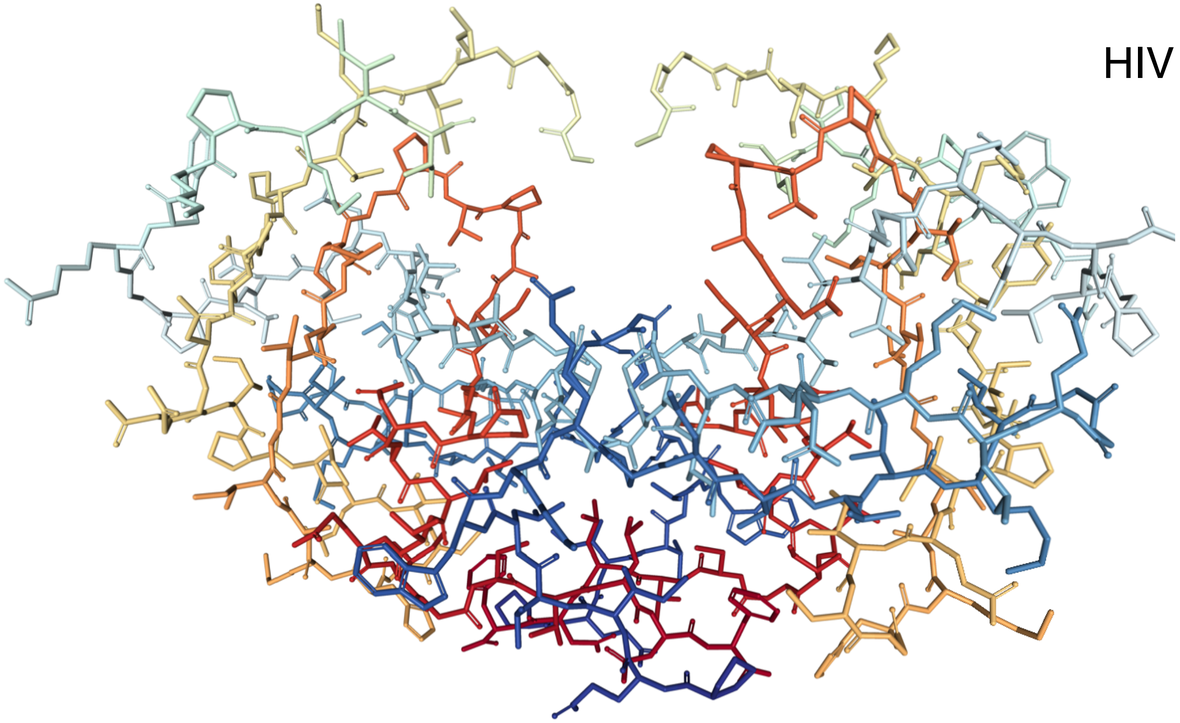
Macromolecules can be tightly complexed



30S subunit from a bacterial ribosome,
which is made of both protein and RNA

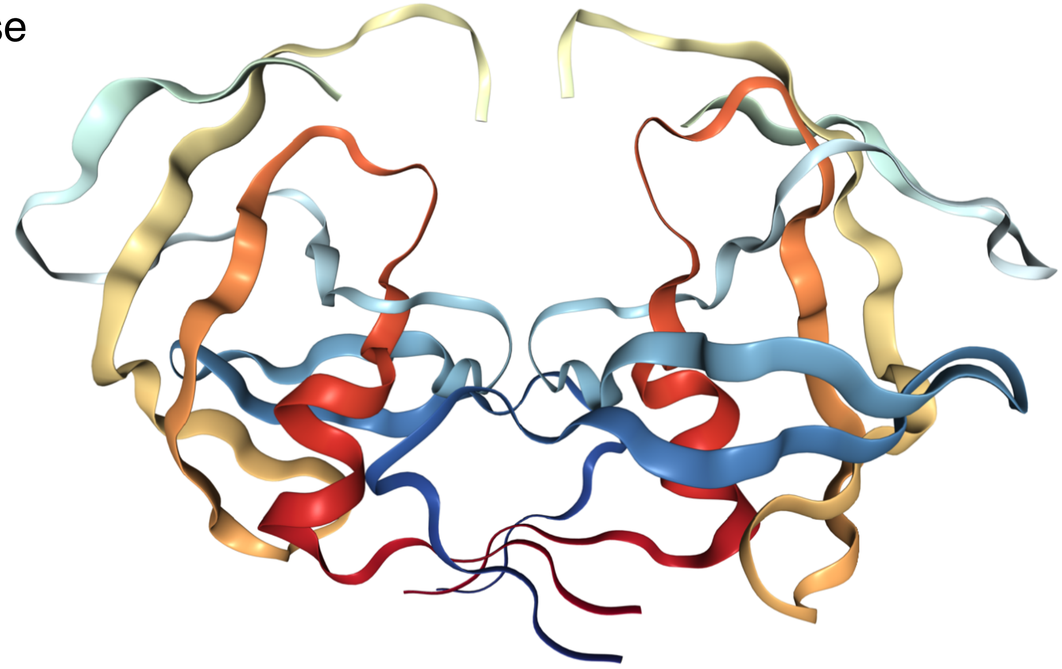
Many biological macromolecules are folded

