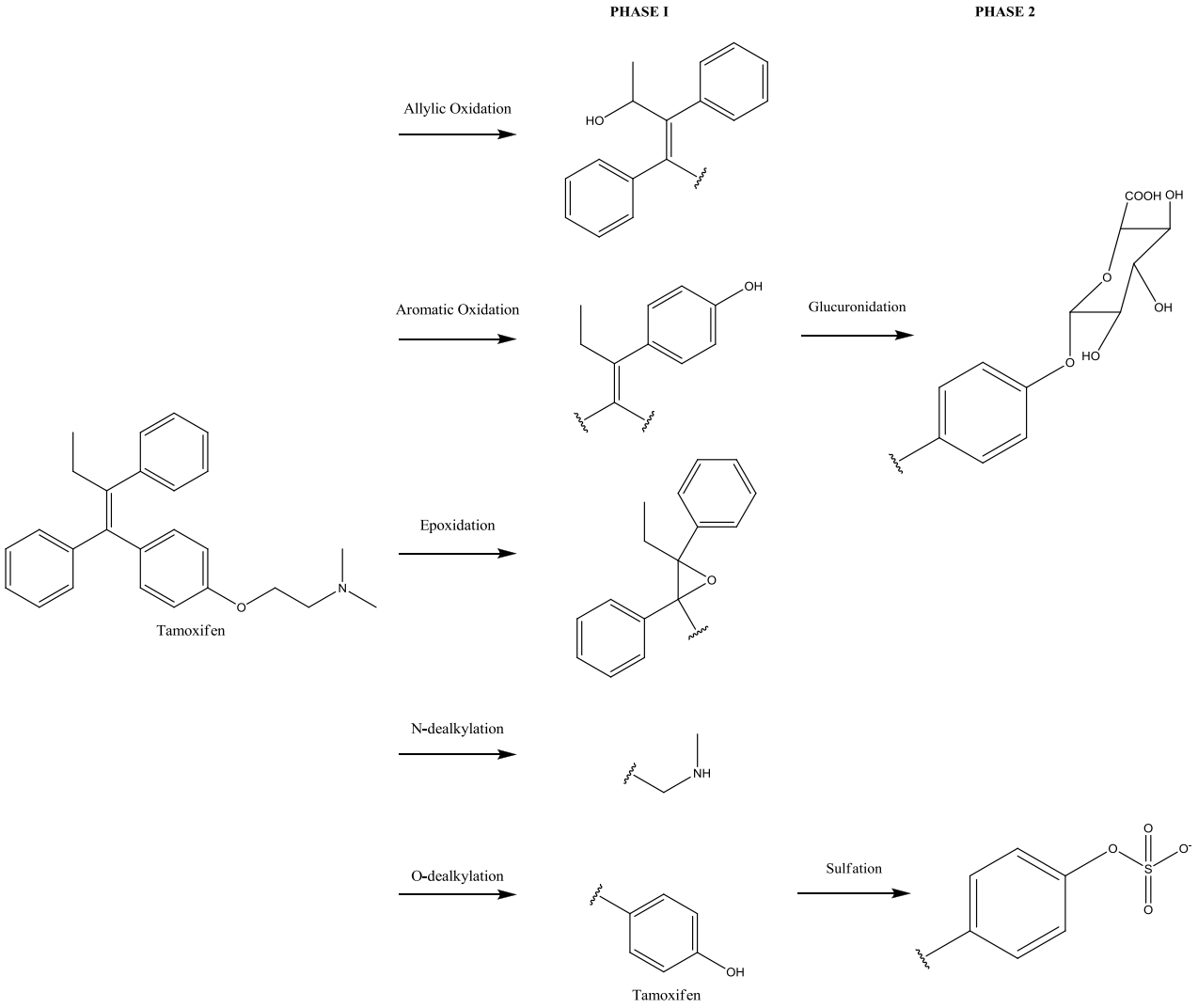
MEDCH 562P
Fall 2011
Problems Set #2 Answer Key

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.

