Faculty of Pharmacy
Dept. of Pharm. Anal. Chem

Prodrugs

by

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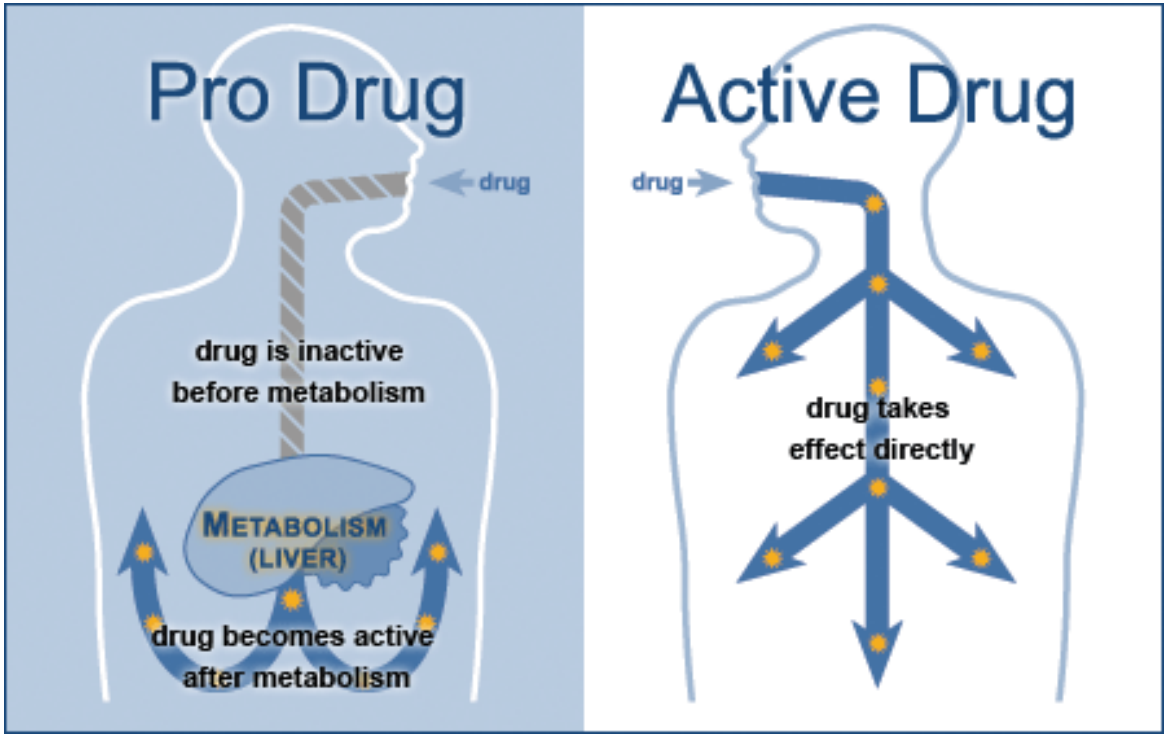
Prodrugs


Pro Drug
drug
drug is inactive
before metabolism
METABOLISM
(LIVER)
drug becomes active
after metabolism
Active Drug
drug
drug takes
effect directly

Introduction

Prodrug

- Almost all drugs possess some undesirable physicochemical and biological properties.

Prodrug

- Drug candidates are often discontinued due to issues of poor pharmacokinetic properties or high toxicities.