HIV protease



“Licorice” view showing all heavy atoms

http://www.rcsb.org/3d-view/2HB2

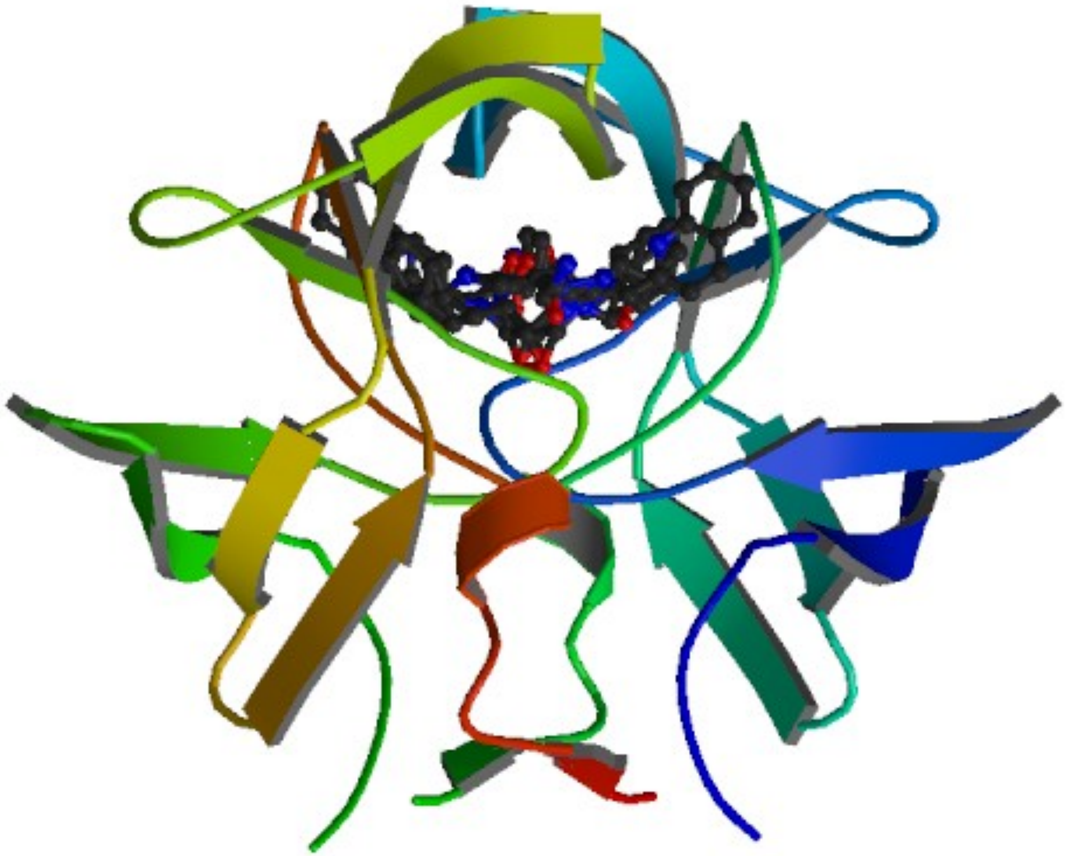


“Ribbon” view showing backbone, emphasizing