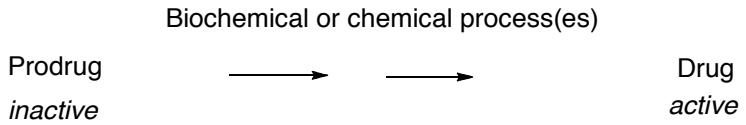
MEDCHEM 562

Prodrugs: Lecture 4; Kent Kunze



Prodrugs are inactive drugs that undergo a chemical or biochemical conversion to the active drug.

The bioconversion can occur in various locations such as the GI tract, depots at injection sites, the target cell itself or compartment (brain). However most bioconversion reactions occur in the liver.

Approximately 7-10% of marketed drugs are considered to be prodrugs and the number is increasing.

The definition of a prodrug is controversial in some circles.
-some consider various salt forms to be prodrugs
-others argue that a prodrug can have some activity in it's own right as long as the bioconversion product dominates the clinical response in vivo.
-are active drugs whose metabolites are also active (e.g. N-dealkylation) then prodrugs?

Terfenadine -> Fexofenadine (was terfenadine really just a toxic prodrug?)

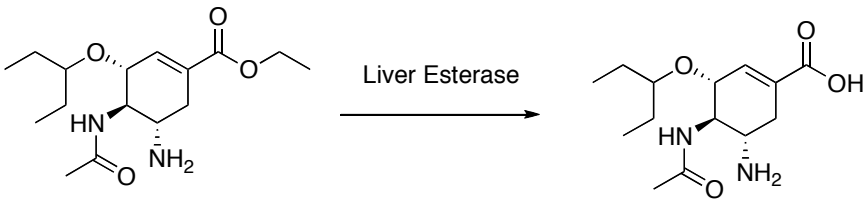
Increasingly drug development focuses on creating active agents against a target in in vitro assays. Then, if bioavailability crops up as an issue, they will seek to create a prodrug.

In some types of disease (cancer) we seek to take advantage of the biochemical machinery in the cancer cell to selectively target a prodrug to that cell type.

Here we will look at some examples of prodrugs.

Esterases

The presence of multiple ionizable groups on a drug can hinder bioavailability. The conversion of a carboxylic acid to an ester removes an ionizable group from the molecule and also increases lipid solubility of the unionized form. While it cannot be guaranteed that an esterase will be active against the putative prodrug, it is reasonably easy to determine if that will be the case in vitro.

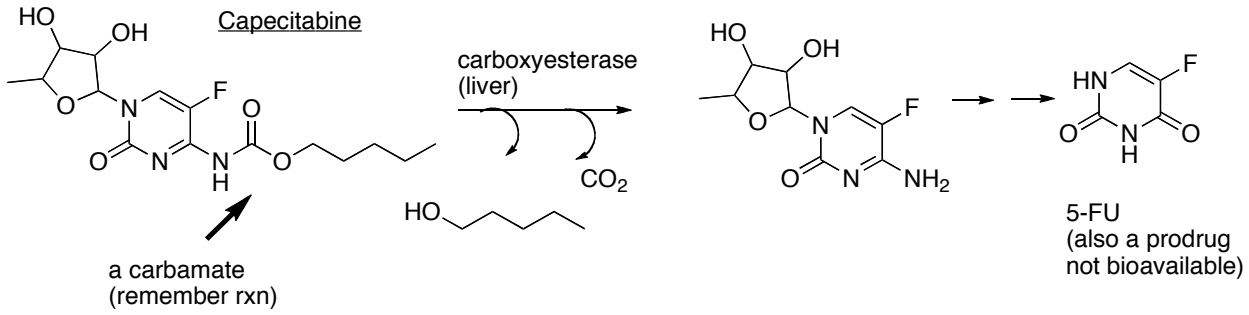


Tamiflu (inactive prodrug)

