Prodrugs concept & Applications

By:
Dr. Dhulfiqar Ali

Prodrugs concept & Applications

- Almost all drugs possess some undesirable physicochemical and biological properties.
  - Limited solubility and poor chemical stability prevent the drug from being **adequately formulated**
  - **Low** or variable **bioavailability** due to incomplete absorption across biological membrane or extensive first-pass effect
  - **Lack of site specificit**y

- Their therapeutic efficacy can be improved by eliminating the undesirable properties while retaining the desirable ones.

This can be achieved through biological, physical or chemical means.

Prodrugs concept & Applications

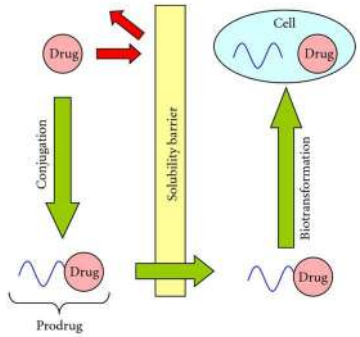
- The Biological approach is to alter the **route of administration** which may or may not be acceptable to patient.

- The Physical approach is to modify the **design of dosage** form such as controlled drug delivery of drug.

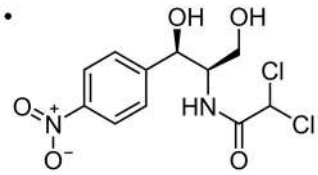
- The best approach in enhancing drug selectivity while minimizing toxicity, is the chemical approach for **design of prodrugs**.

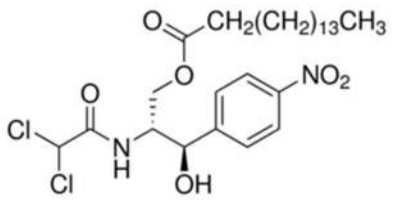
Prodrugs concept & Applications

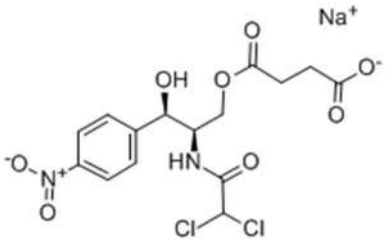
- The term prodrug relates to "Biologically inactive derivatives of drug molecules that undergo an **enzymatic** and/or **chemical conversion** in vivo to release the pharmacologically active parent drug.



- Chloramphenicol:
  - bitter taste → Chloramphenicol palmitate used in the form of suspension in children. (Undesirable taste arises due to adequate solubility and interaction of drug with taste receptors → It can be solved by lowering the solubility of drug or prodrug in saliva)
  - poor solubility in water → Chloramphenicol sodium succinate with a good water solubility.

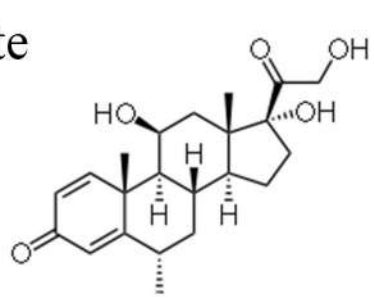


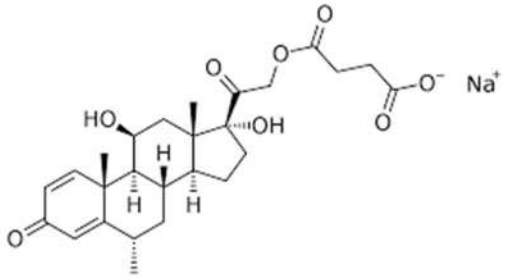




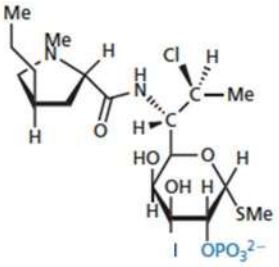
Utility of Prodrug Design

1. To improve aqueous solubility:
   - Methylprednisolone sodium succinate

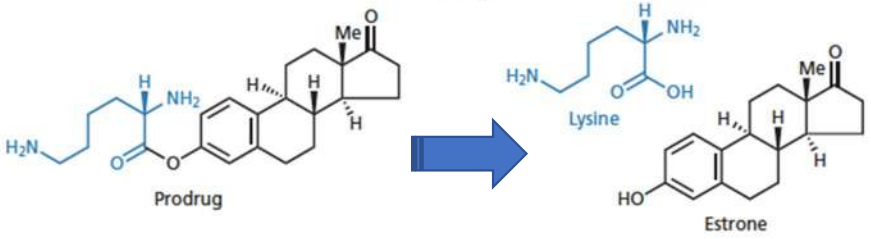




   - Clindamycin phosphate



   - Steroid estrone



Utility of Prodrug Design

2. Increasing lipophilicity to increase systemic bioavailability:
   - Enalapril , which is the prodrug for the antihypertensive agent enalaprilate

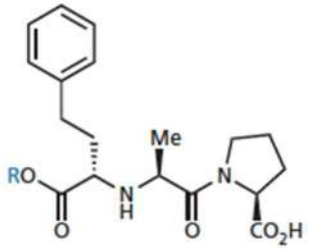


FIGURE 14.19 Enalapril (R = Et); Enalaprilate (R = H).