α helices and β sheets

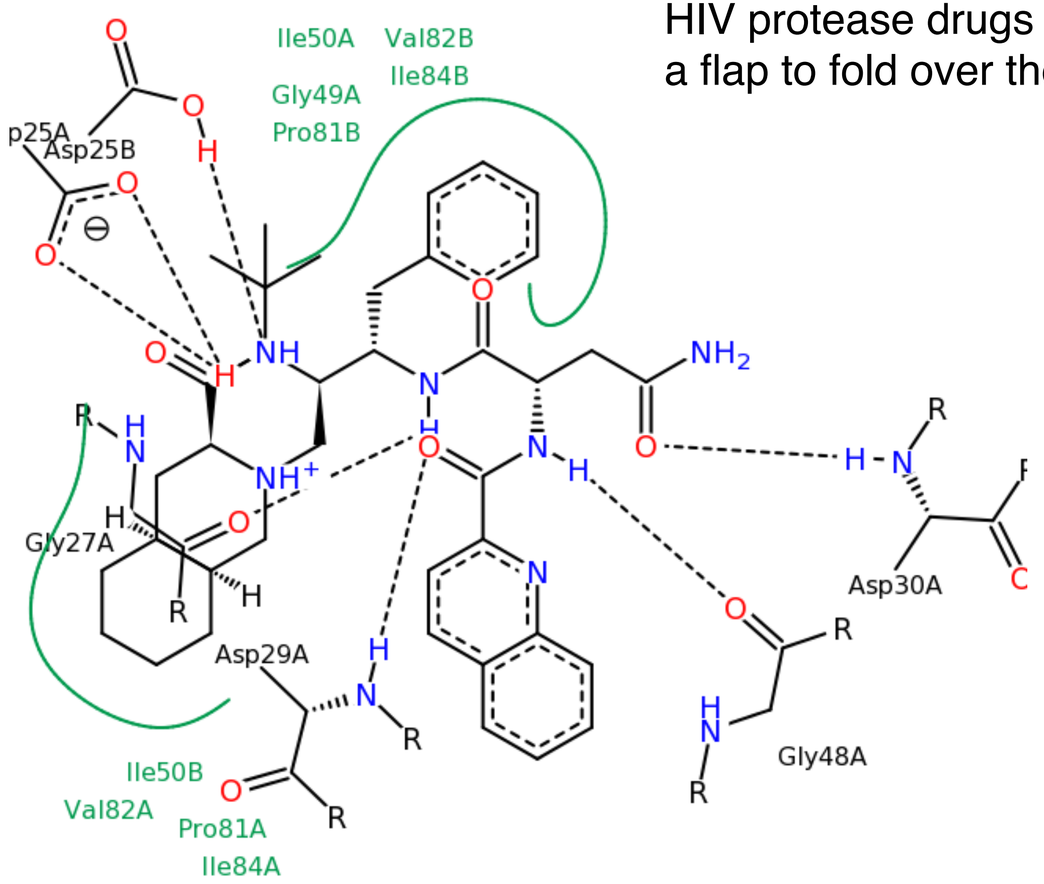
“Folded” does not mean that they are completely rigid, but they are *fairly* well-defined.