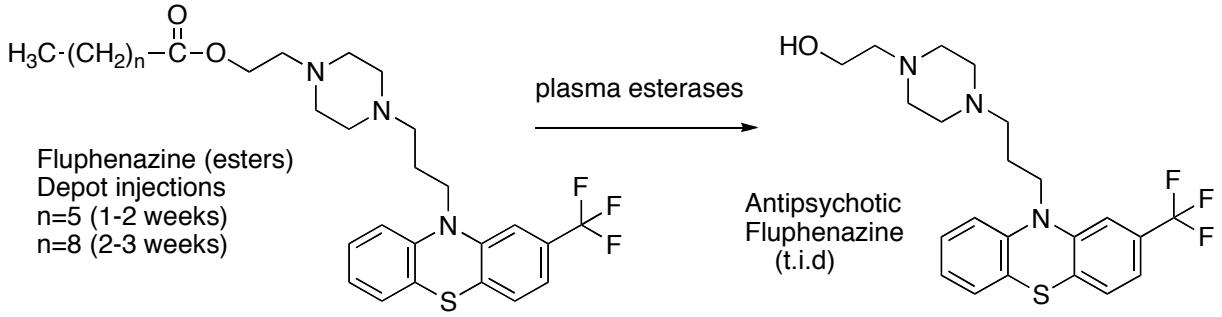
active neuramidase inhibitor

Tamiflu was the first orally-active neuramidase inhibitor for use in flu. Bioavailability of the acid form was poor (why?----it has both an alkylamine and a carboxylic acid group but the ester had good bioavailability). Fortunately a liver esterase (also called carboxyesterase) rapidly catalyzed hydrolysis.

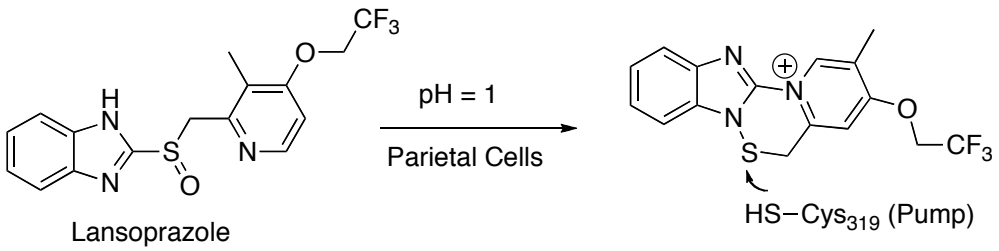
Esterification of carboxylic acids is a major prodrug strategy to increase bioavailability.
In a second example highly relevant to anticancer agents we see that carboxyesterases also will work on carbamates. Note what this gives us is loss of the alcohol followed by spontaneous decarboxylation to give the amine. So a carbamate can be a prodrug strategy for amines.



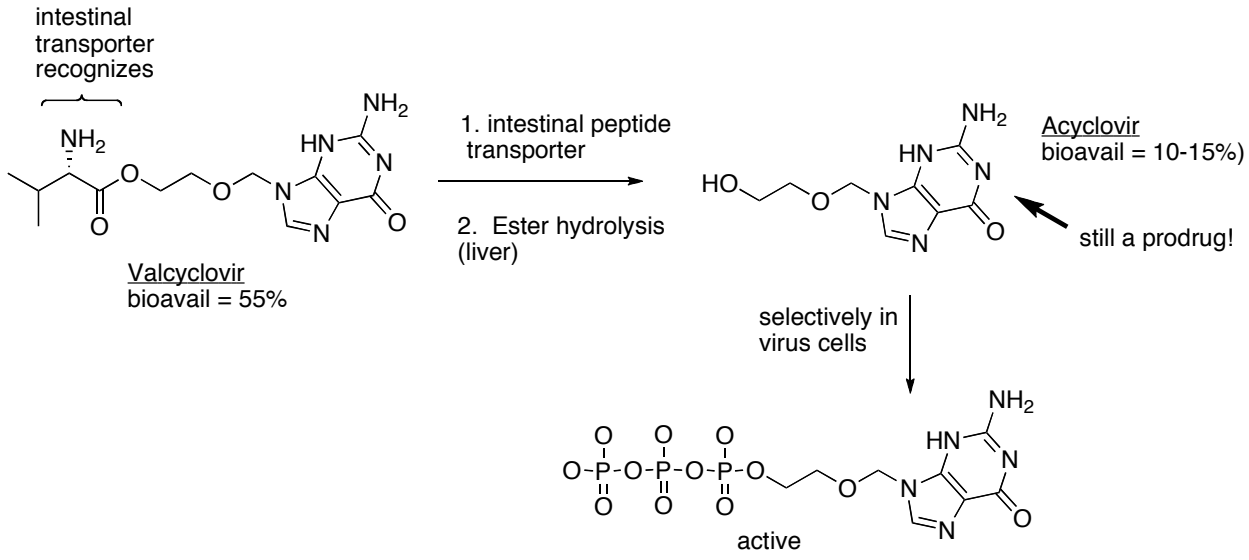
Ester prodrugs for depot injection is a strategy to reduce dosing frequency and to insure compliance over more frequent oral dosing. Note that esterases are also in plasma and we are "throwing away" the carboxylic acid and keeping the alcohol.