Prodrug

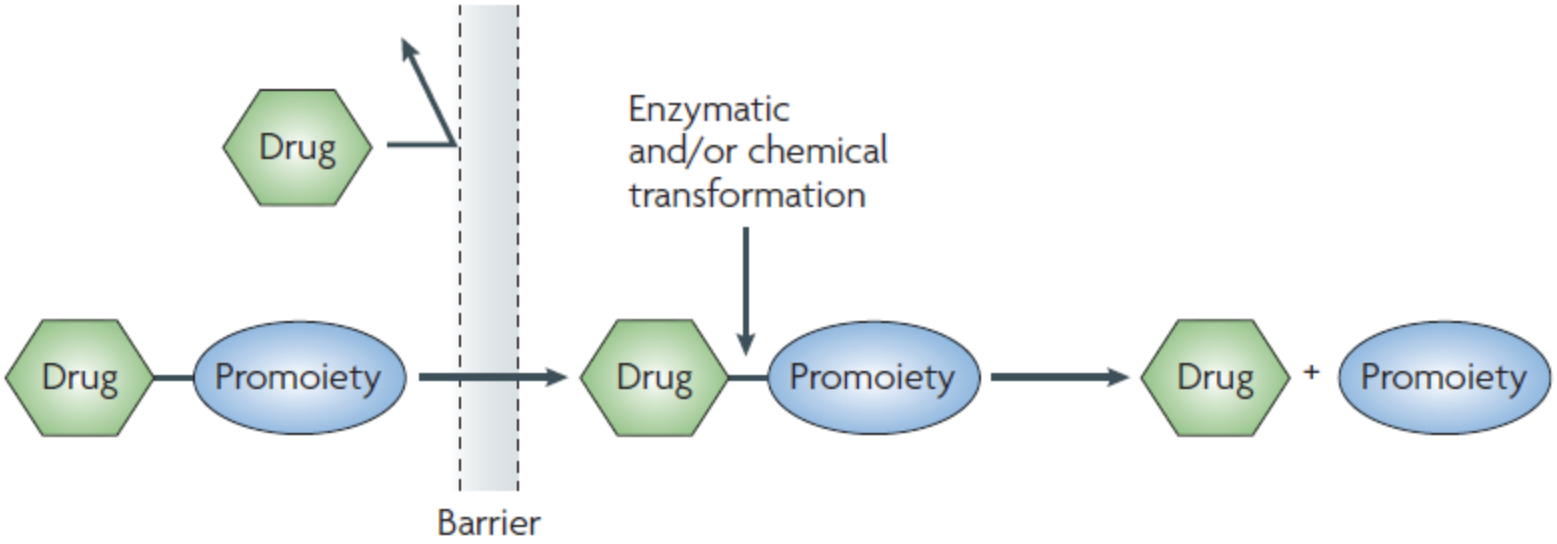
- Their therapeutic efficacy can be improved by eliminating the undesirable properties while retaining the desirable ones.

Prodrug

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

prodrug

Biological approach	• *To alter the route of administration which may or may not be acceptable to patient*
Physical approach	• *To modify the design of dosage form such as controlled drug delivery*
Chemical approach	• *To enhance drug selectivity and minimize its toxicity*



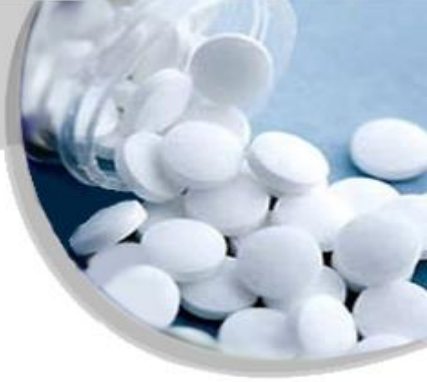
- Sometimes drugs are designed to make use of metabolic processes in order to generate their active form.
- This is done in order to improve some selected properties of the molecule, such as water solubility or ability to cross a membrane, temporarily.

Definition

The term prodrug, introduced in 1958 by Adrien Albert, relates to

"***Biologically inert derivatives of drug molecules that undergo an enzymatic (metabolic) and/or chemical conversion in vivo to release the pharmacologically active parent drug*.**"

