PRODRUGS OF CARBOXYLIC ACIDS

- Ester formation is the most common prodrug design strategy to increase lipophilicity by masking carboxylic acids, phosphates, and other charged groups.

- Such prodrug is activated by enzymatic (esterase) or chemical hydrolysis.

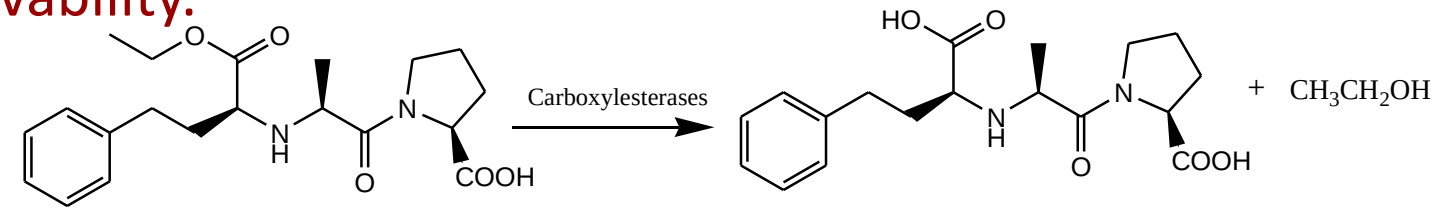
- Ester prodrugs are most often used to enhance oral absorption and thus passive membrane permeability of poorly permeable compounds.

- Enalapril is an angiotensin converting enzyme (ACE) inhibitor used in the treatment of hypertension and some types of chronic heart failure.

- As a prodrug, enalapril is metabolised *in vivo* to the active form enalaprilat and ethanol by various esterases.

- Enalaprilat has potent therapeutic activity when administered intravenously, but its high polarity causes it to be poorly absorbed from gastrointestinal tract.

- Esterification of enalaprilat to enalapril enhances the affinity for the intestinal peptide carrier-mediated transport system, increasing the intestinal absorption and resulting in improved bioavability.

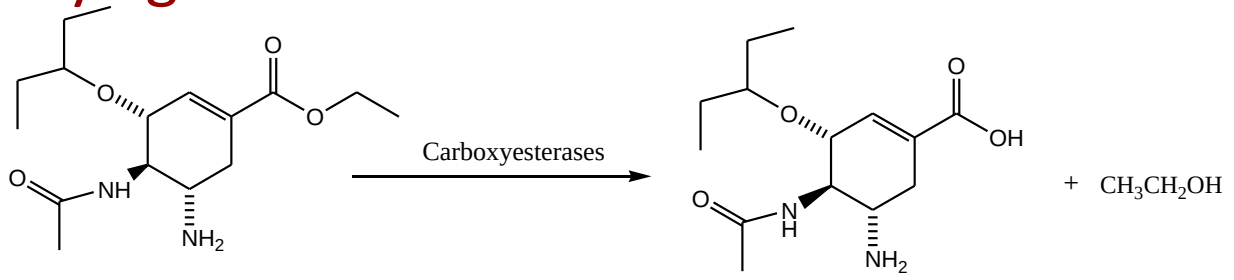


Enalapril Enalaprilat Ethanol

- Oseltamivir is an ethyl ester prodrug of oseltamir carboxylate, requiring ester hydrolysis for conversion to the active form.

- Oseltamivir is readily absorbed from gastrointestinal tract after oral administration and converted by hepatic esterases to oseltamir carboxylate with an absolute bioavability of 80%.

- Oseltamir carboxylate is a potent carboxylic transition-state analog inhibitor of influenza virus, neuraminidase, with activity against both influenza A and B viruses.



Oseltamivir | Oseltamivir Carboxylate | Ethanol

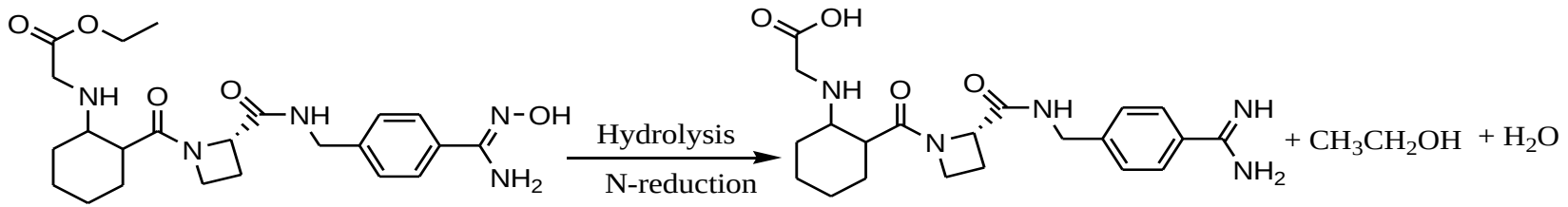
- Ximelagatran was designed to increase the bioavability of melagatran, which was the first member of orally administered potent thrombin inhibitors.

- The double prodrug ximelagatran is composed of an ethyl ester group in place of the carboxylic acid and an N- hydroxyamidine group in the amidine end of melagatran.

- By adding these groups, the highly hydrophilic and charged melagatran is converted into a much more lipophilic molecule that is uncharged at physiological pH.

- Ximelagatran increased bioavability to 18-24% and also improved pharmacokinetic properties relating to lower variability in bioavailability and lack of food effects.

- The formation of melagatran from ximelagatran requires two metabolic reactions. The ester group is cleaved by esterases and N- hydroxyamidine group is reduced to an amidine group in the liver.



Ximelagatran Melagatran Ethanol