MEDCHEM 562

Physicochemical Properties of Drugs: Lecture 2; Kent Kunze

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

The vast majority of drugs contain at least one stereo-center or site of asymmetry. All biological receptors and enzymes have complex 3 dimensional structures and are inherently asymmetric. When we study the ADME and therapeutic properties of individual drug isomers we find that they behave differently. Thus when we give a mixture of two stereoisomers we are, in effect, giving a combination of two separate drugs with overlapping properties. Thus when stereoisomers of a drug are given separately the biological response, side effects, protein binding and pharmacokinetics of the isomers are different, sometime strikingly so. Some drugs are given as mixtures of structural or optical isomers but the use of single isomers in drug development is strongly encouraged. 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 to be given as stereoisomeric mixtures be determined separately whenever possible.

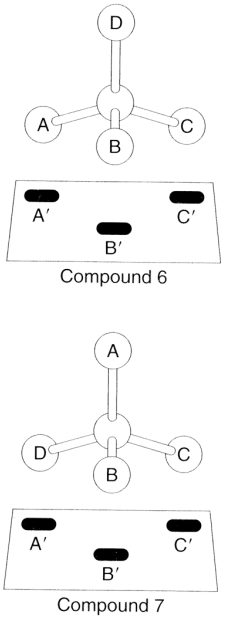


FIGURE 2.18 Optical isomers. Only in compound 6 do the functional groups A, B, and C align with the corresponding sites of binding on the asymmetric surface.

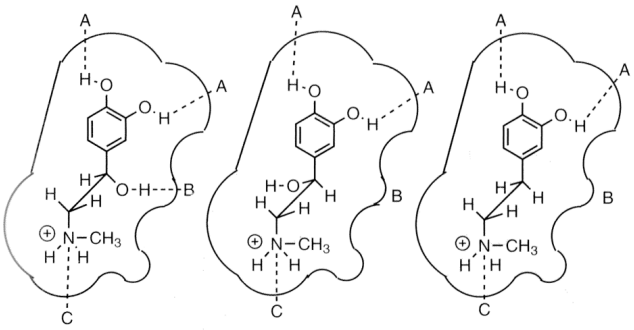
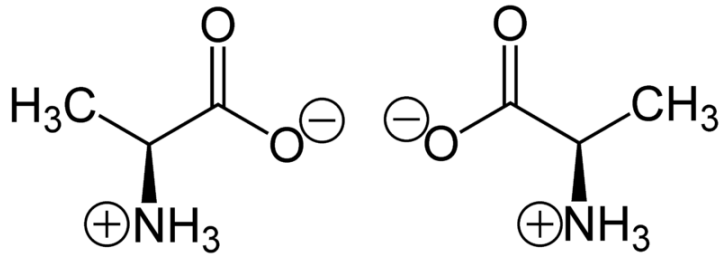


FIGURE 2.19 Drug receptor interaction of *R*-(−)-epinephrine, *S*-(+)-epinephrine, and *N*-methyldopamine.

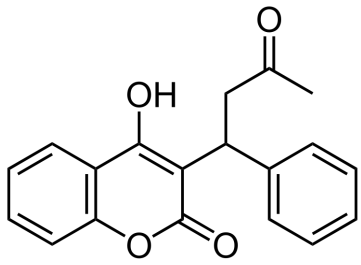
1. Enantiomers: Most chiral centers in drug structures occur at tetrahedral sp^3 carbon atoms where bonds are formed with 4 distinct chemical groups. These groups can be arranged in two ways that are "mirror images" and that are not interconvertable. When there is only one chiral center in the molecule the two isomers are called enantiomers. Note: You should be able to

identify chiral centers, assign group priority and deduce stereochemical identifiers (S (left) and R (right) in a structure like alanine below using the Cahn-Ingold-Prelog rules. Below $-NH_3^+ = 1$; $COO^- = 2$; $CH_3 = 3$ and the hydrogen (not shown) is 4 and directed back.
-The sequence 1,2,3 clockwise is R .
-The sequence 1,2,3 counterclockwise is S.



Many older drugs are given as racemic mixtures.

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



1. Low therapeutic index-individual dosing with monitoring (INR). Sensitive to drug-drug interactions with CYP2C9 inhibitors and inducers.