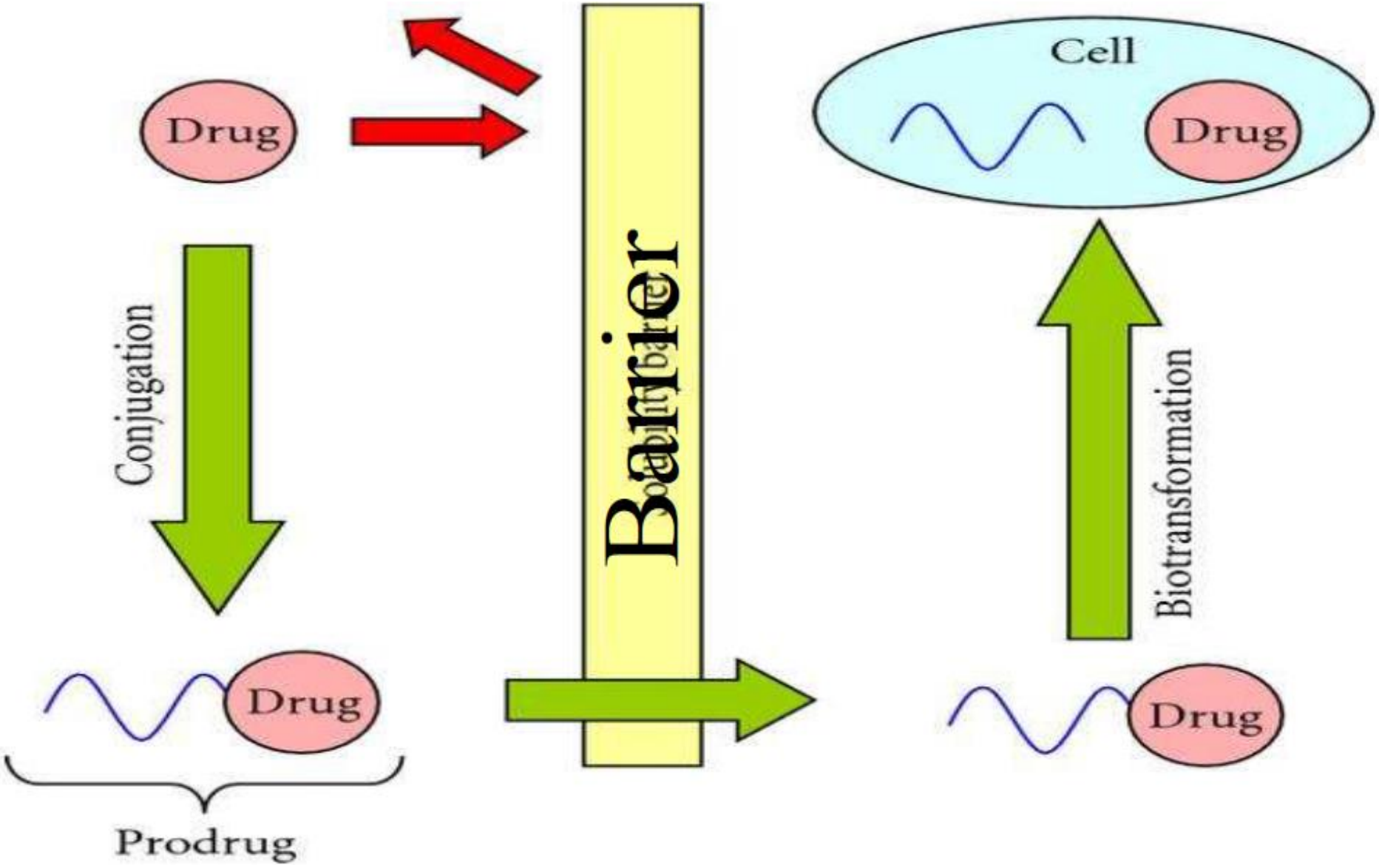
Definition



A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound.

Definition

- Another term drug latentiation, which implies a time lag element or component, was coined by Harper (1962).
- Prodrugs constitute 12 % of known drugs (2017) and a larger percentage of new drugs.

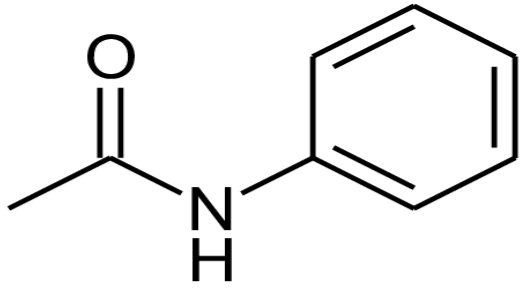

Drug
Cell
Drug
Conjugation
Barrier
Biotransformation
Drug
Drug
Prodrug

History of Prodrugs

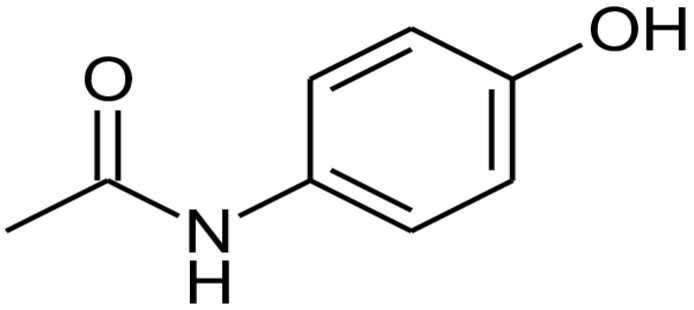
Acetanilide introduced by Cahn and Hepp in 1867 as an antipyretic is **hydroxylated** to biologically active acetaminophen