   - Penicillin prodrugs

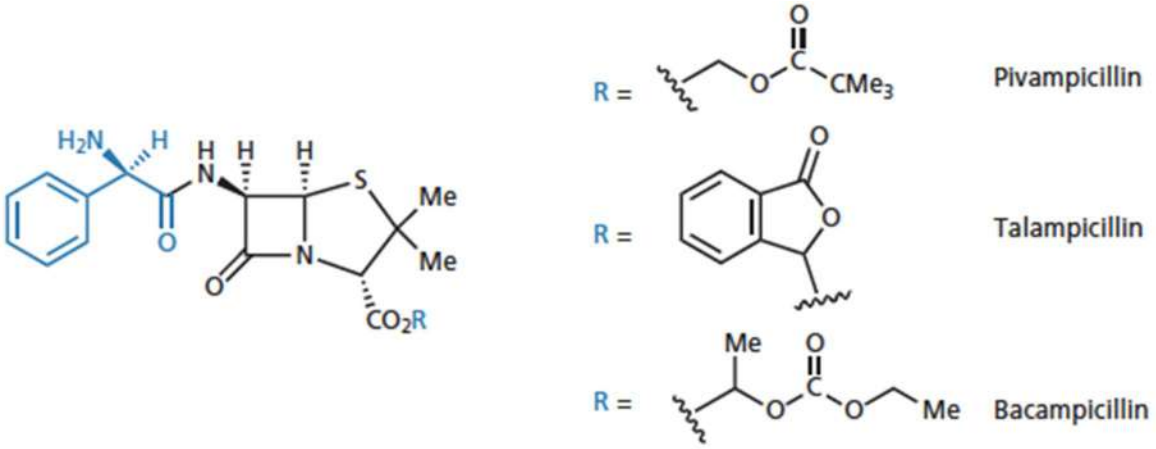


FIGURE 1 Prodrugs used to aid absorption of ampicillin through the gut wall.

Utility of Prodrug Design

2. Increasing lipophilicity to increase systemic bioavailability:
   - Penicillin prodrugs

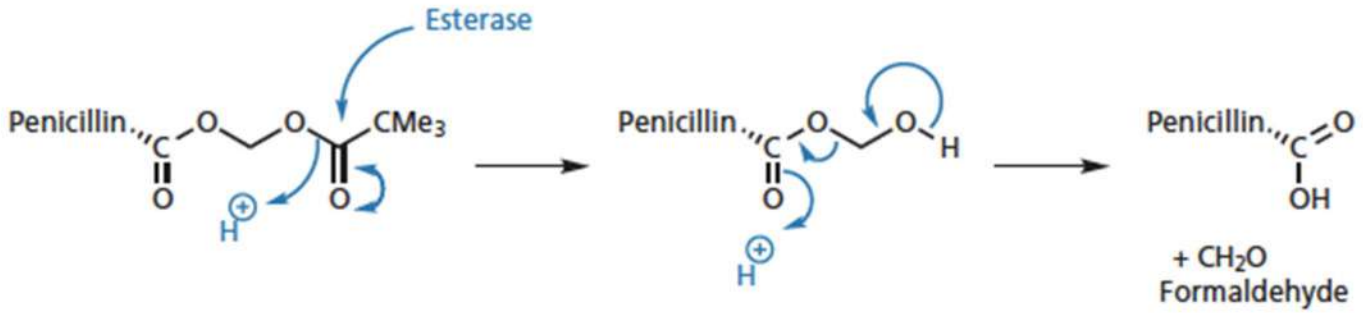


FIGURE 2 Mechanism by which acyloxymethyl esters are hydrolysed.

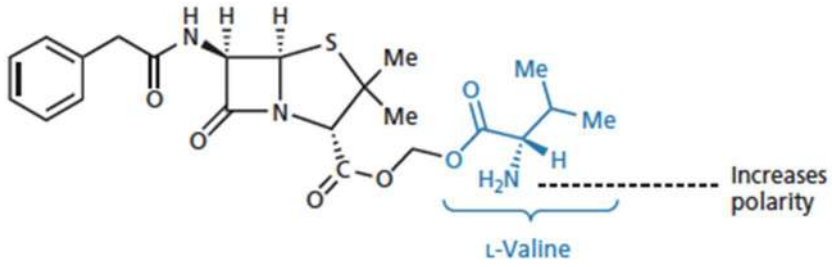


FIGURE 3 Polar extended ester for penicillin G.

