

PRODRUGS

Prodrugs

- Initial definition:
- "Drug Latentiation" - included later
- Why use prodrugs?

Prodrugs

- "Hard Drugs" -
- Increased efficiency by avoiding metabolism
 - No toxic metabolites are formed
 - HOWEVER, less readily eliminated due to lack of metabolism
- "Soft Drugs"

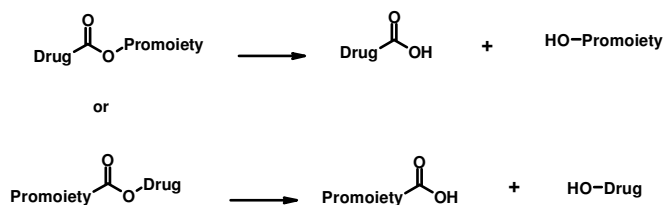
Conversion

- Metabolism (enzyme dependant)
- Chemical Methods (non-dependant)

Prodrugs

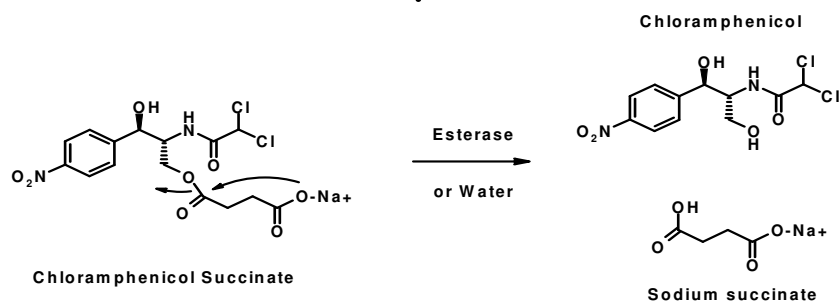
- Carrier-linked prodrugs - drugs that are attached through a metabolically labile chemical linkage to another molecule designated as the _____
 - The _____ alters the physical properties of the drug to increase water or fat solubility or provide site-directed delivery
 - Advantages:
 - Increased absorption
 - Injection site pain relief
 - Elimination of unpleasant taste
 - Decreased toxicity
 - Decreased metabolic inactivation
 - Increased chemical stability
 - Prolonged or shortened action

Functional Groups in Prodrugs

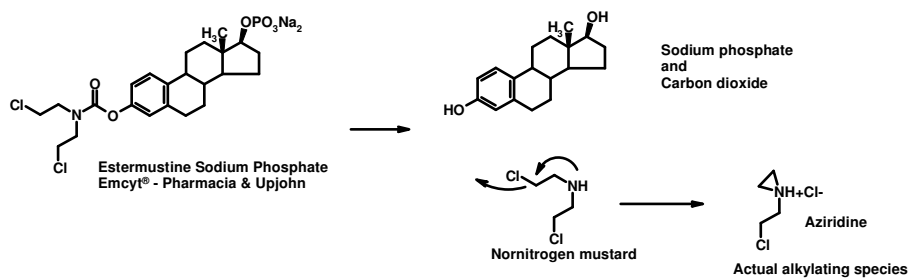


- Types of esterase enzymes mediating the hydrolysis process
 - Ester hydrolase, Lipases, Cholesterol esterases, Acetylcholinesterase, Carboxypeptidase, Cholinesterase
 - Bacterial microflora enzymes
- Wide number of choices of promoiety alcohols available
 - Steric, electronic and hydrophobicity properties allow rate and extent of hydrolysis to be controlled

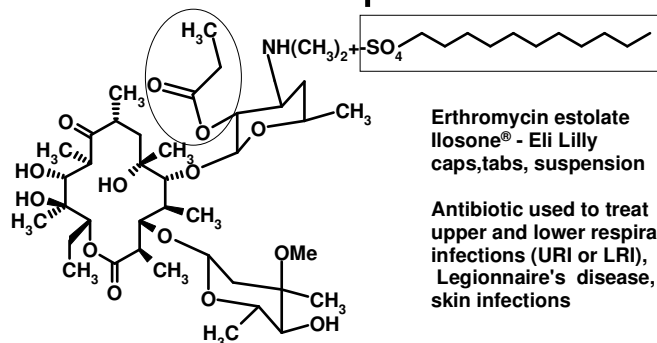
Chloramphenicol



Mutual Prodrug



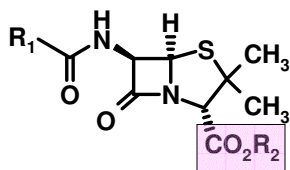
Functional Groups in Prodrugs



Erthromycin estolate
Ilosone® - Eli Lilly
caps, tabs, suspension

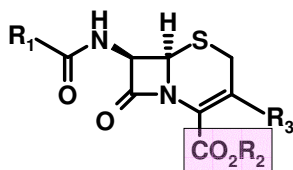
Antibiotic used to treat
upper and lower respiratory
infections (URI or LRI),
Legionnaire's disease,
skin infections