Aspirin (acetylsalicylic acid), synthesized in 1897 by Felix Hoffman (Bayer, Germany)

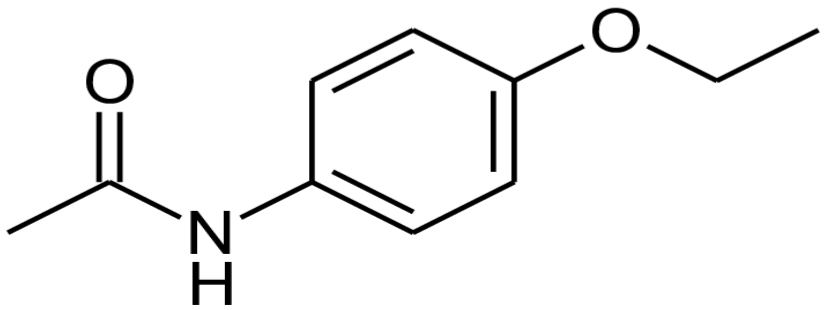
Chloramphenicol structure in order to improve the antibiotic's bitter taste and poor solubility in water



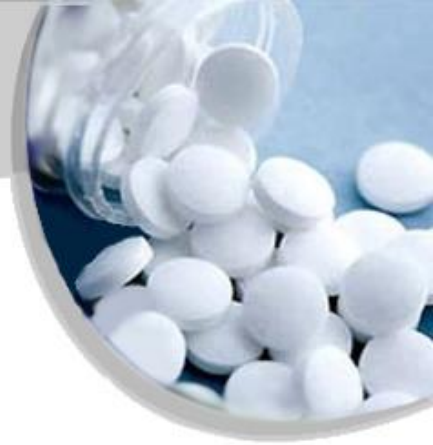
Acetanilide



Acetaminophen



Phenacetin



Objectives of Prodrug Design

Pharmaceutical Objectives:

To improve solubility, chemical stability, and organoleptic properties

To decrease irritation and/or pain after local administration

To reduce problems related with the pharmaceutical technology of the active agent.

Pharmacokinetic Objectives

To improve absorption (oral and by non-oral routes).

To decrease presystemic metabolism to improve time profile

To increase organ/ tissue-selective delivery of the active agent

Pharmacodynamic Objectives

To decrease toxicity and improve therapeutic index

To design single chemical entities combining two drugs (co-drugs strategy).

prodrug

The awareness that the onset, intensity and duration of drug action are greatly affected by the physicochemical properties of drug has promoted the emergence of various prodrugs.

prodrug

Most of the limitations can be overcame by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site

prodrug

The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming various physical, chemical and social barriers is certainly the utilization of the prodrug approach holds great potential