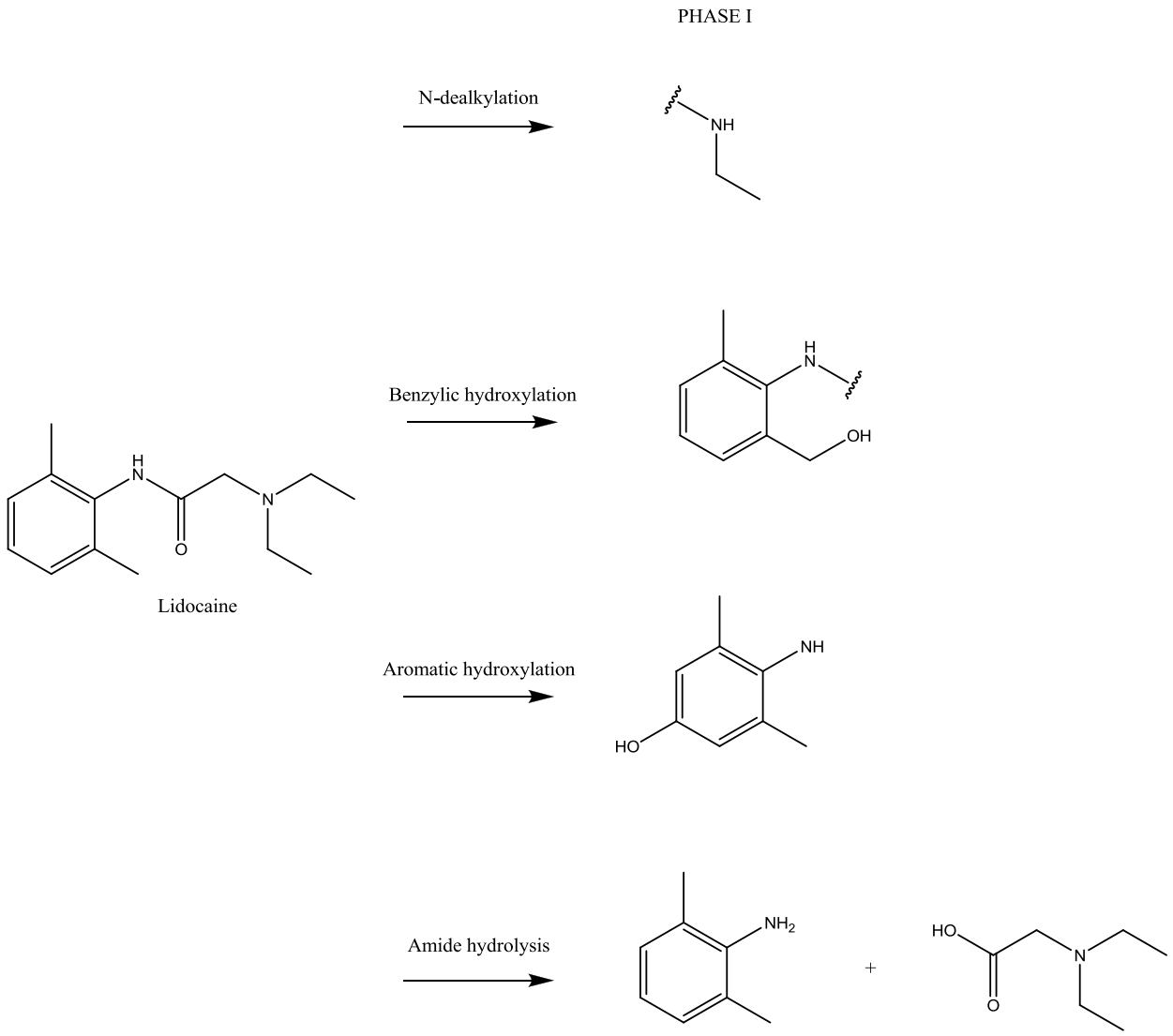
1.) Tamoxifen



*Phase II metabolites are typically formed by conjugation to hydroxyl (-OH) groups.

