Heterocycles as Drugs and Components of Drug Structures


**Three and Four Membered Heterocycles with Nitrogen and Sulfur**

- The purpose of receptors, ion channels, and transporters is to accelerate the permeation of molecules across membranes
  - Heterocycles are recognized by receptors as *endogenous ligands* (meaning, naturally found in the body)
  - Ligand = substance that can bind to a receptor site
- The lipid bilayer is made up of chains of fatty acids with hydrophilic heads and lipophilic tails
- The purpose of 3- and 4- membered heterocycles is to have the right shape and electronic distribution to be recognized as a ligand by a receptor
  - They are usually small, but can bear substituents. It won’t cost so much entropy to go from solvent to a binding site because the molecule is already rigid
    - Entropy = degree of disorder. Easier thought of as the ability to go from thermal energy to mechanical work.

**Heterocycle Nomenclature**

<table>
<thead>
<tr>
<th>Element</th>
<th>oxygen</th>
<th>sulfur</th>
<th>selenium</th>
<th>nitrogen</th>
<th>phosphorous</th>
<th>silicon</th>
<th>boron</th>
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<tr>
<td>Valence</td>
<td>II</td>
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<td>II</td>
<td>III</td>
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<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>Prefix</td>
<td>Oxa</td>
<td>Thia</td>
<td>Selena</td>
<td>Aza</td>
<td>Phospha</td>
<td>Sila</td>
<td>Bora</td>
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<table>
<thead>
<tr>
<th>Ring Size</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<tr>
<td>Suffix</td>
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<tr>
<td>Unsaturated</td>
<td>i</td>
<td>t</td>
<td>e</td>
<td>o</td>
<td>i</td>
<td>e</td>
<td>o</td>
<td>c</td>
</tr>
<tr>
<td>Saturated</td>
<td>rane</td>
<td>etane</td>
<td>elane</td>
<td>inane</td>
<td>epine</td>
<td>ocane</td>
<td>onane</td>
<td>ecane</td>
</tr>
</tbody>
</table>

- IF the ring has nitrogen use *iridine, eitidine, olidine*, etc.
- For numbering, always prioritize the *heteroatom* (N, S, O, etc). If more than one heteroatom, the *higher number goes to the higher atomic number*

*Saturated means no double bonds. Unsaturated means one or more double bonds*
Ex) Heterocycle naming

\[
\begin{array}{c}
\text{aziridine} \\
\text{thiirane} \\
\text{azetidine} \\
\text{thietane} \\
1,3\text{-dithietane}
\end{array}
\]

*At least memorize the abbreviations for nitrogen, sulfur, and oxygen

Ways to help you remember

- Big OL high 5 ! (for 5-membered ring being -ol)
- QuartET is 4 (for 4-membered ring being -et)

**B-Lactams – Memorize names**

B-Lactams are a class of antibiotics that target cell wall synthesis. DD transpeptidase is an enzyme that crosslinks peptidoglycan, a critical part of the bacterial cell wall. The B-lactam resembles the D-alanine D-alanine terminal of the peptidoglycan strand, so it acts as a ligand for DD transpeptidase and doesn’t allow it to finish synthesizing the peptidoglycan strand. A covalent bond is made, which makes this reaction irreversible.
Ways to help you remember

- Penam is the OG. 5-membered ring with sulfur in it, think Penam. Pentagon = 5. One way to remember it
- When you lose the sulfur and its replaced by a carbon, you get the CARBapenam. Almost the OG, but w/out the sulfur
- When you lose the sulfur and its replaced by an oxygen, you get OXapenam.
- Once you add a double bond into the ring, the Penam becomes Penem
  - Double bond always replaces “a” with an “e”
- When the 5-membered ring becomes a 6-membered ring, you get a Cephem. Ceph sounds like 6. One way to remember it
- Clavams and monobactams are the oddballs. The big hint for clavam is the double bond that sticks out of the ring. It sort of looks like a claw = clavam. Sound similar!
  - Monobactams are only one ring and the smallest. Mono = one. Mono sounds like mini, which is small.
  - Real-world example: Augmentin (Amoxicillin-Clavulanate K+)

  ![Clavulanic Acid]

  Some bacteria can become resistant to penicillin-based antibiotics, like amoxicillin. They do this by making an enzyme called β-lactamase.
  Clavulanic acid acts as a β-lactamase inhibitor, and therefore helps make amoxicillin effective again against resistant bacterial

