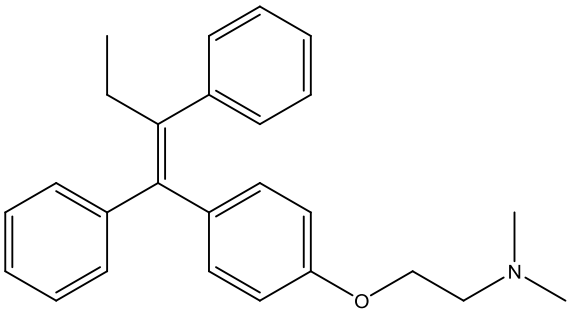
MEDCH 562P
Fall 2011
Problem Set #2

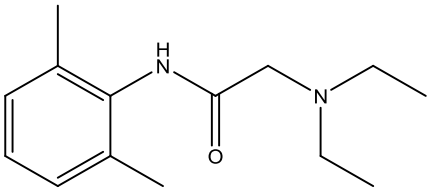
I. Phase I and II Metabolism

A. For each of the following drugs, show two different Phase I metabolites as well as two different Phase II metabolites you might expect to see. Label each metabolic pathway.

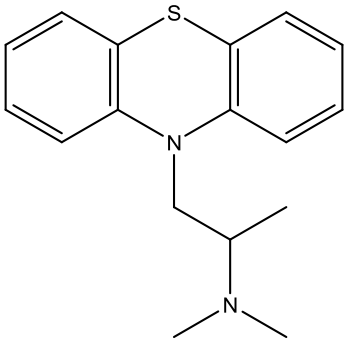
1.) Tamoxifen



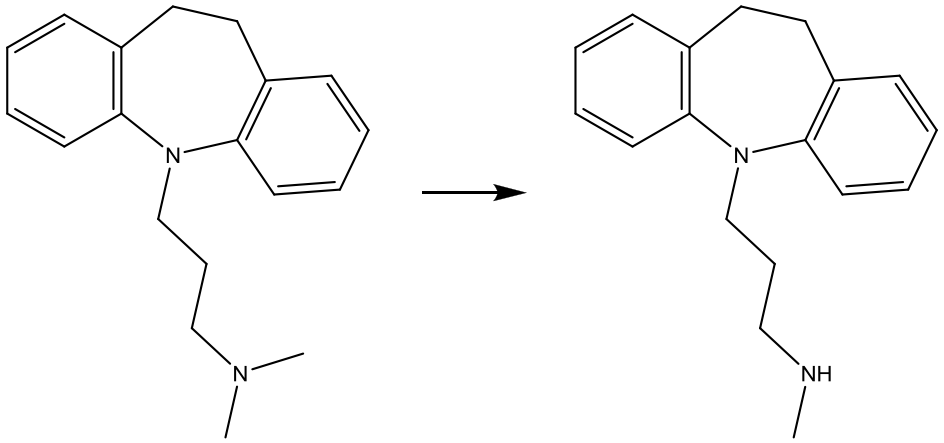
2.) Lidocaine



3.) Promethazine



B. Both Imipramine and Desipramine are tricyclic antidepressants. Imipramine undergoes oxidative metabolism by P450s. One of the metabolites is Desipramine. Write a detailed chemical mechanism that explains the metabolism from Imipramine to Desipramine.

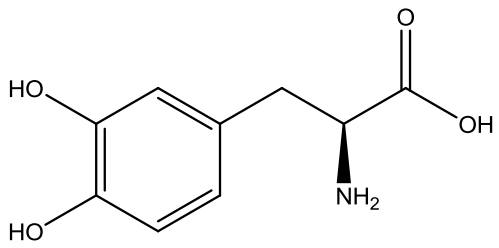


Imipramine Desipramine

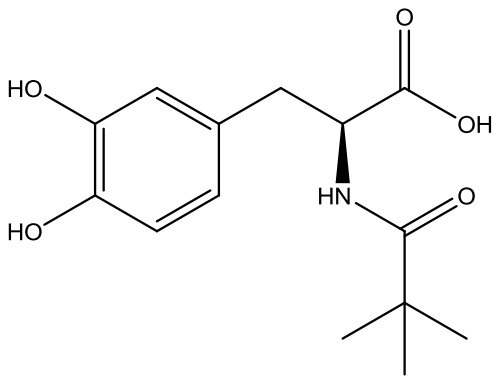
II. Drug Structure Modification

A. Levodopa and L-dopamide are both useful in the treatment of Parkinson's disease. Is L-dopamide an analog or prodrug of Levodopa? Explain your reasoning by drawing a chemical mechanism.

Levodopa

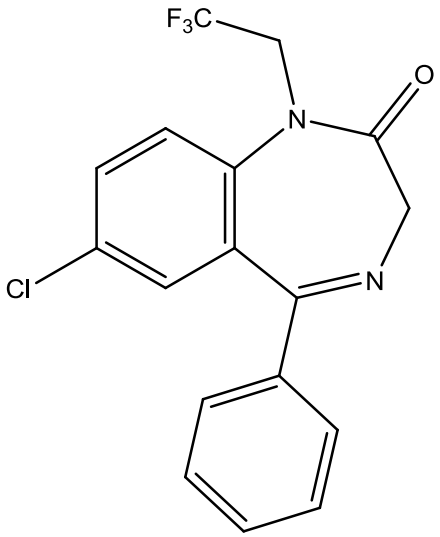


L-dopamide

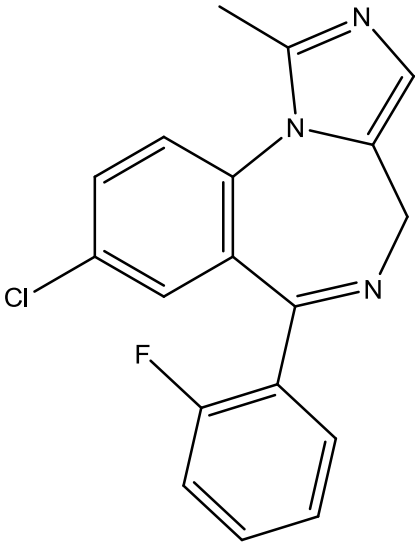


B. Circle all possible ionization sites for the molecules listed below then discuss the structural differences between the two. How might these differences affect their absorption? Is Midazolam an analog or a prodrug of Halazepam?