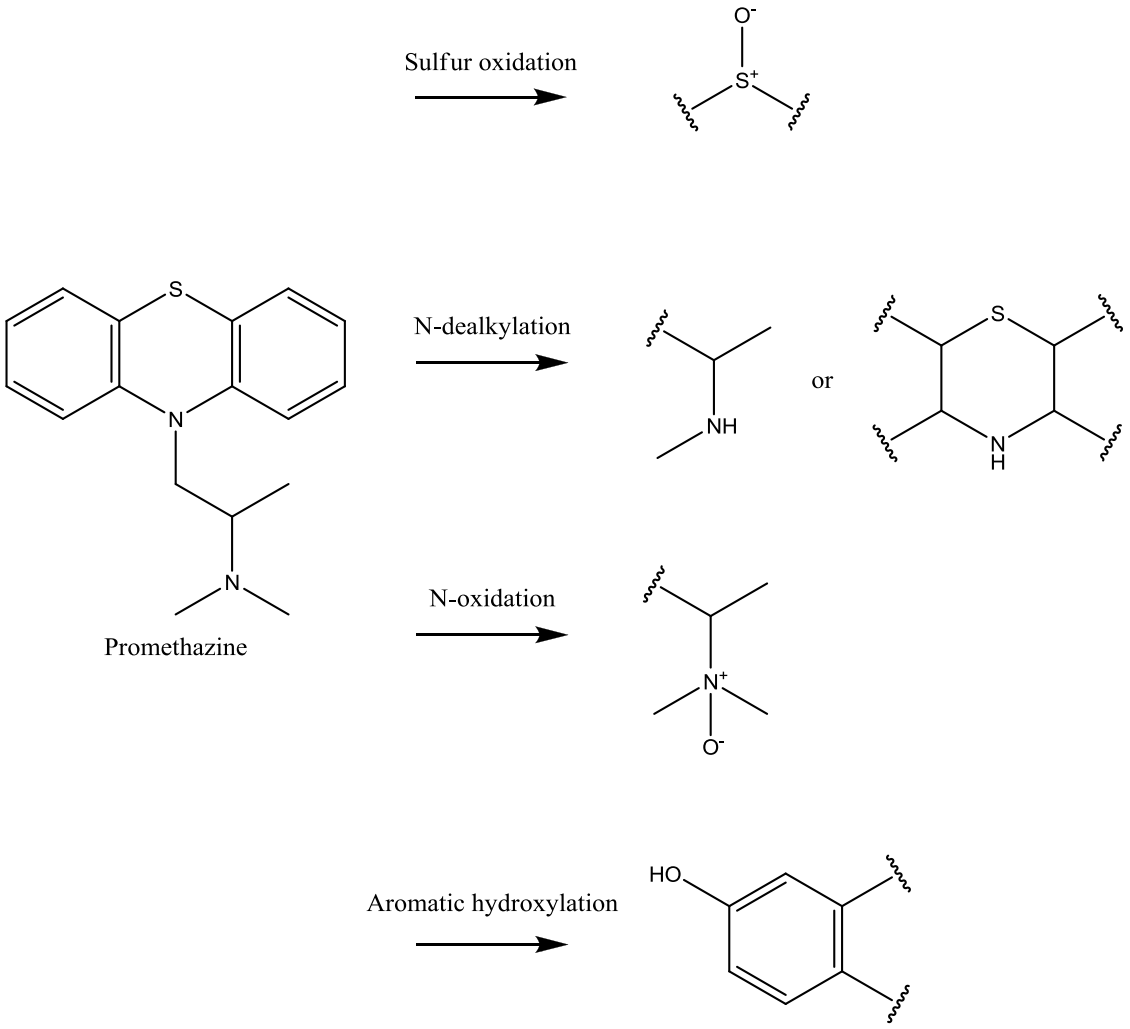
2.) Lidocaine

*See #1 for examples of Phase II metabolites

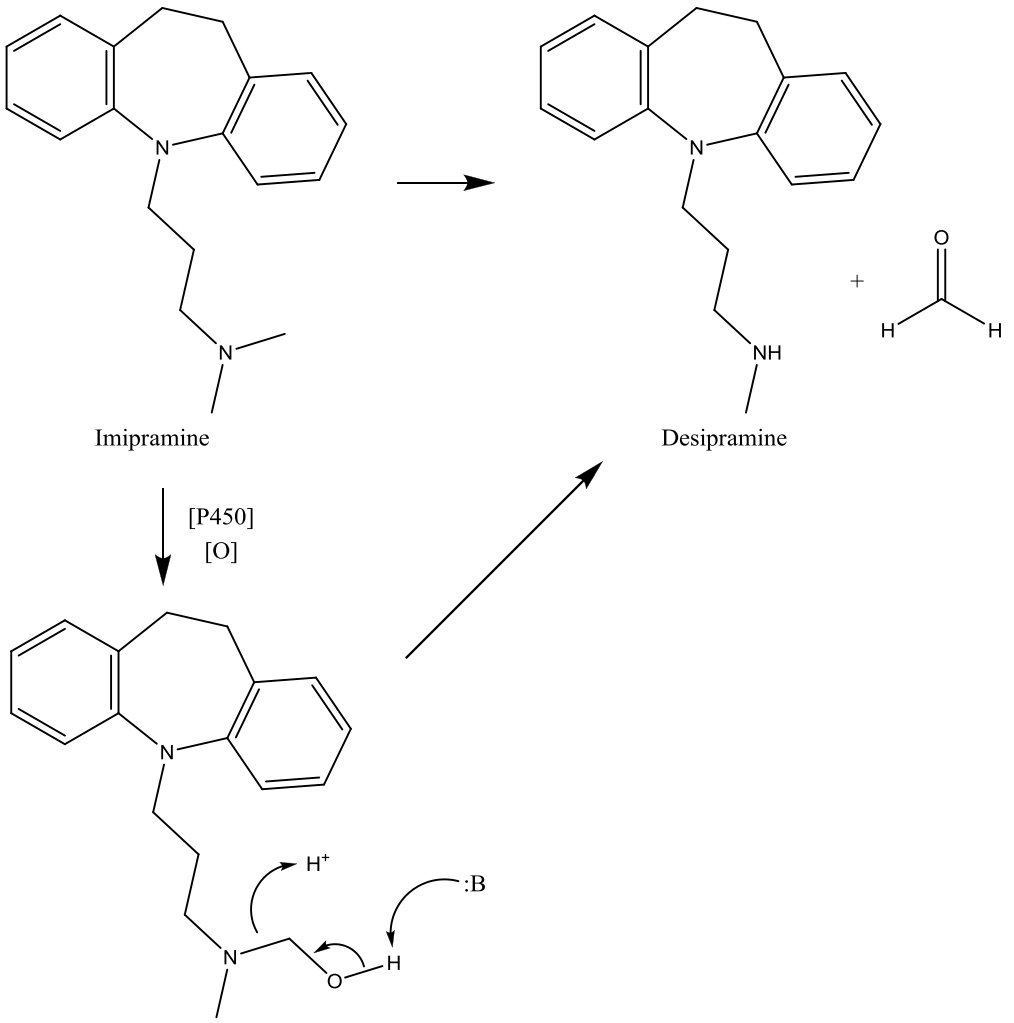


