Chem 124H Organic Chemistry Case Study # 1

"Selective COX-II Inhibitors - the Story of Vioxx®: A Case Study in Drug Discovery"

Before 1st Class

1) Read the case.

2) Read and *familiarize* yourself with the following articles (posted on iLearn):

a) "Vioxx," B. Hileman, *Chem. Eng. News.* (2005), p 134.

b) "Vioxx, the implosion of Merck, and aftershocks at the FDA," Horton, R., *The Lancet*, 364, (2004) p 1995-1996

c) "Nonsteroidal Anti-inflammatory Drugs: A New Generation of Cyclooxygenase Inhibitors," Beuck, M., *Angew. Chem. Int. Ed.*, 38, (1999) p 631-633

3) Answer the pre-case questions and be prepared to submit your response to your discussion group when you arrive to class.

4) Read and familiarize yourself with the case study questions; these will be discussed and answered in groups during the discussion sessions.

Before 2nd Class

1) *Familiarize* yourself with the following article (posted on iLearn); bring all articles to class: "Facile air oxidation of the conjugate base of rofecoxib (Vioxx®), a possible contributor to chronic human toxicity," Reddy, L.R.; Corey, E.J. *Tetrahedron Lett.,* 46, (2005) p927–929.

In Class

1) Class Period #1: You will be divided into collaborative groups for the pre-case discussion in which you identify the major issues of the case, and determine what types of questions need to be answered in order to resolve the case.

2) Class Period 2 (and 3): You will work in your collaborative groups and arrive at answers to the case study questions.

After Class

1) Complete the post-case study individual report. The due date for this final report will be announced in class.

The Case:

Moises and Matty were discussing their father Felipe, who has arthritis. Moises said that Felipe was suffering more joint pain and inflammation recently. He'd been taking aspirin, but he began to suffer from stomach pain, so his doctor prescribed Celebrex®. Matty said that he was worried, because he'd heard about Vioxx®, which sounded similar to Celebrex, and that Vioxx had been removed from the market by Merck after an FDA investigation, costing billions in revenue. Moises said that aspirin was supposed to work the same way as Vioxx®, and that it hadn't been removed from the market. As they weren't familiar with the case, they talked to their friend Roberto, who works for a competing pharmaceutical firm. Roberto told them that Vioxx® was introduced in 1999 by Merck as an anti-inflammatory drug to treat arthritis, among other diseases. By 2003, worldwide sales were $2.5b per year. In 2004, however, Vioxx® was withdrawn from the market after an FDA study of 1.4 million patients. Patients taking more than 25 mg of Vioxx® daily were 3.6 times more likely to suffer heart attacks. An estimated 88,000 to 139,000 heart attacks, 30 to 40 percent of them fatal, were caused by Vioxx®. Trials of the effect of Celebrex on increased risk of heart attacks and strokes are inconclusive, and it is still for sale today, although there are calls for the withdrawal of all COX-II inhibitors.

As this didn't really answer their questions, Matty and Moises decided to do some reading.

Pre-Case Study Questions

1) Read Ch 21.6, 26.1 and 26.11 ("Chemistry of Esters", "Amino Acid Structures" and "How do Enzymes Work?") of your assigned organic chemistry textbook (McMurry, 8th Ed.). (or Ch 17 and 23of S&M, Ed 1).

a) Draw the structure of the amino acid serine.

b) What do the terms "covalent" and "reversible" inhibition of enzymes mean?

c) Familiarize yourself with the mechanism of ester formation.

Case Study Questions

Class Period #1) - refer to Beuck (*Angew. Chem. Int. Ed.*, 1999).

1) Beuck states that "The therapeutic effect of acetylsalicylic acid (aspirin) is based on a covalent modification of cyclooxygenase (COX) and the inhibition of the first step of prostaglandin synthesis". The structure of acetylsalicylic acid is given below; draw the mechanism of its reaction with the alcohol of a *serine* residue in the COX enzyme. Why is this mechanism of action called "covalent (or irreversible)" inhibition?

2) Ibuprofen is a reversible inhibitor of COX. Why do you require a greater dosage of aspirin than ibuprofen? Why do the effects of ibuprofen last longer than aspirin?

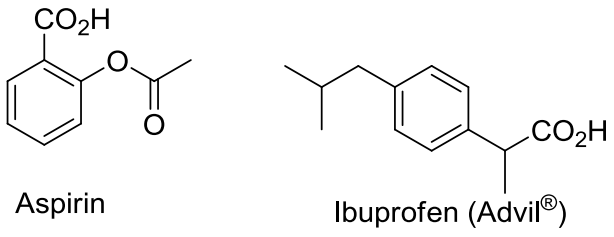

Figure 1. Structures of a) Acetylsalicylic acid (Aspirin) and b) Ibuprofen (Advil®)

3) Both Aspirin and Ibuprofen are nonspecific inhibitors of both COX-I and COX-II. What side effects are often found when taking aspirin/ibuprofen for a long time? Why is this a problem for arthritis patients?

