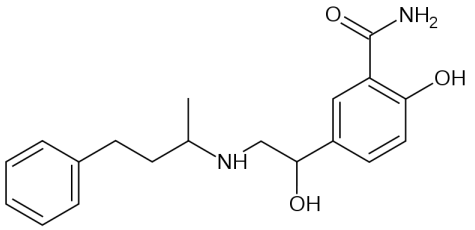
Problem Set 2:

Metabolism, Prodrugs, Receptors

Note: You may find it useful to review the Prodrug and Metabolism Lectures from MEDCH 570.

1. Labetalol (Trandate) is an orally active mixed (binds to more than one kind of adrenergic receptor) adrenergic antagonist that is used to treat hypertension. It is administered as an equal mixture of all possible stereoisomers. Some of the isomers are inactive while others have some selectivity for the different kinds of adrenergic receptors.



a. Labetalol is 100% absorbed but has a bioavailability of 30%. Provide an explanation for this finding.

b. Identify the chiral carbons and assign the (R) stereochemistry in each case by showing whether the group of lowest priority is directed behind (dashed line) or in front of the plane of the molecule as shown. How many total isomers are there of this compound? The all (R) compound is the active beta blocker.

c. What is the natural ligand for the adrenergic receptors and where are the receptors located on the target cell? What general type of receptor are they and generally what happens when the natural ligand binds to the receptor? <u>You will have to look this up.</u>

d. Identify the ionizable groups, provide estimates of the pKa value ranges for these kind of groups (i.e 6-7). Show the predominant ionization states of the functional groups at pH 7.4. Where in the GI tract would you expect absorption to take place and why? The cLogP is 3 and the $cLogD_{7.4}$ is 1. Explain why it make sense for this compound to have a cLogD7.4 that is much less than the cLogP.

e. The major metabolites of labetalol are the sulphate and glucuronide. What kind of metabolites are these (show representative structures)? What are the names of the enzymes that produce them and where are they located? What are the properties of these kinds of metabolites in general and where are they normally excreted? Would you expect that genotype would play an important role in the pharmacokinetics of this drug?

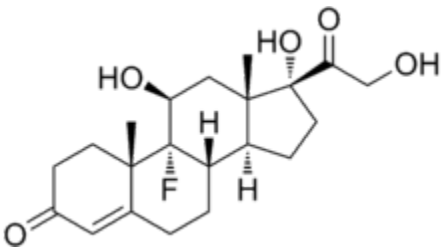
f. This drug may undergo some P450 catalyzed N-dealkylation. Show the two carbons that would be targets for oxidation the structures of the carbinolamine intermediates.

g. Carbamates can be used as prodrugs. Show the structure of a carbamate derivative of labetalol, indicate what kind of enzyme would be required to activate the prodrug and explain why this transformation generally improves bioavailability. Would you expect such a benefit in the case of labetalol? Explain.

2. Detail the major difference between agonists and antagonists

3. What generally happens when small molecules form covalent bonds with enzymes in their active sites?

4. How would you expect this drug to elicit a therapeutic response?



5. Explain how Aldosterone causes increased blood pressure, beginning with the binding event of aldosterone to its receptor.

6. Briefly, describe what happens (what event is triggered) when nicotine binds to a nicotinic receptor. Briefly, describe what happens when acetylcholine binds to an M1, M3 or M5 receptor. Briefly, describe what happens when acetylcholine binds to a M2 or M4 receptors. Where are these receptors located on a target cell?

7. Show an arrow pushing mechanism that details the process of ester hydrolysis: