Synthesis and Physicochemical Properties of a Fluorine Derivative of Acetaminophen

Joshua Boldon and Thomas A. Shell
Department of Chemistry and Physics
Lincoln Memorial University, Harrogate, TN

LMU School of Mathematics & Sciences LINCOLN MEMORIAL UNIVERSITY

ACA Appalachian College Association

Introduction

- 23% of Americans take a drug with acetaminophen as the active ingredient weekly
- Acetaminophen taken in excess can cause acute liver failure/injury with ~500 deaths a year
- A less toxic derivative of acetaminophen that maintains the analgesic properties of acetaminophen would be beneficial could greatly benefit consumer health
- This toxicity is a result of acetaminophen being oxidized by cytochrome p450 to form a toxic metabolite
- Fluorine is more electronegative than hydrogen but has a similar atomic radius
- A fluorinated derivative of acetaminophen will likely have different bioavailability, lipophilicity, and rate of metabolism than aspirin due to fluorine changing the electron distribution of the molecule
- However, substituting fluorine for hydrogen will not change the size and shape of the molecule, which is important for the interaction of the drug with the target biomolecule
- We anticipate that substituting fluorine for hydrogen atoms of the methyl amide of acetaminophen will change the rate of P450 metabolism of the acetaminophen derivative
- An acetaminophen derivative will a lower rate of P450 oxidation would likely be less toxic than acetaminophen
- Therefore, a fluorinated acetaminophen derivative has the potential to maintain the analgesic properties of the molecule while being less hepatotoxic

Molecular Structure of Acetaminophen and Synthesis of the Fluorinated Acetaminophen Derivative

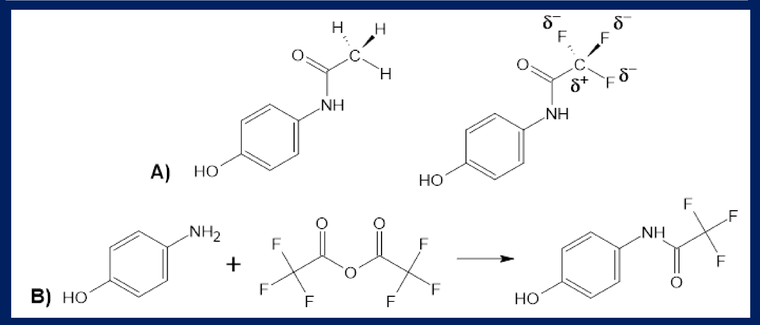

Figure 1. A) Structure of acetaminophen and the fluorinated derivative of acetaminophen. B) Synthesis of fluorinated derivative of acetaminophen.

Partition Coefficient

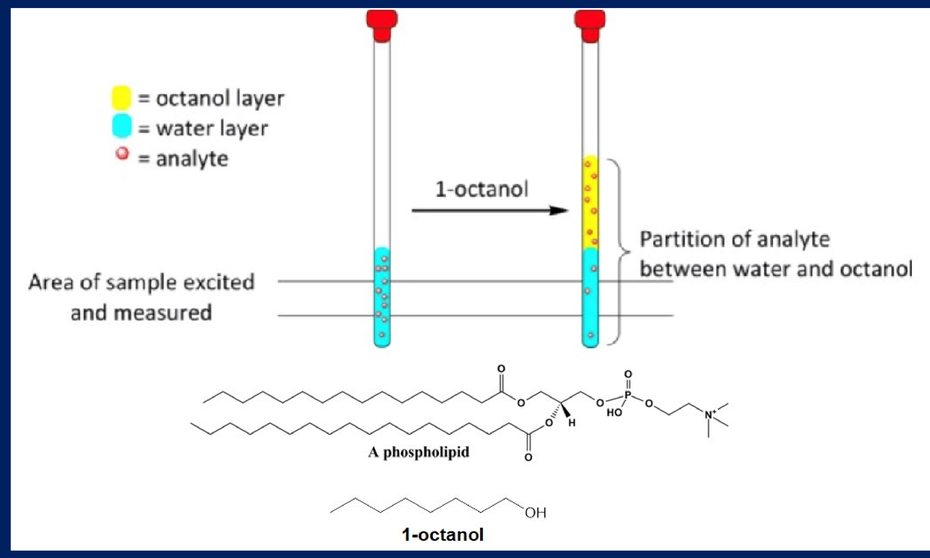

Figure 2. Determination of octanol/water partition coefficient.