4) Describe the difference between the roles of enzymes COX-I and COX-II.

5) Both Celebrex® and Vioxx® (Figure 2) are selective, reversible COX-II inhibitors. Describe the benefit of *selectively* inhibiting only the COX-II enzyme. Why do Celebrex® and Vioxx® have fewer side effects than aspirin?

Class Period #2) - refer to Reddy and Corey (*Tetrahedron Lett.*, 2005)

1) Refer to pre-case study question 1b and discuss how small molecules "reversibly" inhibit enzymes.

2) Your TA will give you molecular models of both Celebrex® and Vioxx®. Compare the two molecules in terms of size and shape. Describe the similarities between the two drugs - why are they both effective?

3) Compare the chemical structures of both Celebrex® and Vioxx® in terms of functional groups. Which groups in Vioxx® and Celebrex are different? How would they affect the binding of the two drugs in the enzyme active site? Describe differences in *reactivity* of both Celebrex® and Vioxx®.

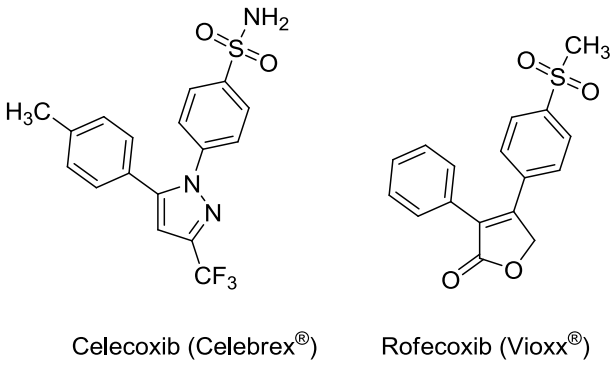

Figure 2. Structures of Celebrex® and Vioxx®

4) Prof. E.J. Corey's paper illustrates the reactivity of Vioxx® with molecular oxygen. His proposed mechanism is shown below. Why is Vioxx® acidic? Draw the resonance structures of the intermediate anion.

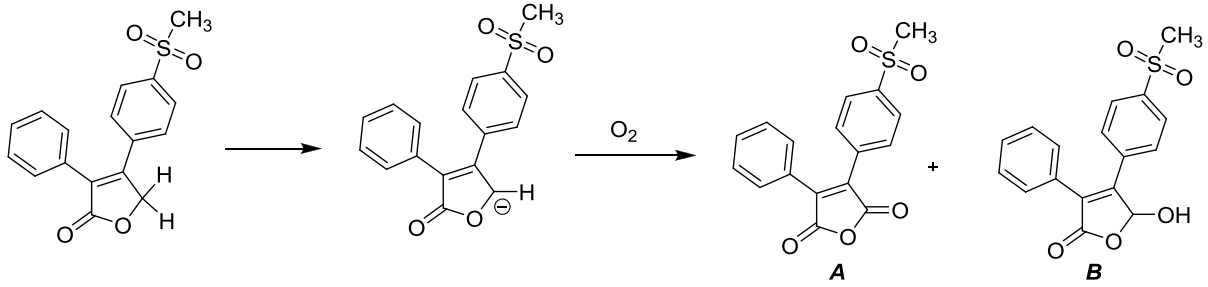

Figure 3. Proposed reactivity of Vioxx®.

5) Why is reaction with Oxygen a problem for drug candidates?

6) Can Celebrex undergo the same oxidation? If not, why not?

7) The central thesis of Prof. Corey's argument is that Vioxx® can undergo reactions that other COX-II inhibitors cannot, and that molecules ***A*** and ***B*** are implicated in the toxicity of Vioxx®.

Do you agree with this thesis? What experiments are reported in Prof. Corey's article that support his thesis. Are these conclusive, and can you think of other tests that might be done to corroborate his theory?

8) “Trials of the effect of Celebrex on increased risk of heart attacks and strokes are inconclusive”. Does this statement change your answers to part 7)?

Post-Case Study Report

In a 1-2 page report, use your answers from the Case Study Questions and information from further reading of the related articles to make general conclusions about the issues/questions raised in the Case Study. Describe why there is a great need for selective COX-II Inhibitors. Why is the risk of heart attack much more serious for molecules used to treat arthritis than

localized pain? Is the increased risk of heart attack for Vioxx® due to its mechanism of action or a side effect? Should all COX-II inhibitors (including Celebrex) be withdrawn? Read the editorial from The Lancet, which condemns both Merck and the FDA for allowing the sale of Vioxx®. Do you agree with their conclusions?