Bioactivation at the site of action. Proton pump inhibitors are formulated to be released and absorbed in the intestine. They travel through the blood to the parietal cells of the stomach where they are converted to the active form by the acid pH of the pump itself and the active form reacts covalently with a critical cysteine residue.

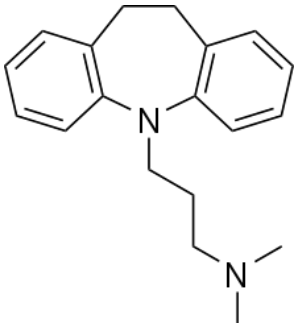


Improved absorption by using a transporter (Valtrex).

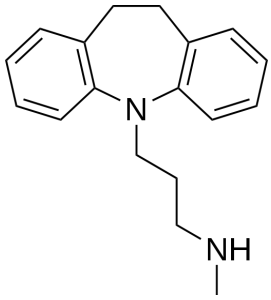


P450 Bioactivation:

Many active drugs are metabolized by the P450 enzymes and very often the metabolites are active against the target as well. While these drugs don't fit the classical definition of a prodrug we often have to be mindful of active metabolites. Remember that metabolites can also circulate at high levels in the blood and may have their own off-target effects and toxicities. The tricyclic antidepressants fall into this category. In some cases the metabolites are drugs themselves.

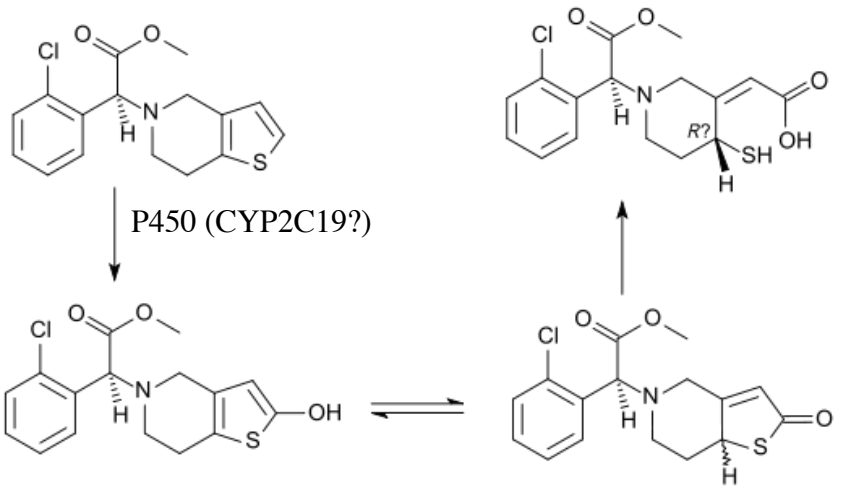


Imipramine



Desipramine

Clopidogrel activation is dependent on oxidation of the thiophene ring by P450 enzymes. The active metabolite binds irreversibly to platelet P2Y12 receptors and inhibits ADP stimulated platelet aggregation. CYP2C19 poor metabolizers don't respond well so it is suspected that CYP2C19 is involved in the first oxidation. The issue is further complicated by the potential for other drugs like fluoxetine and omeprazole to inhibit this enzyme. Clopidogrel has a black box warning and would seem to be a candidate for personalized medicine.



Prasugrel (another antiplatelet drug) also must be bioactivated via the same sequence of reactions so it is also a prodrug. However bioactivation is not P450 dependent so it is a safer drug from that perspective. No black box warning.