**Pharmaceuticals: Does it matter if it’s a dash or a wedge?**

*Organic Chemistry Topic:* **Chirality**

*Toxicology Topics:* **Mechanistic Toxicology**-**Toxicokinetics & Toxicodynamics**

Organic Chemistry Topic: **Chirality**

Example #1: Thalidomide The racemic mixture of this compound was introduced in England in 1956 as a pharmaceutical to prevent morning sickness in pregnant women. While the *R*-enantiomer is an effective sedative, the *S*-enantiomer is a potent teratogen (causes birth defects). The drug was removed from the market in 1962, and, thanks to Frances Oldham Kelsey at the FDA, it was never approved for use in the US. (en.wikipedia.org/wiki/Frances\_Oldham\_Kelsey)

1. Identify the chiral center(s) in thalidomide drawn in the box with an asterisk.
2. How many stereoisomers are possible for thalidomide? \_\_\_\_\_\_\_\_\_\_\_\_
3. Draw both enantiomers of thalidomide in the space below, and label them accordingly.



Example #2: Albuterol Sold as a racemic mixture under the trade name Proventil, this compound is a bronchodilator that is used to treat the symptoms of asthma. Interestingly, only the *R*-enantiomer is active in this role and is sold separately as a pure substance under the brand name Xopenex.

1. Identify the chiral center(s) in Albuterol drawn in the box with an asterisk.

2. Draw the structure of Xopenex below.

3. If the *R*-(-)-enantiomer rotates plane polarized light 32º counterclockwise, what is the optical rotation of the *S*-enantiomer? \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

4. How many signals would be observed in the 13C NMR spectrum of Xopenex? \_\_\_\_\_\_\_\_\_\_\_\_

5. How many signals would be observed in the 1H NMR spectrum of Xopenex? \_\_\_\_\_\_\_\_\_\_\_\_

6. On the structure of Albuterol in the box above, draw a circle around the most acidic hydrogen atom.

7. In the space below, draw the *S*-enantiomer of Albuterol. Then, draw four water molecules interacting with your structure via hydrogen bonds. Denote the hydrogen bonds with a dashed line.

8. Do you think that Albuterol is soluble in water? Explain with one sentence in the space below.

Example #3: Morphine A potent opiate that can be isolated from poppy straw (for all you GOT fans - “milk of the poppy”), morphine is used to alleviate pain. Serious side effects include a decrease in respiratory effort and low blood pressure, which is why an overdose of morphine can be fatal.



1. How many stereoisomers are possible for morphine? \_\_\_\_\_\_\_\_\_\_\_

2. In the space below, draw the enantiomer and one diastereomer of morphine.

3. On the structure of morphine in the box to the right, label each chiral center with the correct *R* or *S* designation.

4. Other opiate derivatives that are close structural relatives to morphine are listed below. Use your favorite search engine to find the structures of each of these compounds and draw them in the corresponding boxes. Label each stereocenter with the correct *R* or *S* designation.



5. Interestingly, diamorphine can be prescribed in the UK to alleviate pain. When injected into a vein, diamorphine is 2-3 times as potent as morphine, meaning smaller amounts are required to generate the desired effect in patients. Based on their structures, which compound is more water soluble? \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Toxicology Topics: **Mechanistic Toxicology**-**Toxicokinetics & Toxicodynamics**

6. Classic Toxicology vs. Mechanistic Toxicology. Read the Introduction, pages 5845-46, and the beginning of section 4.2, page 5850, in the recommended readings.

 Explain, in your own words, what is Toxicology and how mechanistic toxicology differs from the classic definition of the field.

7. *Toxicokinetics and Toxicodynamics:* Read section 4.2.1 pages 5850-51. Define the two terms. Describe the uptake and fate of a compound in a person (or other organism).

8. Toxicity:a dash or a wedge? Read section 4.2.1.1, page 5851 about the toxicokinetics and toxicodynamics of Thalidomide R and S enantiomers. List the differences between the two enantiomers in their toxicity and efficacy.

9*.* What are the ***four criteria*** that are used to ***characterize the toxicokinetics of a drug***?

10. Why do you think diamorphine is a more potent analgesic than morphine?

*Recommended Reading*

Voutchkova, Adelina M.; Osimitz, Thomas G.; Anastas, Paul T. “Toward a Comprehensive Molecular Design Framework for Reduced Hazard”  *Chem. Rev.* **2010**, *110*, 5845-5882.

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