Utility of Prodrug Design

3. Sustained-release prodrug systems: (prodrugs are designed to be converted slowly to the active drug, thus prolonging a drug's activity)

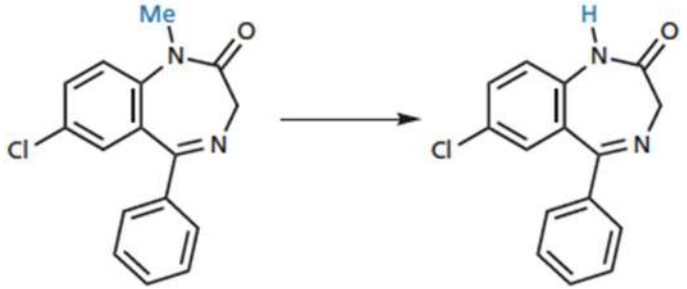


FIGURE 14.25 Valium (diazepam) as a possible prodrug for nordazepam.

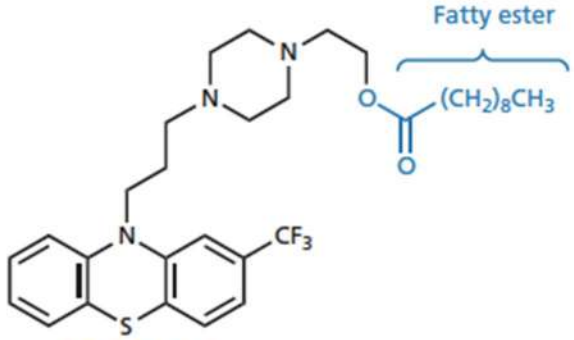


FIGURE 14.27 Fluphenazine decanoate.

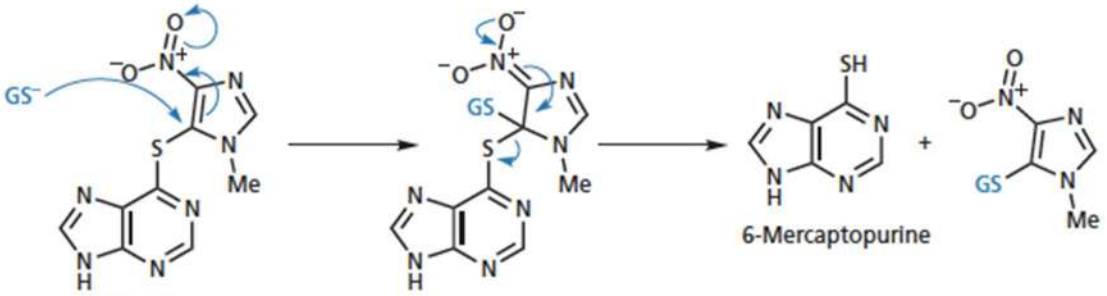


FIGURE 14.24 Azathioprine acts as a prodrug for 6-mercaptopurine (GS = glutathione).

Utility of Prodrug Design

4. Prodrugs masking drug toxicity and side effects: Aspirin (reduce gastric irritation)

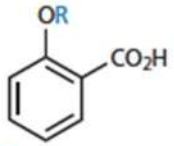
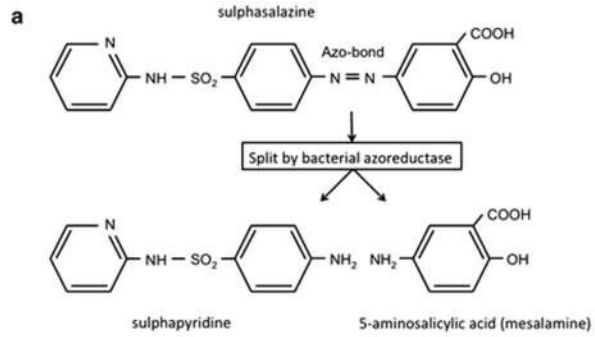
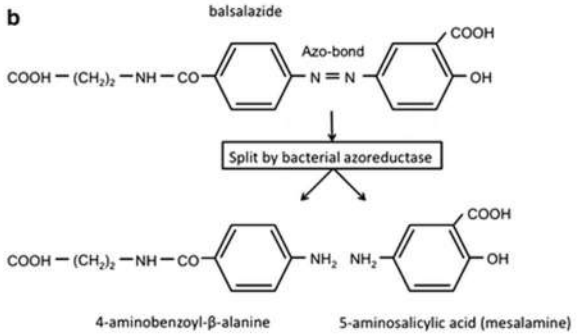
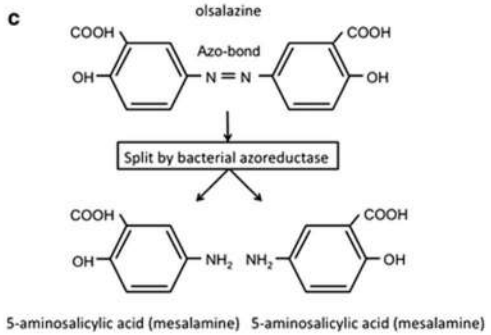


FIGURE 14.28 Aspirin (R = $COCH_3$) and salicylic acid (R = H).

