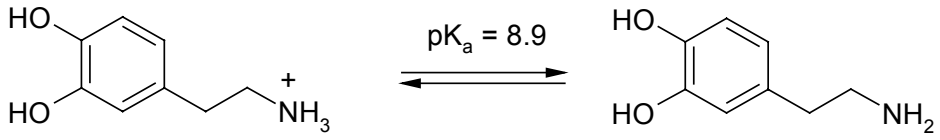
Chem 162/262 (2004) Assignment #7:

Drug Metabolism, Prodrugs

1. Parkinson's disease is characterized by a progressive loss of neurotransmitter dopamine. The equilibrium between the protonated and the neutral form is shown below.



a) Why the oral administration of dopamine is not an effective treatment of Parkinson's disease?

b) Propose a prodrug approach to overcome the limited efficacy of oral dopamine?

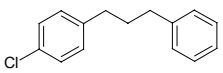
c) How could you ensure that the formation of dopamine from your prodrug occurs mainly in the nervous tissue?

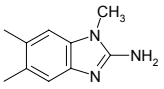
d) Propose a major metabolic reaction that leads to the inactivation of dopamine in the brain

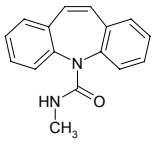
e) Propose a major metabolic reaction that leads to inactivation of the prodrug outside the brain

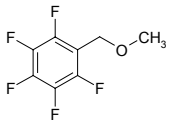
f) Propose approaches to protect the prodrug or dopamine from degradation, thus prolonging their action.

2. Assuming that cytochrome P450 is responsible for the metabolism of the following compounds, show the structure of the major primary oxidation product or the final metabolite from each of the molecules below:

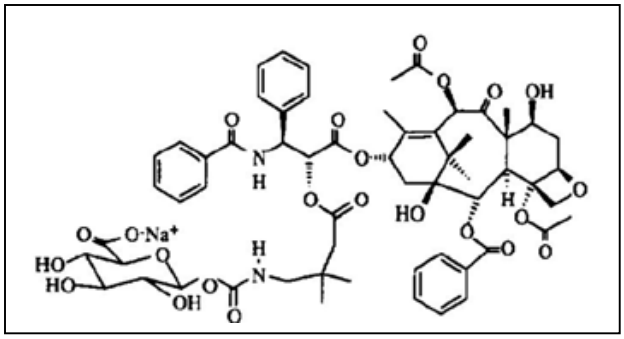








3. Paclitaxel is an antitumor agent that was first obtained by modifying naturally occurring alkaloids from the bark of the Pacific yew tree. The drug inhibits cell replication at the mitosis stage by binding to and stabilizing microtubules, thus preventing temporal disassembly of microtubules that is required for mitosis. Because microtubule dynamics and mitosis are also inhibited in non-cancerous cells, paclitaxel is quite toxic. To overcome the toxicity, a nontoxic prodrug of paclitaxel (shown right) was synthesized. Propose a strategy how to use this prodrug specifically against cancer tissues.



Project development.

You will be submitting a drug design proposal at the end of this course. In this stage, you are expected to focus on pharmacokinetics and drug metabolism of your drug candidates. Some questions that you may want to answer include:

1) What is the lipophilicity of my lead compound? You can calculate logP with the program Dragon. Are my drug candidates soluble enough? What can you do to increase/decrease solubility?
2) Is my drug candidate a drug-like compound? Does it satisfy Lipinski's rule of fives?
3) Do I need to modify the lead compound to ensure that the active drug reaches its target? What approaches can I take to target the drug specifically to diseased tissues?
4) How is my drug metabolized? If it is P450-dependent oxidation, which isoenzyme is most likely to act on the drug? Do I have to worry about different responses from different individuals?
5) Are my drug candidates likely to be too unstable? What can I do to increase stability?
6) Are my drug candidates likely to be too stable and accumulate excessively? Is this a problem? If it is, what can I do to decrease the stability and promote excretion?
7) Are my drug candidates likely to be toxic or mutagenic? Why? What can I do to reduce the toxicity/mutagenicity?

If you do not have answers to these questions because you are developing something so unique that there is no information about the metabolism and toxicity of your compounds, describe what kind of tests you need to perform to determine metabolic products, mutagenicity, and toxicity.