Esters Failure as Prodrugs



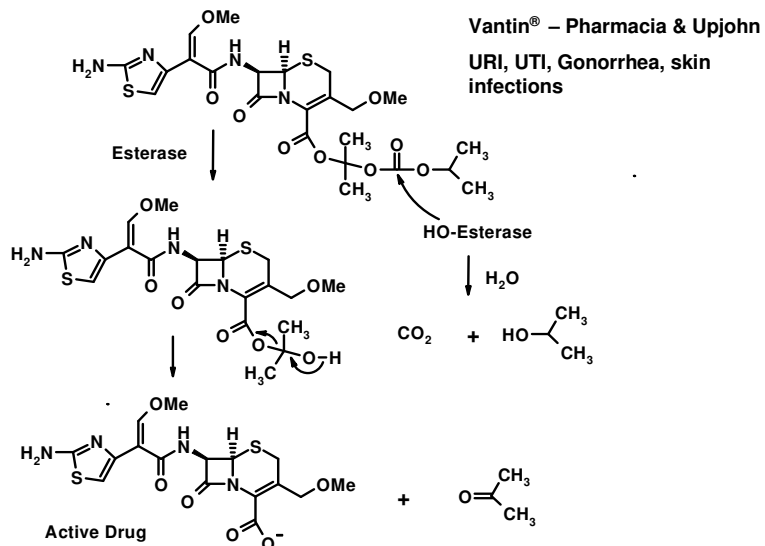
R₂ = ethyl, propyl, butyl, phenyl
Penicillin esters

Esterases → NO REACTION!



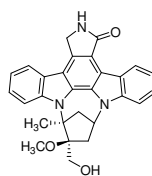
R₂ = ethyl, propyl, butyl, phenyl
Cephalosporin esters

β -Lactam prodrug - Double esters

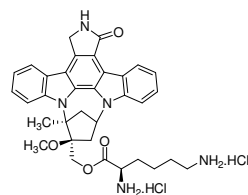


Esters as Prodrugs

development candidate
for the treatment of
prostate cancer



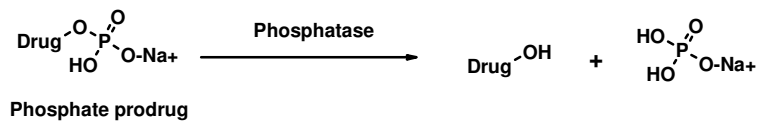
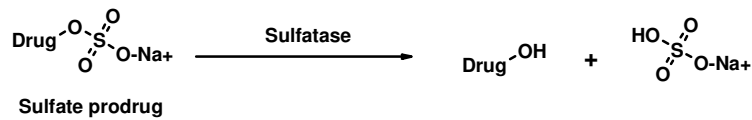
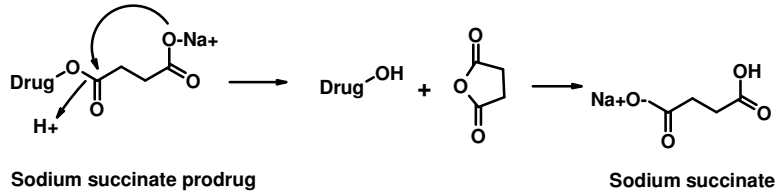
CEP-751