- Reactivity of B-lactams
  - The higher the height of the ring, the more reactive

  ![double bond]

  The double bond requires a planar structure. However, a 4-membered ring is forced into 90° which distorts the structure. This raises the height of the ring and destabilizes the double bond. Since the double bonded oxygen is what is cleaved in the reaction, the higher the ring is the more destabilized the double bond is and the easier it is to cleave it = MORE REACTIVE
- Order of reactivity based on height:
  Clavams > Carbapenems > Penams > Cephams > Monobactams

  * Note: when the nitrogen contributes more of an sp\(^2\) hybridization, it has partial double bond character and the ring is flattened = less reactive. When the nitrogen contributes more an sp\(^3\) hybridization, it has more pyramidal character and the ring is heightened = more reactive

  - When too reactive, can get quickly metabolized. Medium reactivity is better. **Low reactivity B-lactams are used to inhibit B-lactamases**, which are enzymes the bacteria can sometimes make to resist B-lactams and “kill” the antibiotics

- There aren’t many drugs with 3-membered rings, some chemotherapy
  - 3-membered rings have very distorted angles and so are very reactive

- The 3-membered and 4-membered nitrogen and sulfur containing heterocycles are very rigid. Saturated (no double bonds) rings are not flat → better solubility
  - Very reactive and can have off-target effects

**Five Membered Heterocycles with Nitrogen and Sulfur**

*Same naming as above. Here are some examples of 5-membered rings:

- The ones circled are pretty commonly seen, so it would be a good idea to be able to recognize and name them. Knowing how to name the rings in a general sense is good to know too.

- 5-membered heterocycles with nitrogen and sulfur are found in many drugs
- Saturated 5-membered rings act no different than acyclic compounds
- Unsaturated 5-membered rings are usually aromatic
  - Huchel’s Rule for aromaticity: Must have \(4n + 2 = \pi\) electrons
• Nitrogen containing aromatic heterocycles can undergo resonance
• Sulfur containing aromatic heterocycles don’t undergo resonance
  o Sulfur is more electronegative than nitrogen and is also larger. It does not like to share electrons
• Nitrogen containing aromatic heterocycles are weak bases with strong conjugate acids
• Sulfur containing aromatic heterocycles are neither acidic or basic
  o They are more hydrophobic than nitrogen containing heterocycles
• 5-membered aromatic heterocycles are flat
• Saturated 5-membered heterocycles are usually puckered
• Different substituents can change the geometry and electronics of the molecule
• The higher fraction of carbons have sp³ character, the more soluble the drug is

*sp³ vs. sp² character: These are ways of categorizing how the electrons fill the orbitals on an atom. For simplicity purposes, the easiest way I think of sp³ is as a tetrahedral shape that is not flat. I think of sp² as a trigonal planar that is flat.

* Really easy (kind of incorrect) way to think about it is double bond carbon = sp² and single bond carbon = sp³
• The higher the fraction of sp³ carbons (Fsp³), the more soluble the drug is (higher logS)
This is because the more flat a molecule is the more stacking can occur (aromatic stacking = density of packing). This makes it harder to interact with water molecules and for the molecule to dissolve

### Partition Coefficient: LogP

\[
P = \frac{[\text{drug}]_{\text{octanol}}}{[\text{drug}]_{\text{water}}}
\]

Higher logP means the drug is more lipophilic

pH must be at a value where the drug is unionized to use this equation

### Distribution Coefficient: LogD

\[
P = \frac{[\text{drug}]_{\text{ionized octanol}} + [\text{drug}]_{\text{ionized octanol}}}{[\text{drug}]_{\text{ionized aq}} + [\text{drug}]_{\text{ionized aq}}}
\]

LogD takes into account ionization state of the drug

With higher pH, the drug becomes ionized and moves out of the octanol phase into the aqueous phase

The higher pH, the lower logD value. Lower logD value means more hydrophilic drug

- More off target reactivity with aromatic 5-membered heterocyclic rings than the saturated rings
- Remember, the less flat the molecule is the more reactive it is
  - More aromatic rings = more flat
Six Membered Heterocycles with Nitrogen and Sulfur

- 6-membered heterocycles are in many drugs
- Saturated 6-membered rings act no different than acyclic compounds
- Unsaturated 6-membered rings are usually aromatic

- Nitrogen containing aromatic heterocycles are weak bases with strong conjugate acids
- Sulfur containing aromatic heterocycles are neither acidic or basic
  - They are more hydrophobic than nitrogen containing heterocycles
- 6-membered aromatic heterocycles are flat
- 6-membered saturated heterocycles have same conformations as hexane (chair conformation)