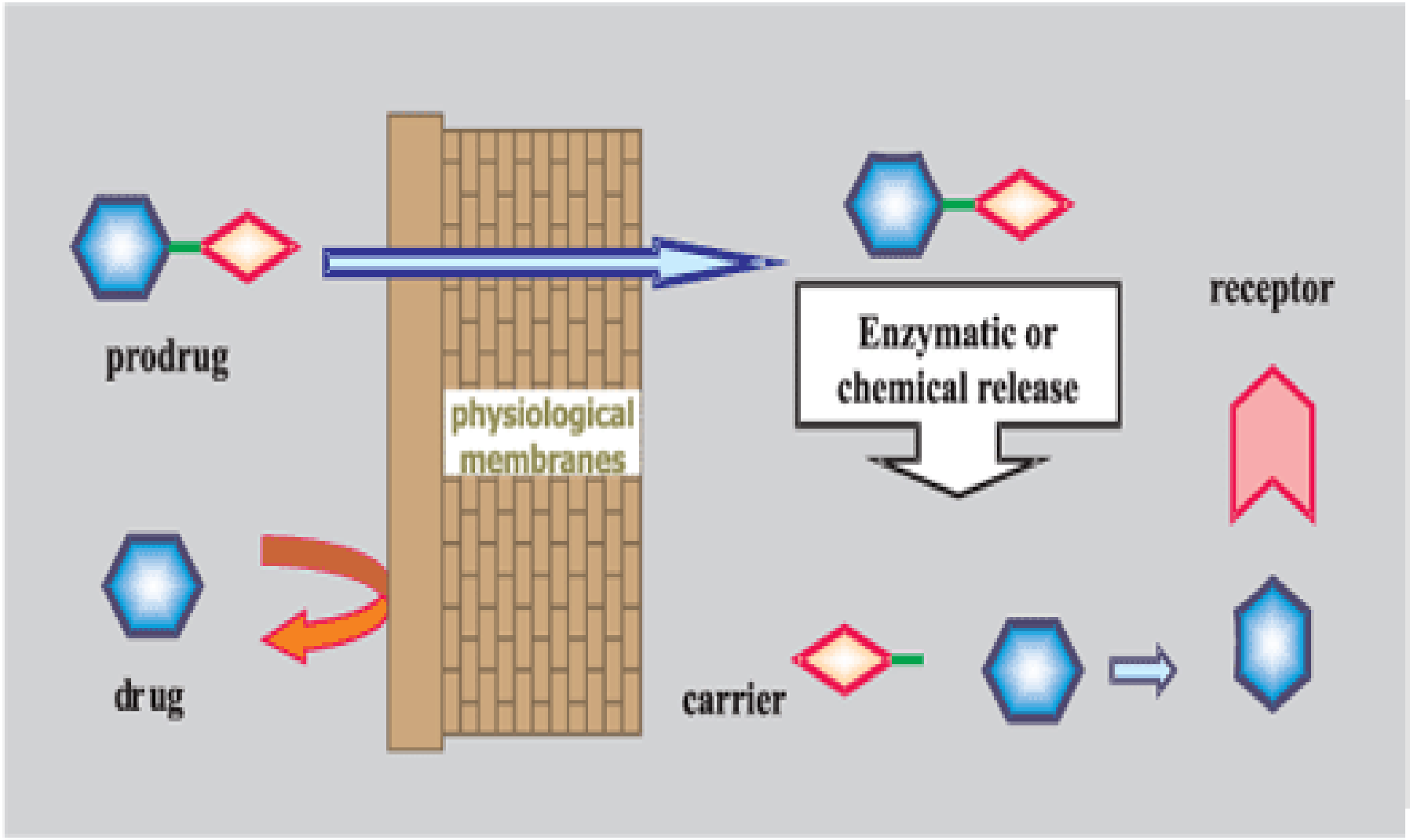