5. Site specificity: these prodrugs undergo metabolism by the bacterial enzyme azo reductase when they reach the colon, releasing 5-ASA

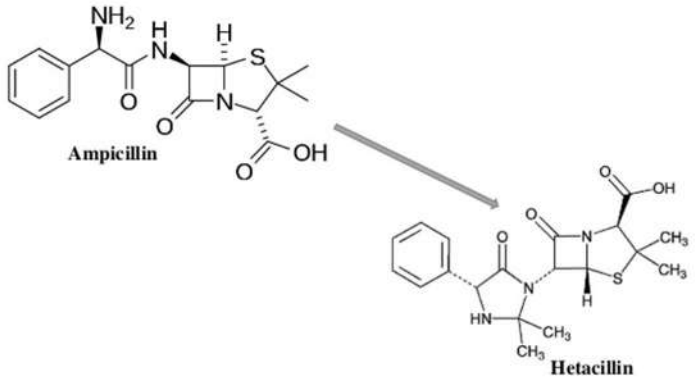




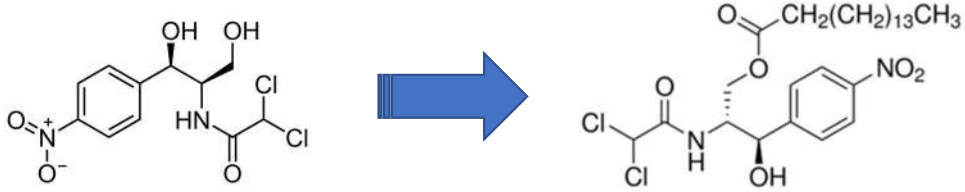


Utility of Prodrug Design

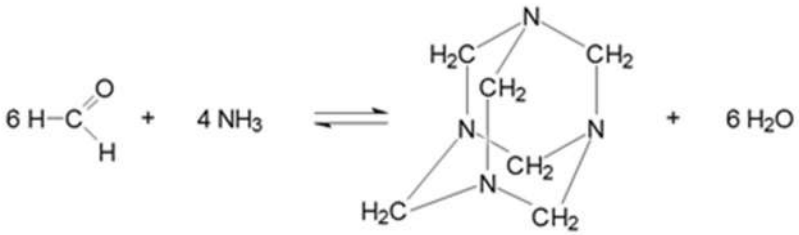
6. Enhancement of chemical stability:



7. Improving taste: Chloramphenicol palmitate used in the form of suspension in children



8. Formulation problem: Methenamine, Formaldehyde is gas → stable as a solid , decompose in aqueous acid, PH of urine in bladder is about 4.8 → urinary tract disinfectant.



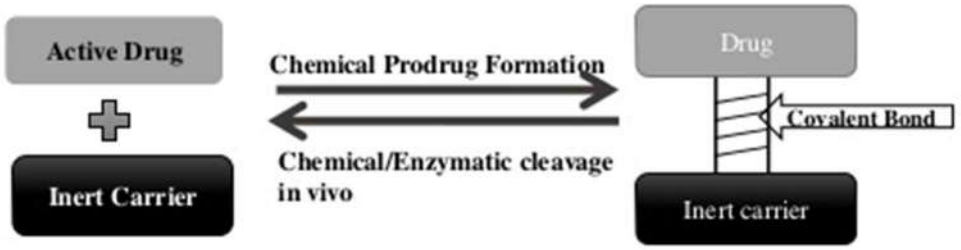
Types of Prodrug

A. According to mechanism of drug delivery: Prodrugs have been classified according to mechanism of drug delivery into two main classes- Carrier-linked prodrugs and Bioprecursors.

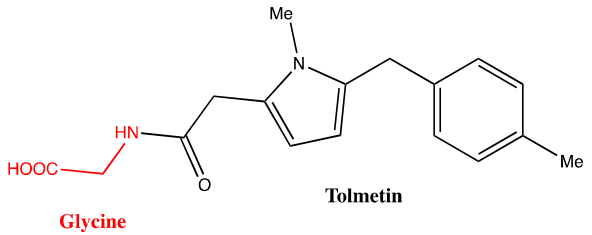
B. Based on chemical structures: Prodrugs have been categorized into four classes, namely Bipartite Prodrugs, Tripartite prodrugs, Mutual Prodrugs and Polymeric Prodrugs.

Types of Prodrug

1. Carrier-linked prodrug: A compound contains an active drug linked to a carrier group that is removed enzymatically or chemically.