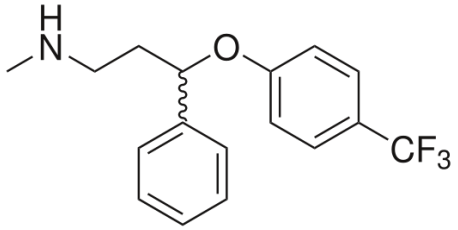
2. Inhibits Vitamin K epoxide reductase

3. (S) isomer (CYP2C9 substrate) is 3 fold more potent than the (R) enantiomer (not a substrate for CYP2C9).

4. Half-life for (S) is 24 hours; (R) is 45 hours

5. Development of single isomers attempted and failed.

Example: Fluoxetine (Antidepressant; Prozac; serotonin reuptake inhibitor (SSRI) (pKa = 9; Log P = 3.5)



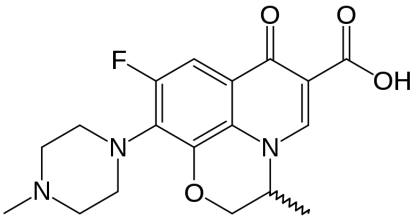
1. Note the use of a wavy bond to indicate chiral center that is not defined (fairly common).

2. Approved for use during pregancy.

3. N-demethylated metabolite concentrations can exceed parent at multiple dosing due to extremely long half-lives. Metabolites are pharmacologically active and inhibit metabolism of the parent isomers. Parent and metabolites are potent inhibitors of CYP2D6 and CYP2C19.

4. Efforts to develop and market the enantiomers failed.

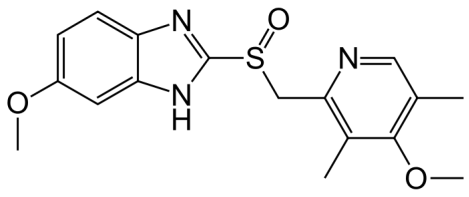
Ofloxacin (fluoroquinolone antibiotic; topoisomerase inhibitor)



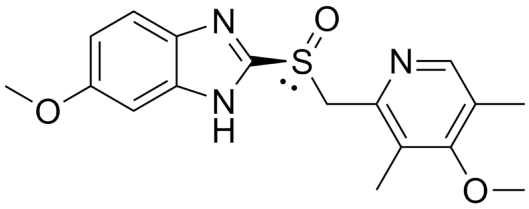
1. (S) enantiomer (Levofloxacin (Levaquin)) is much more active than the (R) enantiomer and is marketed as a separate drug. Quinolones are infamous for causing spontaneous tendon ruptures. There are two Black box warnings on Levofloxacin. (Levaquin).

2. Note that there are multiple ionizeable 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



Omeprazole (Prilosec)



Esomeprazole (Nexium)

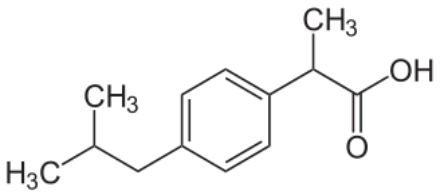
1. Note the unusual chiral center at sulphur. The lowest priority group here is the lone electron pair. All of the PPI's (Lanzoprazole) have this structural feature and are chiral.

2. Metabolism is by CYP2C19 which is polymorphic. Evidence suggests that administration of (S) omeprazole (Nexium) provides better AUC and less individual variability. For other PPI's it is the (R) enantiomer.

3. Overall controversial whether Nexium (off-patent next year) is worth the extra cost.

4. The PPI's are unstable to the acid pH in the stomach and are formulated for release in the intestine.

Ibuprofen (NSAID) (inhibits cyclo-oxygenase enzyme that produces the prostaglandins)



1. The (S) enantiomer is the active form.

2. Efforts to develop the single enantiomer were discontinued when it was realized that an acyl-CoA racemase converts the (R)-enantiomer to the (S). Other NSAIDs like ketoprofen also undergo racemization (also called epimerization). In the mechanism of racemization the proton is lost.

Multiple Chiral Centers (Diastereoismers)

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.

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 sterocenter 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 isomers differ in chemical properties as well as in biological activities. Note to you chemist types there are also "meso forms" in special cases with additional planes of symmetry in the molecules. We won't worry about meso forms.