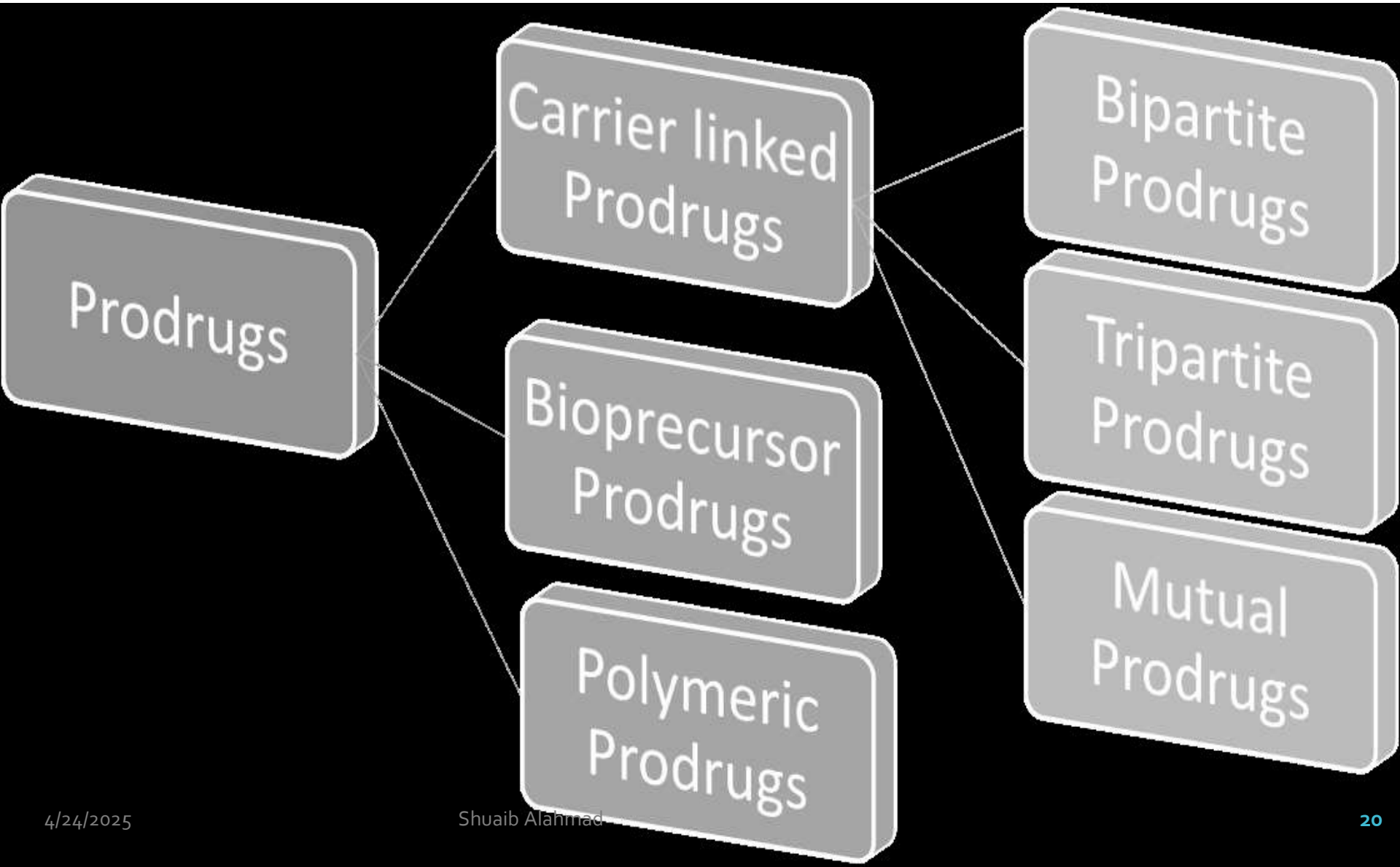