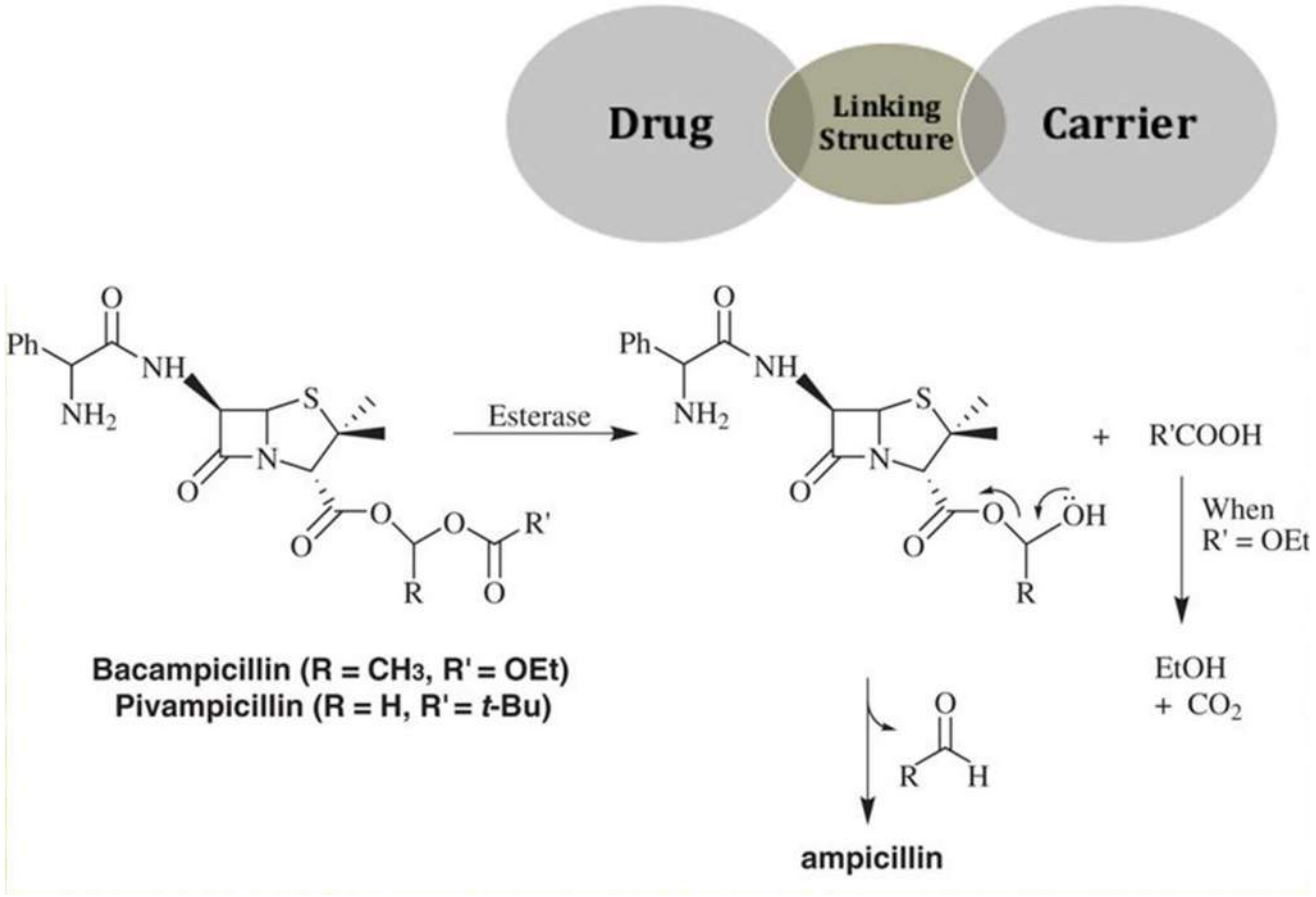


   a. Bipartite prodrug: It is composed of one carrier (group) attached to the drugs. e.g. Tolmetin-glycine prodrug.



