Physicochemical Properties of Drugs and Drug Disposition

**Stereochemistry (Double the trouble…. or…… double the fun?)**

The vast majority of drugs contain at least one stereo-center or other type of site of asymmetry. All biological receptors and enzymes have complex 3 dimensional structures and are inherently asymmetric and important pharmacological differences between drug isomers is expected. When we study the ADME and therapeutic properties of individual drug isomers we find that they behave differently. Thus when we administer a mixture of two stereoisomers we are, in effect, giving a combination of two separate drugs with overlapping properties. As a result when stereoisomers of a drug are given separately the biological response, side effects, protein binding and pharmacokinetics of each isomer is different, sometime strikingly so. Many drugs currently in use are given as mixtures of structural or optical isomers. However the use of a single isomer in drug development is strongly encouraged by the FDA today. In fact, in some cases the therapeutics and safety of old drugs that were given as mixtures of stereoisomers has been improved substantially using single isomers and patent protection extended. The FDA now requires that the properties of stereoisomers of drugs that are intended to be given as stereoisomeric mixtures be determined separately whenever possible.

**FIGURE 2.18** Optical isomers. Only in compound 6 do the functional groups A, B, and C align with the corresponding sites of binding on the asymmetric surface.

**FIGURE 2.19** Drug receptor interaction of $R^\text{-}(\cdot)$-epinephrine, $S^\text{(+)}$-epinephrine, and $N$-methyldopamine.
Note on the use of the terms Stereospecific vs Stereoselective:

When one isomer has a particular property and the other isomer does not we use the term stereospecific to denote the property (e.g. stereospecific metabolism of the (S) enantiomer by CYP2C9).

When the isomers have a common biological property but different magnitude of effect we use the term stereoselective (e.g. stereoselective binding of the (R) isomer by the serotonin reuptake transporter). This indicates that the (S)- and (R) enantiomer bind to the transporter but that the (R) enantiomer is more potent.

1. Chiral Centers—Enantiomers: Most chiral centers in drug and biological structures occur at tetrahedral sp³ carbon atoms where 4 bonds are formed with distinct chemical groups. These groups can be arranged in two ways that are “mirror images” of each other and are not superimposable. When there is only one chiral center in the molecule the two possible isomers are called enantiomers. Sometimes stereocenters can invert and eventually racemize. A racemate or racemic mixture is a 50:50 mixture of two isomers.

Note: You should be able to identify chiral centers in a molecule, assign chemical group priority and deduce stereochemical identifiers (S left) and R (right) in a structure like alanine shown below using the Cahn-Ingold-Prelog rules.


1. Compare the atomic number (Z) of the atoms directly attached to the stereocenter; the group having the atom of higher atomic number receives higher priority.

2. If there is a tie, we must consider the atoms at distance 2 from the stereocenter—as a list is made for each group of the atoms bonded to the one directly attached to the stereocenter. Each list is arranged in order of decreasing atomic number. Then the lists are compared atom by atom; at the earliest difference, the group containing the atom of higher atomic number receives higher priority.

3. If there is still a tie, each atom in each of the two lists is replaced with a sub-list of the other atoms bonded to it (at distance 3 from the stereocenter), the sub-lists are arranged in decreasing order of atomic number, and the entire structure is again compared atom by atom. This process is repeated, each time with atoms one bond farther from the stereocenter, until the tie is broken.

4. If an atom A is double-bonded to an atom B, A is treated as being singly bonded to two atoms: B and a ghost atom that has the same atomic number as B but is not attached to anything except A. In turn, when B is replaced with a list of attached atoms, A itself is excluded in accordance with the general principle of not doubling back along a bond that has just been followed, but a ghost atom for A is included so that the double bond is properly represented from both ends.
Below for alanine: \(-\text{NH}_3^+ = 1\); \(-\text{COO}^- = 2\); \(\text{CH}_3 = 3\) and the hydrogen (not shown) is 4 (lowest priority and directed back out of the plane).

- The sequence 1,2,3 clockwise is R.
- The sequence 1,2,3 counterclockwise is S.

Many older drugs still in use are given as racemic mixtures and we see differences in stereoselectivity for pharmacological and ADME properties.

**Example:** Warfarin (Coumadin) anticoagulant (pKa = 5; Log P = 3.5)

1. Warfarin is given as the racemate (50:50 mixture of (R) and (S)). It has a very low therapeutic index and individualized dosing with monitoring (INR) is required. PK and pharmacodynamics are very sensitive to drug-drug interactions with CYP2C9 inhibitors and inducers. The following is observed

2. **Stereoselective** (not stereospecific) inhibition Vitamin K epoxide reductase (favors (S))

3. The (S) isomer (CYP2C9 substrate) is 3 fold more potent in vivo than the (R) enantiomer based on a similar dose so potency is **stereoselective** for (S).