TPSA – topological polar surface area
- Surface area of all the polar parts of a molecule
- The higher the TPSA, the more polar the molecule is and the less likely it will cross cell membranes
  - >140 angstrom, poor cell membrane permeability
  - >90, poor blood brain barrier permeability

HSA – hydrophobic surface area
- Surface area of all the hydrophobic parts of a molecule
• vdW_SA – van der Waals surface area
• SASA – solvent accessible surface area
  o surface area of a molecule accessible to a solvent
• Density of packing = takes more energy to disrupt aromatic ring stacking and allow them to interact with water molecules to dissolve.
• CNS drugs overall are more lipophilic than non-CNS drugs
  o Best CNS drugs are smaller, minimally flexible, minimally hydrophobic, and neutral or basic (NOT acidic)
  o So if you see a molecule and it has lots of hydrogen bonding/donating, heavier molecular wt., higher PSA, it is probably a non-CNS drug vs CNS drug
• 6-membered nitrogen (but not sulfur) containing heterocycles are widely used in making drugs
  o Tend to be less reactive than 5-membered nitrogen containing heterocycles

Seven Membered Heterocycles with Nitrogen and Sulfur

• 7-membered rings are a little more bent, so the electron density can’t be evenly spaced out and the aromaticity decreases.
  o They ARE NOT PLANAR
  o Unsaturated 7-membered heterocycles are usually anti-aromatic
• No drugs have 7-membered sulfur containing saturated heterocycles because they can’t be metabolized

Imino groups in 7-membered heterocycles are basic. Conjugate acids have pKa between 2-4.
Ligand more likely to bind with enzyme if the delta G (change in free energy) goes from higher to lower. When the ligand is dissociated, the total delta G is a combination of the change in free energy of the enzyme being hydrated with water, the ligand being hydrated with water, and the water associating with both the enzyme and ligand. When the ligand binds to the enzyme, the total delta G is a combination of the change in free energy of the ligand bound to the enzyme plus the change in free energy of water bound to another water molecule.

- **Too many flexible bonds gives poor solubility b/c too great of a loss of entropy when the ligand binds to a receptor**

\[
\Delta G = \Delta H - T\Delta S
\]

- \(\Delta G\) = Gibbs free energy
- \(\Delta H\) = enthalpy
- \(\Delta S\) = entropy

Loss of entropy (or number of flexible bonds) is a penalty for the ligand binding to the enzyme. This must be compensated for by an increase in enthalpy.

The binding site is like a cage – rotatable bonds are not rotatable anymore.

*Entropy = amount of randomness in a reaction
*Enthalpy = amount of heat energy in a reaction

**Number of Flexible Bonds**

\[
\text{no. of rb} = (\text{no. of nonterminal single bonds}) + \sum_i (n_i - 4)
\]

- \(n_i\) = no. of bonds in ring \(i\)
- \(i\) - must contain at least two atoms in sp\(^3\) hybridization
Therapeutic Heterocyclic Natural Products Derived from Plants

- We can make drugs that mimic peptides and the way natural ligands interact with receptors
- Split into two groups
  - Non-mammalian natural products (NMNPs)
  - Mammalian biochemical natural products (BCNPs)
- Privileged scaffolds – common building blocks used in making drugs that interact with common protein motifs (alpha-helix, beta-turn, gamma-turn, beta-strand)
  - Category 1: found in drugs and natural products
  - Category 2: found primarily in drugs
  - 80% of drugs have the 37 most common privileged scaffolds – they interact with multiple receptors built from similar building blocks
  - Many natural products derived from plants contain privileged scaffolds

I would be familiar with the purpose of privileged scaffolds but wouldn’t necessarily memorize the 37 most common ones