- Partition coefficient: a method to mathematically determine distribution of a molecule between immiscible solvents
- Octanol/water is a simple model for the phospholipid bilayer of cells
- Octanol has a polar hydroxyl group with a long nonpolar hydrocarbon (8 carbons), which is similar to the polar head groups and long hydrocarbon tails of phospholipids of cellular membranes.
- Therefore, the octanol/water partition coefficient is a measure of lipophilicity and membrane permeability
- Lipophilicity and membrane permeability are important for absorption, excretion, biodistribution, and storage of molecules in biological systems

Cytochrome P450 Assay

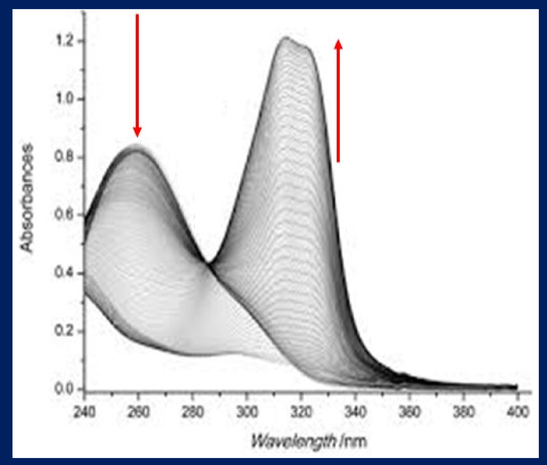

Figure 3. Assay for Cytochrome P450 of oxidation of acetaminophen, Oxidation of the acetaminophen metabolizes it into a molecule with a different UV/Vis absorption spectrum. Monitoring the time-dependance of the changes in the UV/Vis spectra provides the rate of the oxidation reaction. Acetaminophen and the fluorinated acetaminophen derivative will be incubated with rat liver microsomes and the UV/Vis spectra of the reaction will be monitored over time.

Metabolism of Acetaminophen

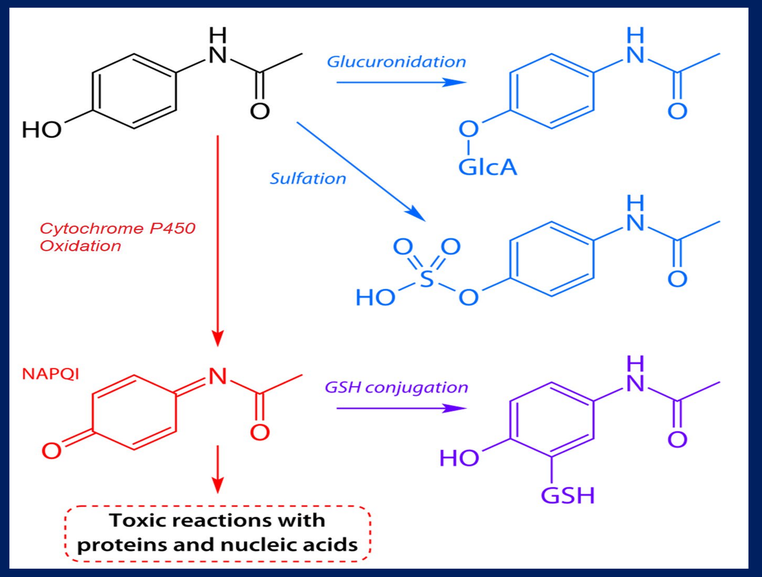

Figure 4. Metabolism of acetaminophen

- Cytochrome P450 is an enzyme that oxidizes foreign molecules to typically metabolize them to less toxic molecules with greater excretability
- However in the case of acetaminophen, P450 enzymes oxidizes the molecule into a toxic metabolite, NAPQI
- NAPQI is responsible for the hepatotoxicity of acetaminophen
- NAPQI consumes cellular glutathione and reacts with other biomolecules, such as proteins and nucleic acids, resulting in cellular death
- An acetaminophen derivative with a slower rate of a reaction would be expected to be less toxic because the slower metabolic production of NAPQI would allow cells to maintain a homeostatic level of glutathione preventing cellular death

Potential Impact

- This research has the potential of producing an acetaminophen derivative that is less hepatotoxic but maintains the analgesic properties of acetaminophen

Acknowledgments

Research Funded by the Appalachian College Association

- The Lincoln Memorial University Department of Chemistry and Physics for allowing me to use their laboratory space to conduct my research this summer.
- Dr. Thomas Shell for all of the help he has given me throughout this research.