Types of Prodrug

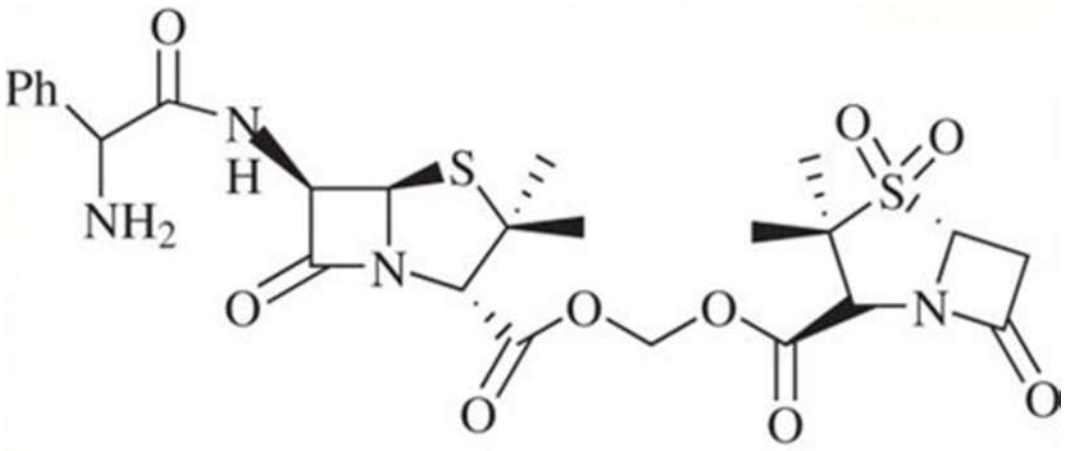
b. Tripartite prodrug: The carrier attached via a linker to drug.



Types of Prodrug

c. Mutual Prodrugs: two , usually synergistic , drugs attached to each other.

e.g. Sultamicillin is an oral form of the antibiotic combination ampicillin/sulbactam. It contains esterified ampicillin and sulbactam

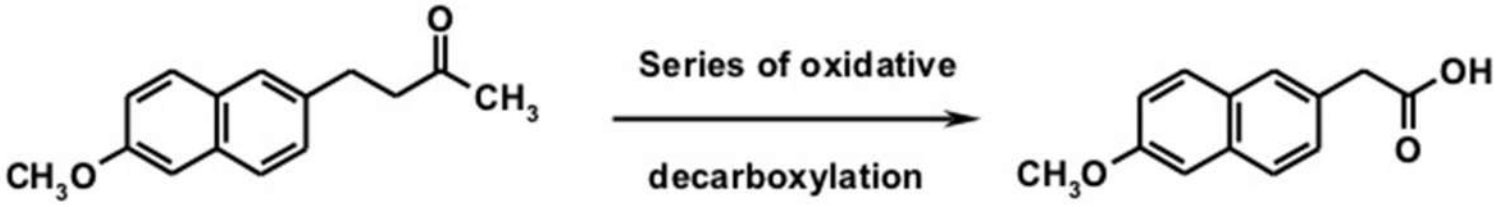


Sultamicillin

Types of Prodrug

2. Bioprecursor Prodrug: is a prodrug that does not contain the linkage to a carrier group, but results from a molecular modification of the active principle itself.
   - ➢ This modification generates a new compound, transformed metabolically or chemically, the resulting compound being the active principle.
   - ➢ Types of activation: Oxidative, reductive, phosphorylation

   e.g. Nabumetone



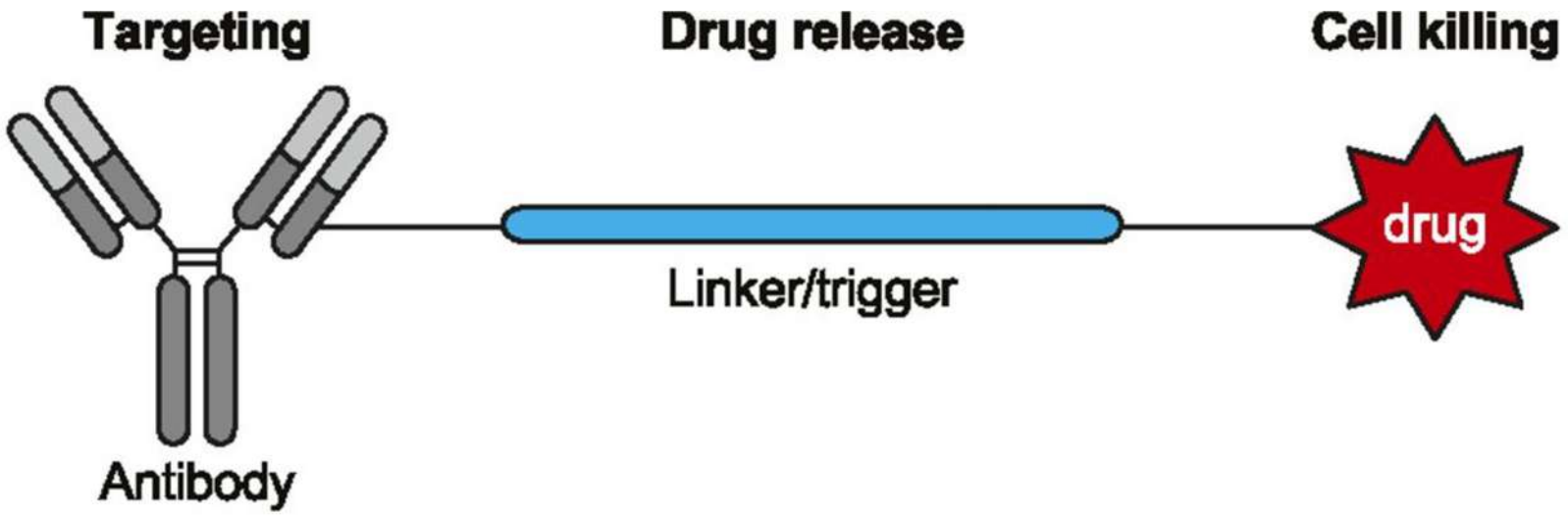
Non-steroidal antiinflammatory

Use: Arthritis

Active form of the drug that inhibits Prostaglandin biosynthesis by cyclooxygenase

