

Prodrugs

Concept

- A prodrug is an inactive derivative that will be converted to the active drug *in vivo*
- Prodrugs are used when drugs have unattractive physicochemical properties

Undesirable Properties

- Physical Properties
 - Poor aqueous solubility
 - Low lipophilicity
 - Chemical instability
- Pharmacokinetic Properties
 - Poor distribution across biological membranes
 - Good substrate for first-pass metabolism
 - Rapid absorption/excretion when long-term effect desired
 - Not site-specific

Steps in Prodrug Design

- Identification of drug delivery problem
- Identification of desired physicochemical properties
- Selection of transport moiety which will
 - give prodrug desired transport properties
 - be readily cleaved in the desired biological compartment

Derivative Types

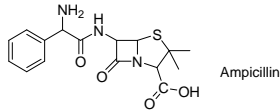
- Small molecule
 - Prodrug has MW in 200-500 g/mole range
 - Called a low molecular weight prodrug
- Macromolecule
 - conjugate drug reversibly to biomolecule
 - antibody
 - hormone
 - Objectives
 - Target specific cell type (cancer cells antigens)
 - Extend duration of action (longer circulation life time)
 - Improve solubility
 - Improve chemical stability of therapeutic agent

Reversible Derivatives

Functional Group	Derivative
-COOH Carboxylic Acid	$\begin{array}{ccc} \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel \\ \text{—O—R} & \text{—NHR} & \text{—O—R}_1\text{—O—R}_2 \\ \text{Esters} & \text{Amides} & \alpha\text{-Acylalkoxyalkyl esters} \end{array}$
-OH Alcohol	$\begin{array}{ccc} \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel \\ \text{—O—R} & \text{—O—R} & \text{—O—R} \\ \text{Esters} & \text{Carbonate Esters} & \text{Ethers} \end{array}$ $\begin{array}{ccc} \text{O} & \text{O} & \text{O} \\ \parallel & \parallel & \parallel \\ \text{—O—P—OH} & \text{—O—R}_1\text{—O—R}_2 & \text{—O—R}_1\text{—O—R}_2 \\ \text{Phosphate Esters} & \alpha\text{-Acylalkoxyalkyl ethers} & \end{array}$
-NH ₂ Amine	$\begin{array}{ccc} \text{O} & \text{O} & \text{R}_1 \\ \parallel & \parallel & \parallel \\ \text{—N—R} & \text{—N—OR} & \text{—N—C} \\ \text{Amides} & \text{Carbamates} & \text{Imines} \\ & & \text{R}_2 \end{array}$ $\begin{array}{ccc} \text{R} & \text{R}_1 & \text{O} \\ \parallel & \parallel & \parallel \\ \text{—N—R}_2 & \text{—N—O—R}_1\text{—O—R}_2 & \text{—N—O—R}_1\text{—O—R}_2 \\ \text{Enamines} & \text{N-Acylalkoxyalkoxycarbonyl} & \end{array}$

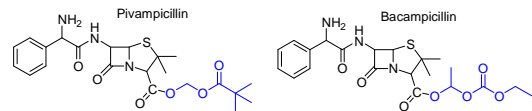
Oral Bioavailability Exercise

- Ampicillin is poorly absorbed from the GI tract (~30% absorbed)
- Show the form of ampicillin that will be observed in the intestine (pH ~8)
- Suggest prodrug forms of ampicillin that might be better absorbed after oral dosing

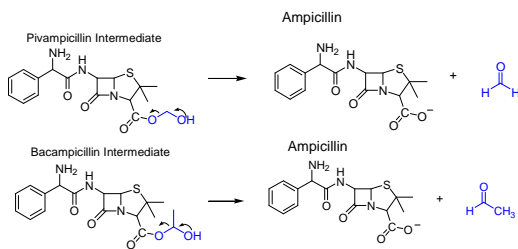


Ampicillin Prodrugs

- Esters of ampicillin are not good esterase substrates due to the steric crowding
- α -acyloxyalkyl esters or carbonates undergo initial enzymatic cleavage of the terminal ester to generate unstable intermediates
- Show the intermediate and determine why it is unstable and spontaneously generates ampicillin *in vivo*



Ampicillin Generation *In Vivo*



Transdermal Delivery

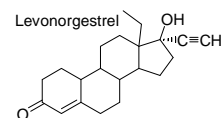
- 'Patch'-based delivery of drugs is becoming more common
 - Contraceptives
 - Nicotine addiction therapy
- Delivery through the skin requires biphasic solubility
 - Lipid solubility
 - Water solubility

Biphasic Solubility

- Is $\log P \sim 0$ sufficient to ensure biphasic solubility (and therefore dermal permeability)?
- Why or why not?

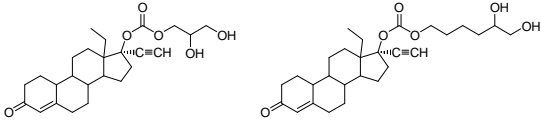
Transdermal Contraceptive Delivery

- Levonorgestrel is a potent contraceptive
- What solubility properties need to be changed?
- Suggest prodrug derivatives that might be useful



Levonorgestrel Prodrugs

- The two structures below enhance transdermal delivery 15 and 30 times over levonorgestrel
- Which shows the 30 x improvement?
- Why?



Reading

- Chapter 8
- 8.4 Problems 1-3, 5, 7