Halazepam

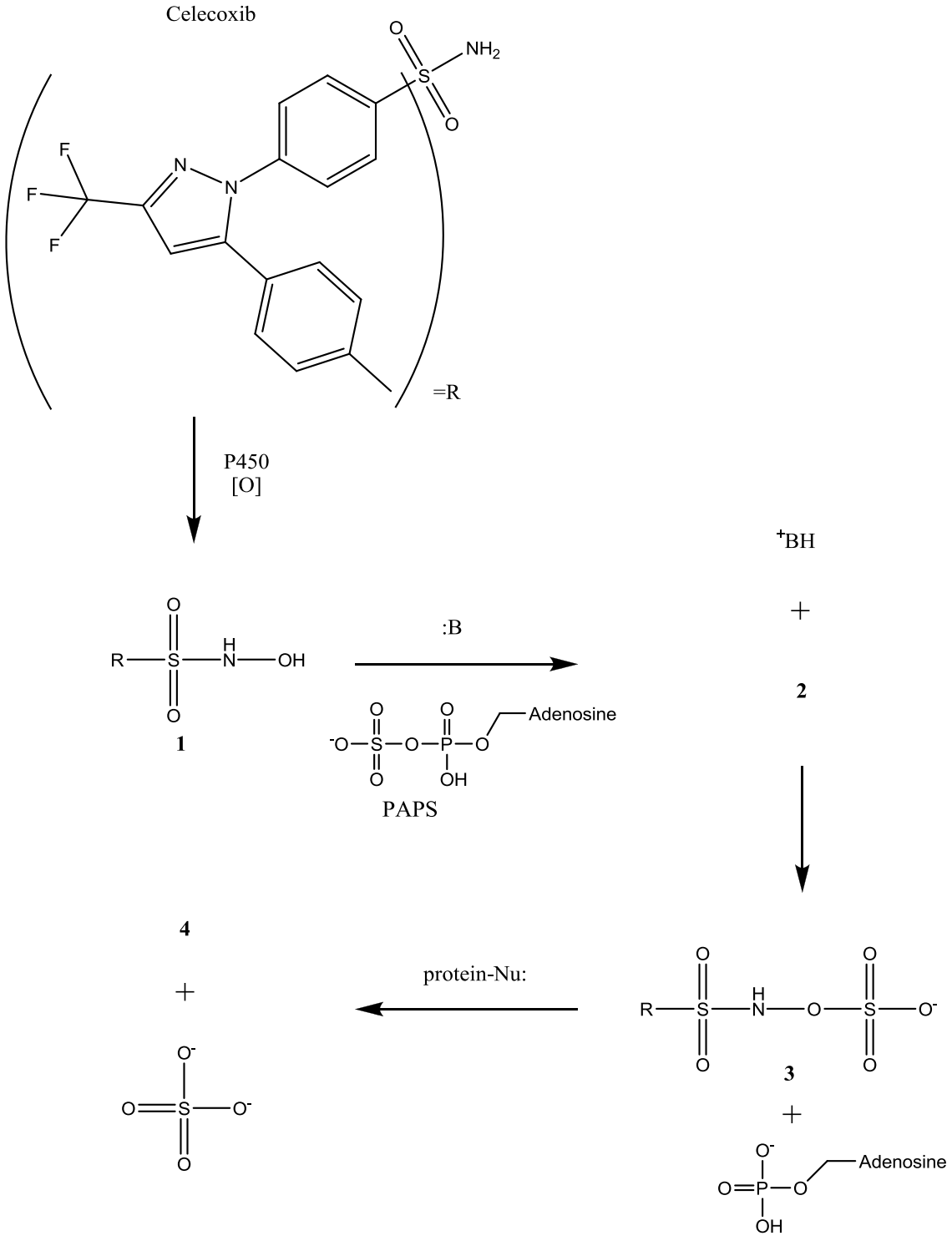


Midazolam



III. Reactive Metabolites

Celecoxib (Celebrex®) was the first selective cyclooxygenase-2 (COX-2) inhibitor approved to treat arthritis. It came with a warning for patients allergic to sulfonamides. One possible mechanism for the initiation of sulfonamide-mediated immunotoxicity is shown in the incomplete scheme below.



1. Show mechanistically how the hydroxysulfonamide **1** reacts with the cofactor PAPS to form a tetrahedral intermediate **2**. Draw a structure for **2**.

2. Show mechanistically how intermediate **2** eliminates phosphoadenosine to generate the reactive sulfate metabolite **3**.

3. Show mechanistically how the protein nucleophiles can react with **3** to form **4** and hydrosulfate. Draw a structure for **4**.

4. If the P450 that catalyzes the oxidation shown above is a member of the CYP3A family with a known genetic polymorphism, would a rapid or slow-metabolizing phenotype be more at risk of the sulfonamide-mediated immunotoxicity?