Most drugs are small molecules that specifically interact with the folded structures

HIV protease with saquinavir



HIV protease drugs often cause a flap to fold over the active site



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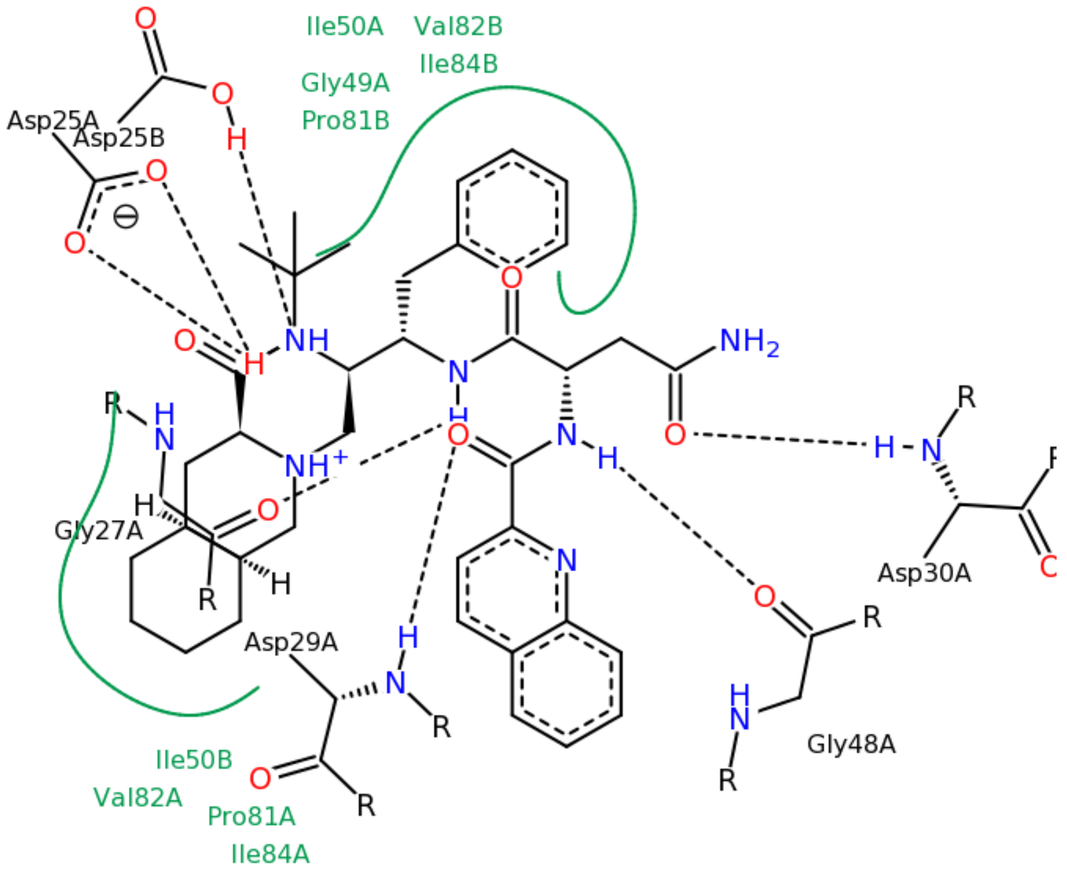
Most drug-target interactions are noncovalent

- The interactions driving drug binding are primarily
  - steric - van der Waals. atoms like to be close but not *too* close.
  - electrostatic - like charges repel and opposite charges attract. H bonding often treated as electrostatic.
- Water can play an important role.
- Some drugs (like penicillin) bind to their targets covalently.



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Review Questions

- What are biological macromolecules made of?
- What does it mean for a biological macromolecule to be folded?
- How do most drugs interact with their targets?

Misc

- A beautiful short video on “A basic introduction to drugs, drug targets, and molecular interactions”: https://www.youtube.com/watch?v=u49k72rUdyc