3.) Promethazine

*See #1 for examples of Phase II metabolites

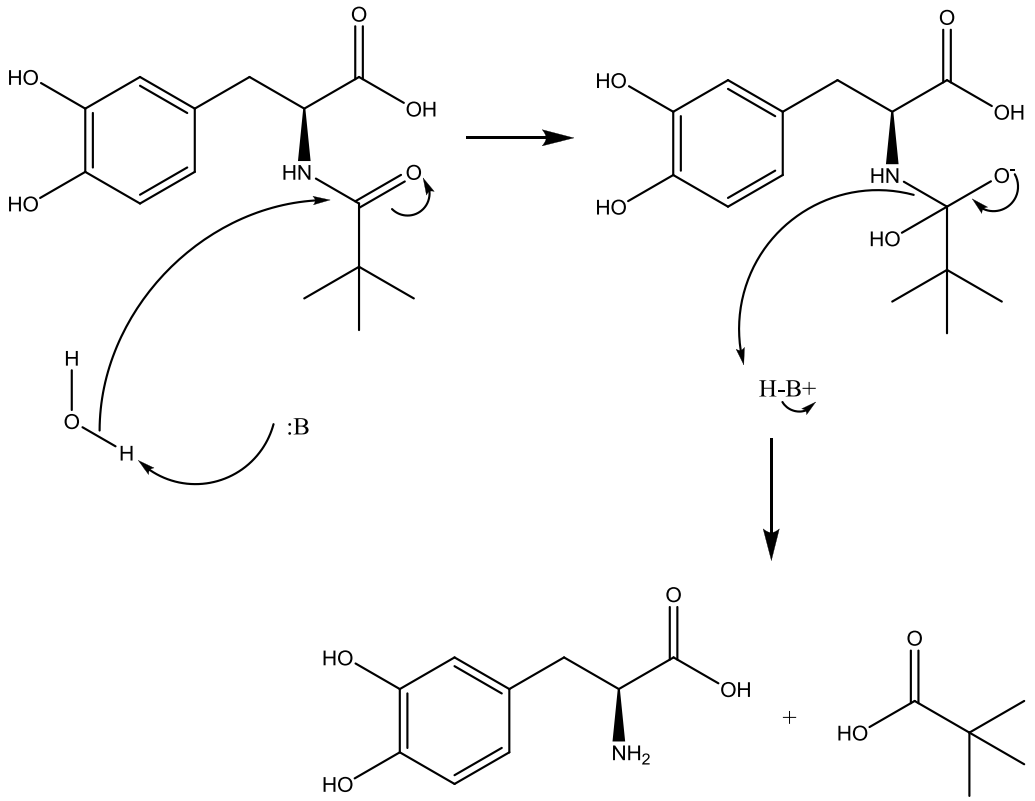


B)



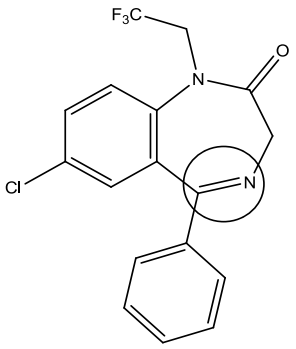
II. Drug Structure Modification

A. L-dopamide is a prodrug of Levodopa.

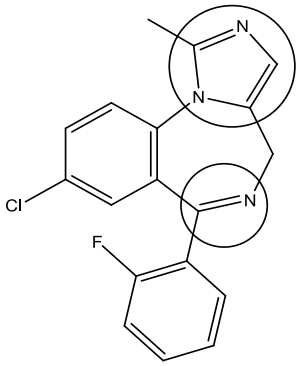


B.