4. The (S) isomer is a substrate for CYP2C9 (fm<sub>2C9</sub> = 0.85). The (R) enantiomer is not a substrate for CYP2C9. Metabolism by CYP2C9 is **stereospecific**

4. Stereoselective plasma half-life: (S) is 24 hours; (R) is 45 hours as well as stereoselective protein binding

5. Development of both single isomers was attempted and **failed to improve outcomes**.
Example: Fluoxetine (Antidepressant; Prozac; serotonin reuptake inhibitor (SSRI) (pKa = 9; Log P = 3.5)

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{CF_3} & \quad \text{N} \\
\end{align*}
\]

1. Note the use of a wavy bond to indicate chiral center that is not defined (fairly common).

2. Only SSRI approved for use during pregnancy.

3. N-demethylated metabolite concentrations of both isomers can exceed parent concentrations during multiple dosing due to extremely long half-lives. The metabolites are pharmacologically active and stereoselectively inhibit the metabolism of the parent isomers so it is pretty complicated. Parent and metabolites are potent inhibitors of CYP2D6 and CYP2C19. Parent and metabolites accumulate with repeat dosing.

4. Considerable efforts to develop and market the enantiomers by Lilly failed.

Ofloxacin (fluoroquinolone antibiotic; topoisomerase inhibitor)

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{OH} & \quad \text{CON} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

1. (S) enantiomer (Levofloxacin (Levaquin)) is much more active than the (R) enantiomer and is marketed as a separate drug. Quinolones are infamous for causing spontaneous tendon ruptures. There are two Black box warnings on Levofloxacin. (Levaquin).

2. Note that there are multiple ionizable groups and that the molecule is drawn as the neutral species. It is a zwitterionic (think about it). However bioavailability is good (>95%).

Omeprazole (Prilosec); Irreversible proton pump inhibitor (PPI) generic
1. Note the unusual chiral center at sulphur which is why I chose it. The lowest priority group here is the lone electron pair on sulphur. This center does no invert so the drug does not undergo racemization. All of the PPI’s (Lansoprazole for instance) have this structural feature and are chiral.

2. Metabolism and clearance is by CYP2C19 which is a polymorphic enzyme. Evidence suggests that administration of (S) omeprazole (Nexium) provides better AUC and less individual variability. For other PPI’s it is the (R) enantiomer. So there is some PK stereoselectivity that is not preserved among the class of drugs.

3. Overall controversial whether Nexium was worth the extra cost.

4. The PPI’s are unstable to the acid pH in the stomach, are formulated for release in the intestine and are irreversible inhibitors of the proton pump.

**Ibuprofen** (NSAIDs inhibit cyclo-oxygenase enzyme that produces the prostaglandins)

1. The (S) enantiomer is the active form and is a stereospecific inhibitor of the enzyme

2. Efforts to develop the single enantiomer to improve potency were discontinued when it was realized that an acyl-CoA racemase enzyme converts the (R)-enantiomer to the (S). Other NSAIDs like ketoprofen also undergo this type of racemization (also called epimerization). In the mechanism of racemization the hydrogen is removed and replaced.
Multiple Chiral Centers (Diastereoisomers)

A large number of drugs have multiple chiral centers. The total number of isomers possible is $2^n$ where $n$ is the number of chiral centers present in the molecule.

1. Each isomer has one enantiomer (see below) where the stereochemistry at each chiral center is inverted (R,R -> S,S). (These compound have identical properties in an achiral environment but act differently as drugs due to the 3 dimensional structures of enzymes and receptors. (-ephedrine and + ephedrine) below are enantiomers because both stereocenters are inverted. Note: the benzylic carbon in (-)-ephedrine is (R) and the other stercenter is (S). Quickly write in the sterechemistry for the other isomers.

2. The remaining isomers are diastereoisomers so (-) ephedrine has two diastereoisomers which are denoted a pseudo. These various isomers differ in chemical properties as well as in biological activities. Wikipedia entries for ephedrine and pseudoephedrine are interesting.

![Diagram of ephedrine and pseudoephedrine](image)

**FIGURE 2.21** Relationship between the diastereomers of ephedrine and pseudoephedrine.

Multiple stereocenters are common particularly in steroids and drugs that bind to enzyme or receptors of peptides. Often "natural" amino acid stereochemistry will be required.

Drugs derived from natural products usually have multiple chiral centers but only a single isomer is found.
Here are a couple of examples to go through.

Perindopril (an ACE inhibitor)
- 5 stereocenters
- 8 of 32 possible isomers active
- 1 isomer chosen

Saquinavir (HIV protease inhibitor)
- 4 stereocenters??
- 1 isomer marketed

Checklist of things to expect or worry about when isomeric drugs are compared.

1. Different ADME properties are almost always observed since transporter, metabolic enzyme and albumin are complex 3D structures and interact stereoselectively or stereospecifically.

2. Different pharmacology at receptors (you will see cases where one isomer is an agonist and another isomer is an antagonist of the same receptor).

3. Different off-target effects and side effects.

4. Racemization of stereocenters sometimes occurs most often obviating the need for single isomers.

5. We often see cases where industry markets a mixture (racemate) and later does a follow-on drug of a single isomer. Typically the racemate goes generic first and gets inexpensive. The drug company has to demonstrate that the follow-on single isomer is different enough to

a. Warrant separate patents
b. Provide a health benefit for the patient (FDA) over other compounds on the market
c. Be cost effective (Nexium vs Prilosec).