- Lipinski’s Rule of 5 – gives better idea on if a drug will be soluble/absorbable or not
  1. MW > 500 (>35 heavy atoms)
  2. logP>5
  3. >5 H-bond donors (OH + NH groups)
  4. >10 H-bond acceptors (O + N atoms)
  5. Exceptions (with active transporters) – vitamins, antibiotics, antifungals, cardiac glycosides
- If a compound has two or more of these, probably won’t be absorbed well
- Transporters
- Uptake transporters – help absorption of drugs in intestines, in hepatocytes for biliary/metabolic clearance, and help distribution into organs
  - Oligopeptide transporters (PEPT1, PEPT2)
  - Organic anion transporters (OATP1, OAT2, OAT3)
  - Organic cation transporters (OCT1)
  - Bile acid transporters (NTCP)
  - Nucleoside transporters
  - Vitamin transporters
  - Glucose transporters (GLUT1)
- Efflux Transporters – prevent toxic compounds from building up, efflux them back out. Stop distribution on drugs into certain organs like brain
  - P-glycoprotein (Pgp, MDR1)
  - Breast cancer resistance protein (BCRP)
- Drug-drug interactions can happen with drugs that compete for certain transporters
  - If one drug has a higher affinity for the p-glycoprotein, then the other drug won’t be effluxed out as much and will build up in the body
- Ex.) Substrates for Oligopeptide transporters (PEPT1, PEPT2) are dipeptides and tripeptides only. If a drug has poor absorption, can add an amino acid appendage so it will be a substrate for PEPT1/2 and be absorbed better
- Ex.) Large neutral amino acid transporter (LAT1) transports amino acids and certain drugs (L-Dopa) across the apical membrane on the epithelial cells of the blood brain barrier (BBB)
- Ex.) Monocarboxylic acid transporter (MCT1) on the epithelial cells of the BBB and the intestines transports salicylic acid and certain statin drugs
- Ex.) Organic anion transporter polypeptide (OATP1) transports antibiotics, NSAIDs, antivirals, AZT, acyclovir, etc into the renal tubule cells for drug excretion

For transporters, know the examples given in lecture and what types of drugs are substrates for which transporters. Really only focus on the specific examples given in lecture. Drug transporters are going to be seen again and again and again in your classes, so the sooner you get familiar with them, the better.
Drugs-Receptor Interactions

- Better definitions of enthalpy and entropy
  - **Enthalpy**: a thermodynamic quantity equivalent to the total heat energy in a system = internal energy of system + (pressure)*(volume)
  - **Entropy**: a thermodynamic quantity expressing unavailability of a system’s thermal energy to do mechanical work = degree of disorder

\[
\Delta G = \Delta H - T\Delta S
\]

- \(\Delta G\) – Gibbs free energy
- \(\Delta H\) – enthalpy
- \(\Delta S\) – entropy

- This diagram is showing what happens when a drug interacts with a receptor and how the Gibb’s free energy changes.
  - \(\Delta G_1\) represents the change in free energy when a ligand binds to protein without water interacting
  - \(\Delta G_2\) represents the change in free energy when water molecules bind to free ligand and free receptor
  - \(\Delta G_4\) represents the change in free energy when water molecules bind to ligand already bound to receptor. The ligand bound to receptor has an overall different geometry than the free ligand and free receptor, so the number of water molecules interacting will be different as well (hence, \((H_2O)_2\))
  - \(\Delta G_3\) represents the change in free energy when ligand bound to water binds to receptor bound to water.

- The overall change in Gibb’s free energy should be negative for the reaction to be thermodynamically favorable
• **Receptor-ligand binding process**: Water molecules must be removed from the receptor site before the drug can bind. Once the drug binds, water molecules can re-solvate the ligand with the receptor but there will be less water molecules this time
  - Expressed by $K_{on}$ (association constant) vs. $K_{off}$ (dissociation constant)
  - $K_d = K_{off}/K_{on}$ therefore, lower $K_d$ means it is more likely the ligand won’t stay bound to the receptor (see constants explained later in this study guide)

• **Enzyme Inhibition**
  - **Non-covalent** – when the ligand binds to the enzyme, no chemical bond is made
  - **Covalent** – when the ligand binds to the enzyme, a covalent chemical bond is made
    - Can be reversible or irreversible. Many antibiotics act irreversibly

• **The Hydrophobic Effect** – when water molecules, that are normally in a high energy state of random hydrogen bonding, surround a hydrophobic molecule by forming structures spheres around the molecule
  - Entropy decreases when a hydrophobic molecule is introduced, so when the molecule “hides” in a hydrophobic pocket, this decrease in entropy is minimized
  - Don’t want to decrease entropy because that would increase $\Delta G$ which is thermodynamically NOT favored
  - **Main driving force for ligand-receptor binding**
    - If a ligand comes in and removes the structured water from the hydrophobic pocket, the water can randomly hydrogen bind again, entropy increases, and the reaction is thermodynamically favored