Halazepam

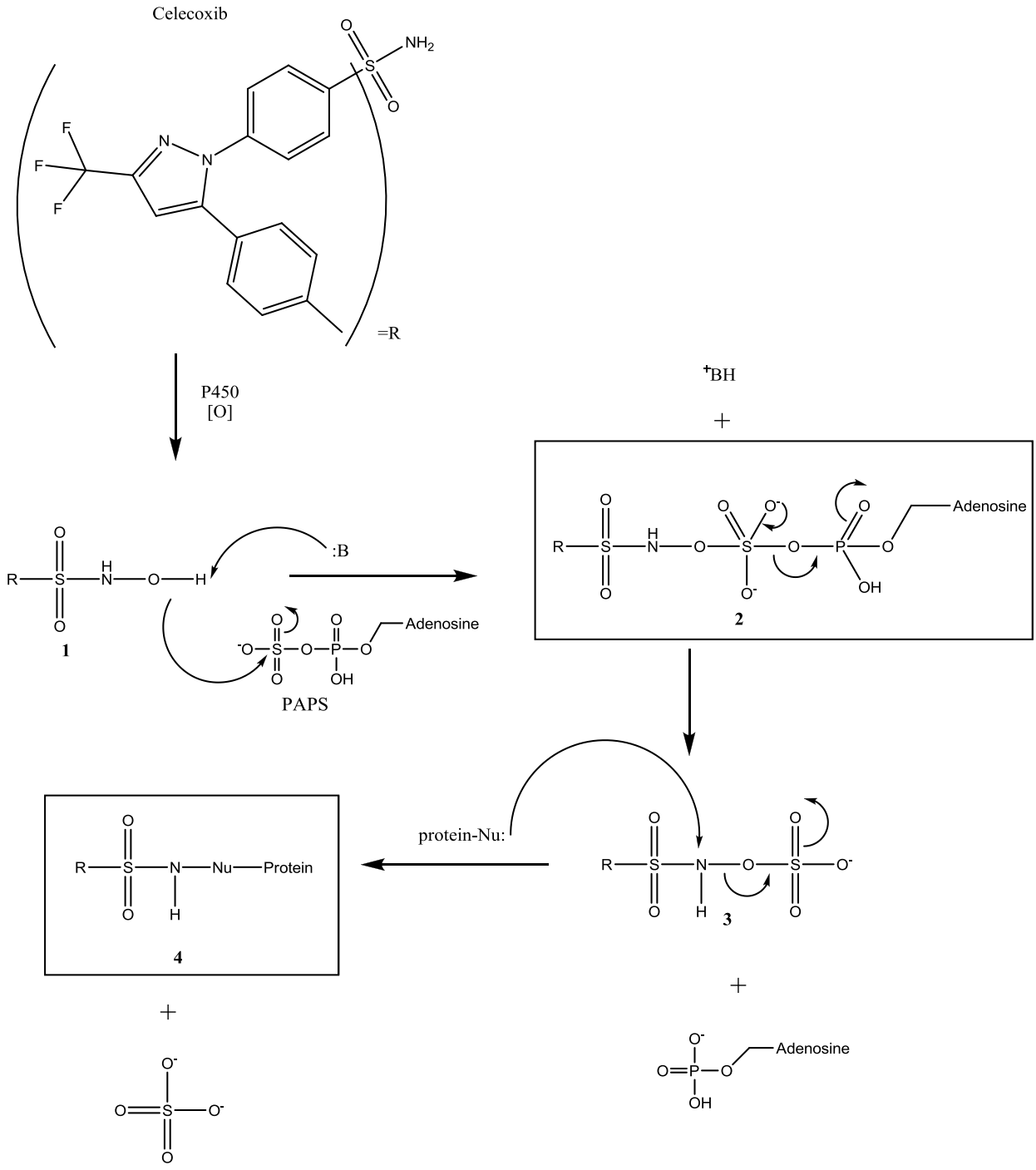


Midazolam



CF_3 of Halazepam and F of Midazolam are both electron withdrawing groups that increase the lipophilicity and absorption of the drugs. The imines circled in both (pK_a of ~5) ionize at physiological pH, thereby decreasing absorption of the drug. The imidazole ring of Midazolam (pK_a of ~7) ionizes at physiological pH, thereby decreasing absorption of this drug. Also, compared to Halazepam, Midazolam may be absorbed at a slower rate because of the very lipophilic substitution of the trifluoromethyl-ethyl group in Halazepam for the ionizable imidazole ring in Midazolam. **Midazolam is an <u>analog</u> of Halazepam**.

III. Reactive Metabolites



A rapid-metabolizing CYP3A phenotype would be more at risk of the sulfonamide-mediated immunotoxicity due to a more rapid accumulation of the toxic metabolite **3**.