Types of Prodrug

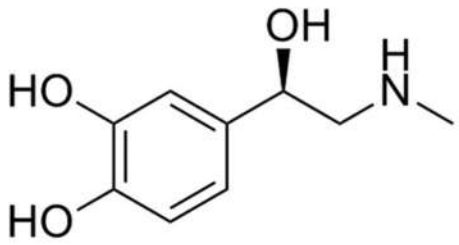
1. Small molecule Prodrug: is a prodrug has MW 200-500 g/mole
2. Macromolecule prodrug: drug conjugated to a biomolecule (antibody, hormone)



Steps in Prodrug Design

1. Identify of drug delivery problem
2. Identify the desired physicochemical properties
3. Select the appropriate transport moiety (carrier) that has to be released readily in the desired biological compartment

Epinephrine (E)
catechol: easily oxidized
less lipophilic than dipivefrin
poor absorption and poor penetration of the eye
irritating to eyes when used in treatment of glaucoma



Epinephrine

Steps in Prodrug Design

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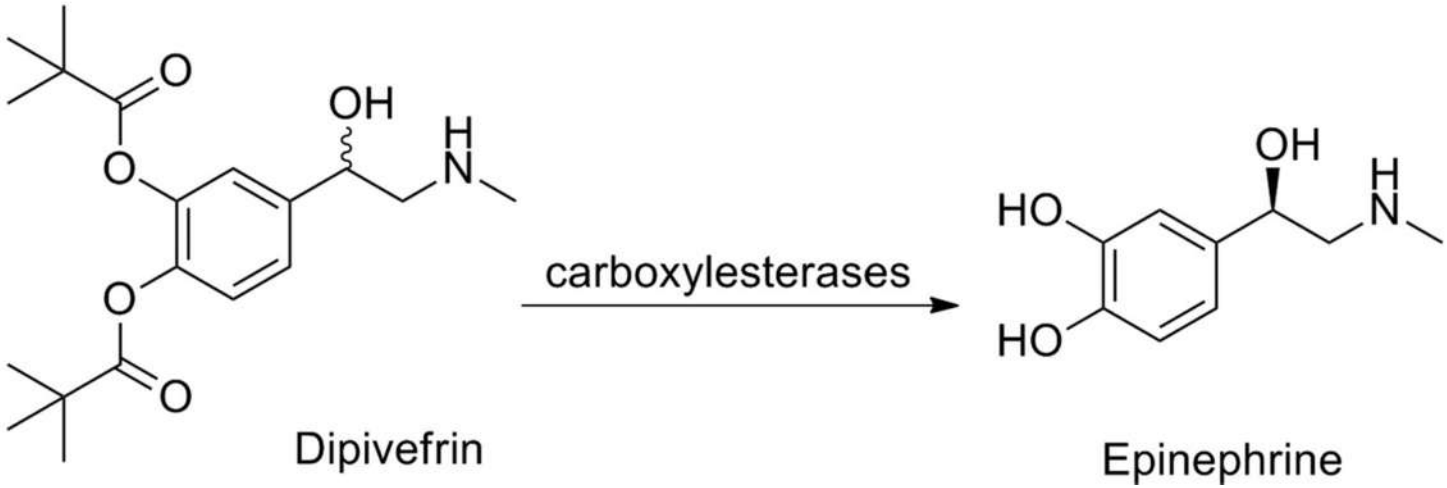


Dipivefrin

Epinephrine

Ideal Drug Carriers

1. Protect the drug until it reaches the site of action
2. Localize the drug at the site of action
3. Allow for release of drug
4. Minimize host toxicity
5. Are biodegradable, inert, and nonimmunogenic
6. Are easily prepared and inexpensive
7. Are stable in the dosage form

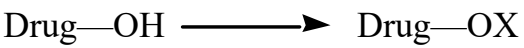
Carrier Linkages for Various Functional Groups

Alcohols, Carboxylic Acids, Amines and Related Groups

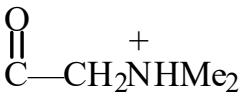
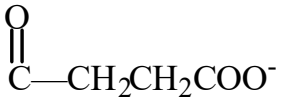
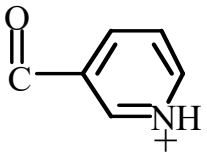
- Most common prodrug form is an ester
- Ester prodrug activation by Esterases / hydrolysis
- Can prepare esters with any degree of hydrophilicity or lipophilicity
- Ester stability can be controlled by appropriate electronic and steric manipulations