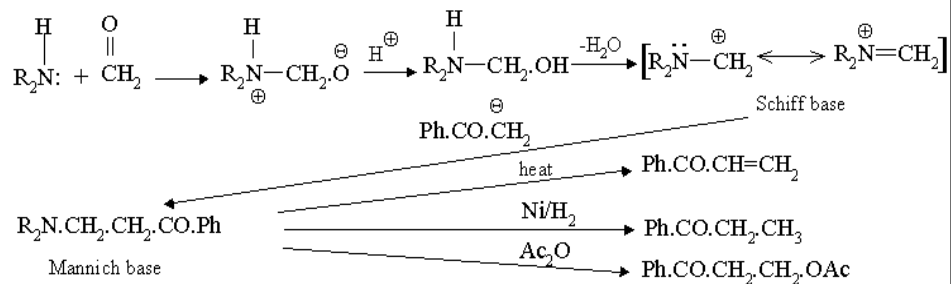
CEP-2563

Hudkins et al. *Bioorganic & Medicinal Chemistry Letters* 8 (1998) 1873-1876

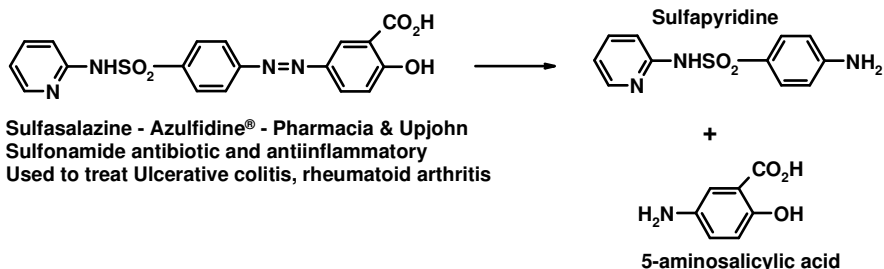
Other ester prodrugs - soluble



Mannich Base Chemistry - FYI



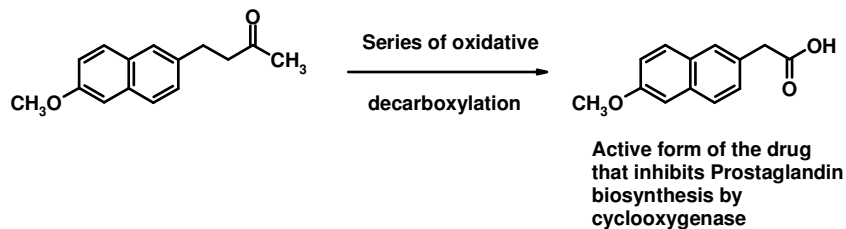
Azo Prodrugs



Bioprecursor Prodrugs

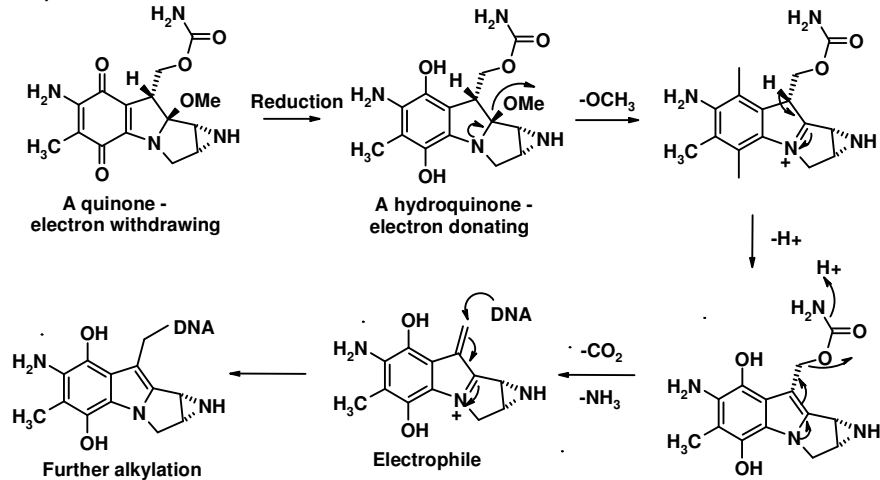
Do NOT contain a carrier or promoiety

- Contain latent functionality
- Metabolically or chemically transformed into an active drug
- Types of activation are predictable
 - Oxidative (most common method)
 - Reductive
 - Phosphorylation (antiviral agents)
- Oxidation Example - Nabumetone - Relafen® - Smith Kline Beecham



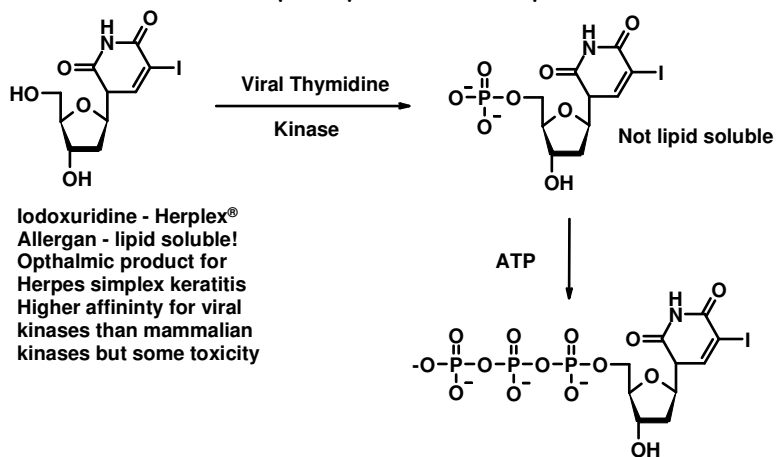
Bioprecursor Prodrugs

Reduction example - Mitomycin C - Mutamycin® -
Bristol Myers Adenocarcinoma of the stomach and
pancreas



Bioprecursor Prodrugs

Phosphorylation example -



TWO mechanisms of action: 1. Inhibits DNA polymerase 2. Incorporated into DNA affording incorrect base pairing and template activity