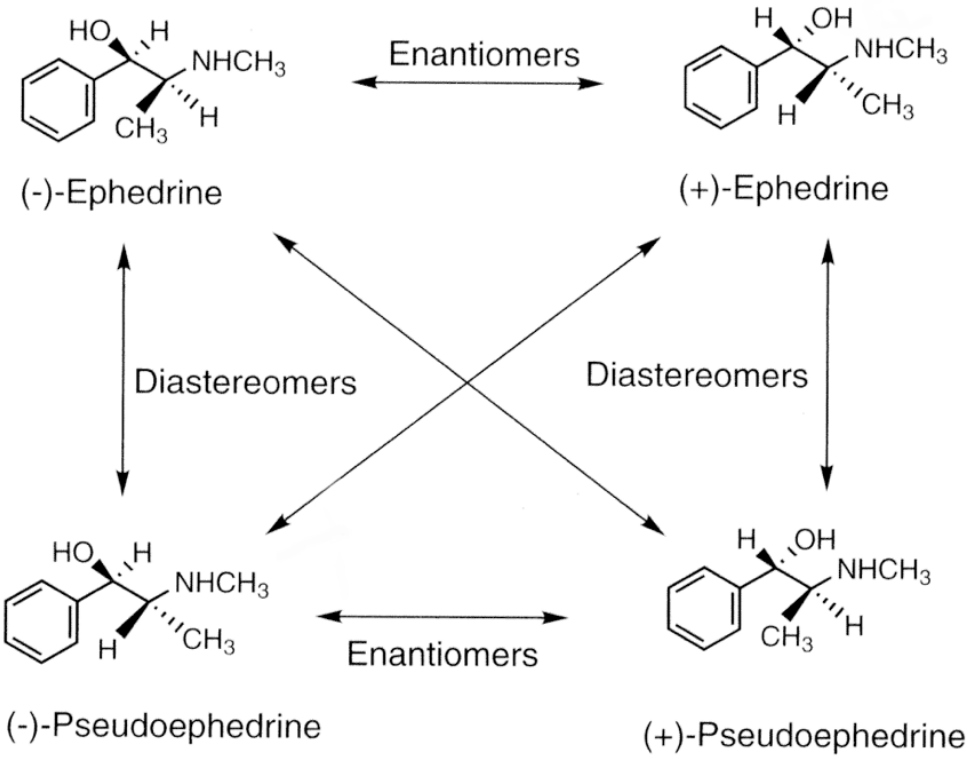
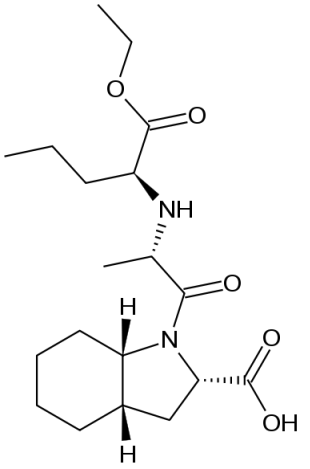
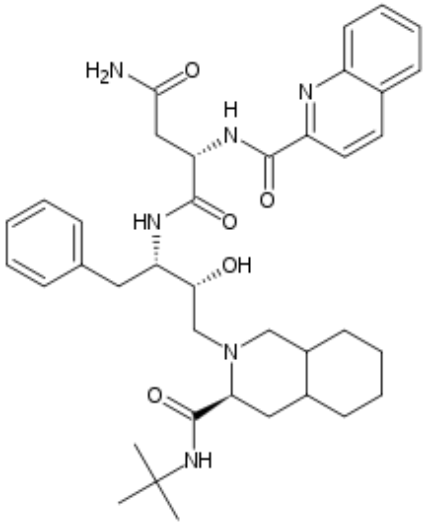


FIGURE 2.21 Relationship between the diastereomers of ephedrine and pseudoephedrine.

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



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 (remember that is 4 things and a lot of biological space)

2. Different pharmacology at receptors (we see cases where one isomer is an agonist and another isomer is an antagonist).

3. Different off-target effects and side effects.

4. Racemization of sterocenters.

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 to itself, and to others, that the follow-on isomer is different enough to

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

6. Increasingly it is up to formulary boards at hospitals and other healthcare organizations to make these kinds of evaluations as cost is not an FDA mandate. Pharmacists are right in the middle of it.