Prodrugs for Alcohol Containing Drugs

Ester analogs as prodrugs can affect lipophilicity or hydrophilicity



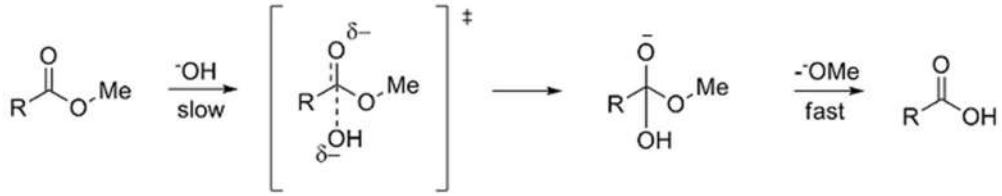
alcohols

X	Effect on Water Solubility
	(R = aliphatic or aromatic) decreases (increases lipophilicity)
	increases (pK_a ~ 8)
	increases (pK_a ~ 5)
	increases (pK_a ~ 4)
$PO_3^{=}$ (phosphate ester)	increases (pK_a ~ 2 and ~ 6)
	increases (pK_a ~ 1)

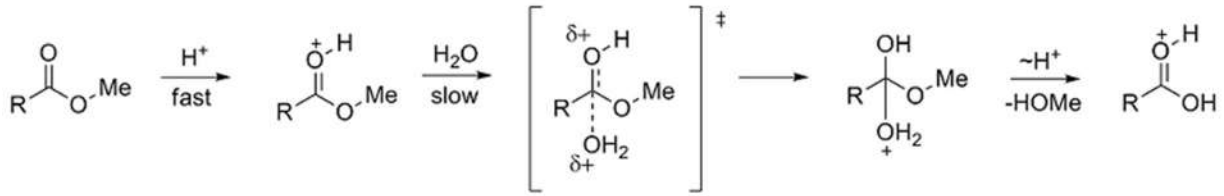
To accelerate hydrolysis rate:

- attach an electron-withdrawing group if a ***base hydrolysis*** mechanism is important
- attach an electron-donating group if an ***acid hydolysis*** mechanism is important

Base Catalyzed Ester Hydrolysis:



Acid Catalyzed Ester Hydrolysis:



To accelerate hydrolysis rate:

- attach an electron-withdrawing group if a ***base hydrolysis*** mechanism is important
- attach an electron-donating group if an ***acid hydolysis*** mechanism is important

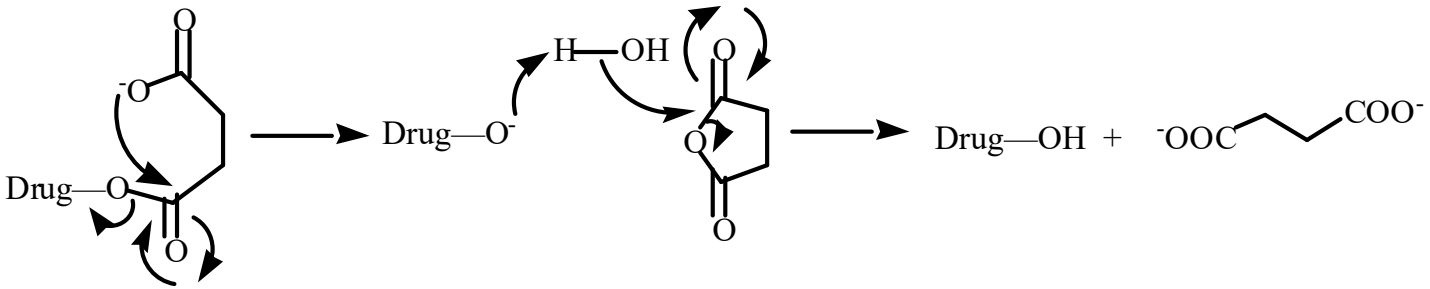
To slow down hydrolysis rate:

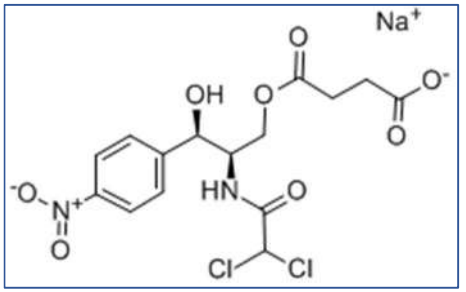
make sterically-hindered esters

make long-chain fatty acid esters

Another Approach to Accelerate Hydrolysis

Intramolecular hydrolysis of succinate esters





Also, acetals or ketals can be made for rapid hydrolysis in the acidic medium of the GI tract.