**Explaining all the constants**

$K_{on}$ = association constant ($s^{-1}$). Represents amount of time ligand is associated with receptor

*The higher* this value is, the more likely that the ligand will be bound to the receptor [RL]

$K_{off}$ = dissociation constant ($s^{-1}$). Represents amount of time ligand is dissociated from receptor

*The lower* this value is, the more likely that the ligand will be bound to the receptor [RL]

$K_d$ = dissociation constant (more accurate) = $K_{off}/K_{on}$ = $[R][L]/[RL]$ (unit = M). Inversely represents the amount of ligand that is bound to receptor

*Lower* $K_d$ means ligand is more strongly bound to the receptor (*higher affinity* between ligand and receptor)
$K_i =$ inhibition constant. Almost equivalent to $K_D$. Represents the concentration required to produce half maximum inhibition

**Lower** $K_i$ means less ligand is required to cause inhibition of the enzyme (it’s easier for the ligand to bind to the receptor)

$\Delta G = -RT\ln(K_i)$

This is a little confusing. But the way I think of it is, the lower $K_i$ the higher the $\Delta G$ which means it is less likely the ligand will dissociate from the receptor

*Remember, lower the $\Delta G$ the more favorable the reaction is

- Know general changes in energy when certain groups are bound in the pocket
  - 1-2 hydrogen bonds gives 1 order in $K_i$ (ex. Going from $K_i = 100$ nM to $K_i = 10$ nM)
  - Addition of a methyl group in the n-binding pocket gives a 10-fold increase in potency (ex. Going from $K_i = 1$ nM to $K_i = 100$ pM)
  - Takes 1-2 kcal/mol of energy to release structural water

$$\text{μM} = 10^{-6}$$

$$\text{nM} = 10^{-9}$$

$$10\text{nM} = 10^{-8}$$

$$\text{pM} = 10^{-12}$$

$$10\text{pM} = 10^{-11}$$

$$100\text{pM} = 10^{-10}$$

So an increase in potency by 10-fold goes from 10$^{-9}$ to 10$^{-10}$

(remember, ↑ potency means $K_i$ ↓)
• **Binding affinity** – very much based on the distance between the molecules

  - Short-range repulsion \( (\sim 1/r^{12} - 1/r^{10}) \)
  - Electrostatic interactions:
    - Coulombic
      - charge-charge \( (\sim 1/r) \)
      - Charge-dipole \( (\sim 1/r^2) \)
      - Charge-induced dipole \( (\sim 1/r^4) \)
  - Nonelectrostatic interactions:
    - Van der Waals (Lennard-Jones potential) \( 1/r^{12} - 1/r^6 \)
      - dipole-induced dipole \( (\sim 1/r^6) \)
      - induced dipole-induced dipole \( (\sim 1/r^6) \)
      - dipole-dipole \( (\sim 1/r^6) \)
  - Hydrogen bonds (dipole – dipole interaction) \( (\sim 1/r^3) \)
  - “Hydrophobic” effect
  - Dielectric problem and solvation
  - Potential surface (interactions between the ensemble of atoms)
  - salt bridges

  o **Electrostatic interactions** can occur at a **further distance** (a distance of \( 1/r \) is much greater than a distance of \( 1/r^{10} \))
    - Coulombic interactions = charge-charge interactions. Do not require H-bonding, but can have some with a salt bridge
    - Salt bridge = H-bond + charge + charge
    - Dipole moments like to minimize the overall dipole moment
  o **Short range repulsions** can only occur at a **very small distance** between molecules
  o Nonelectrostatic interactions can occur at a medium distance between molecules
    - Van der Waals
      - Debye = dipole – induced dipole
      - London dispersion forces = induced dipole – induced dipole
  o Dielectric Problem/Shielding – essentially when you have two molecules with opposite charges that are attracting one another, they can be “shielded” by water molecules that dissipate the charge
    - The coulombic interactions become weaker
  o Hydrogen bonds tend to occur in a coplanar direction
    - Usually have to have -N or -O for H-bonding but can have weaker H-bonding with halogens
• **Cooperativity** – all interactions between molecules working together
  
  o “If both feet are in the mud, you can’t jump. It’s much easier to break out when only one foot is in the mud. Two holds you in better than one”
  
  o The more small interactions you have, the harder it is for molecules to become dissociated from each other = lower $K_{off}$
  
  o **Positive cooperativity** = binding energy associated with multiple interactions working together is larger than the sum of their individual binding free energies
    - Enthalpically favored but not entropically favored