FIGURE 2 - Representation of a prodrug design to enhance bioavailability.

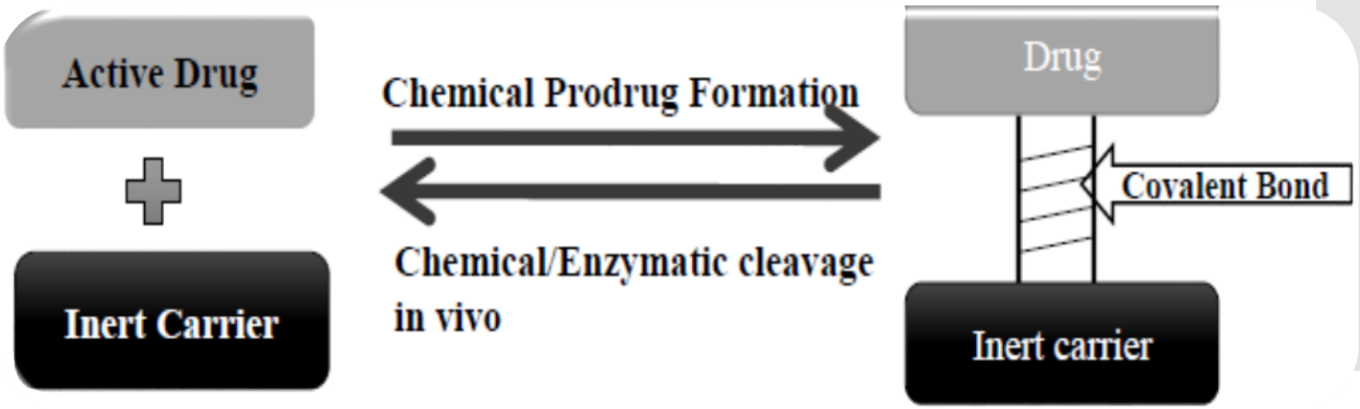
Classification of Prodrugs



Carrier linked prodrug

Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties

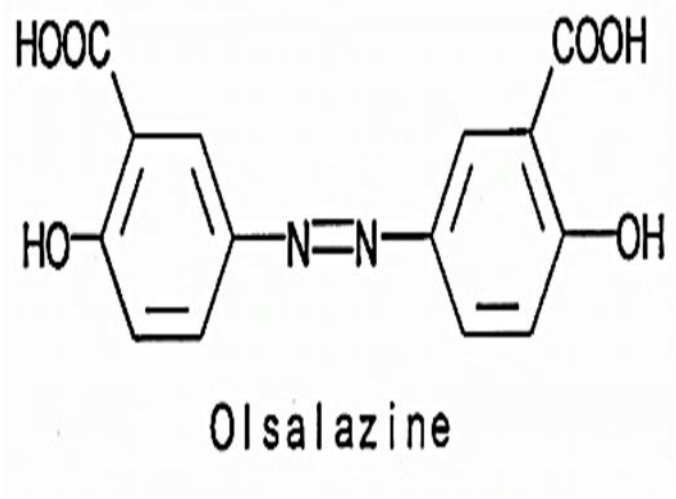
The subsequent enzymatic or non enzymatic mechanism releases the active drug moiety.



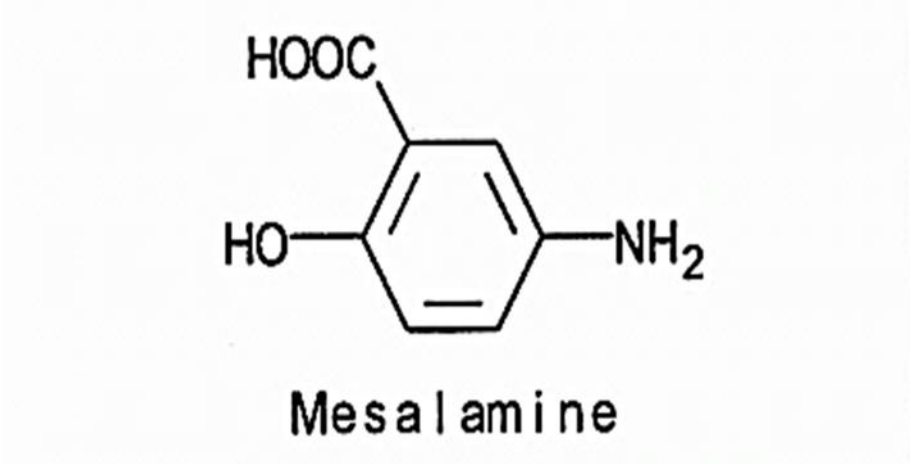
Covalent bond

Olsalazine and Chloramphenicol palmitate are examples of prodrugs

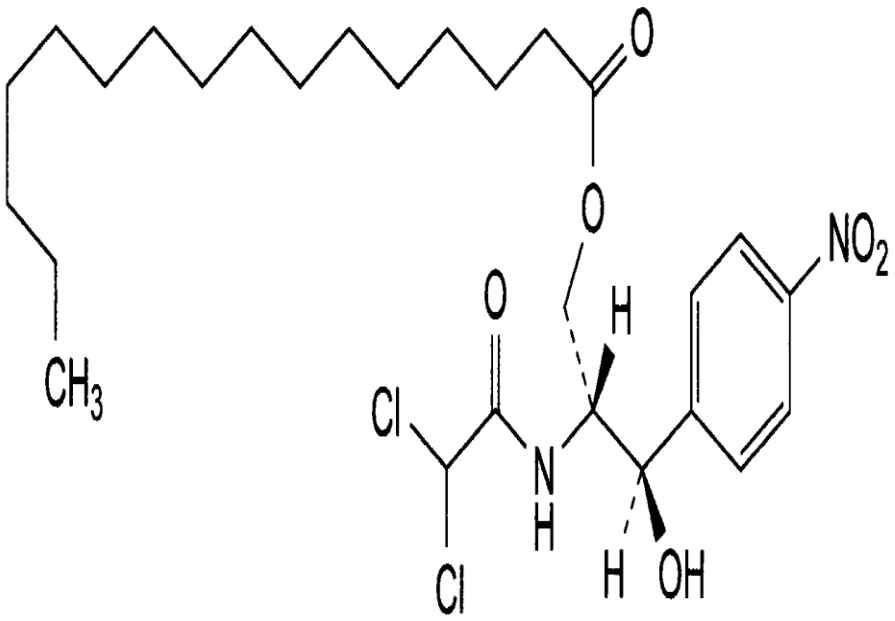
that are cleaved to smaller compound, one of which is the active drug.



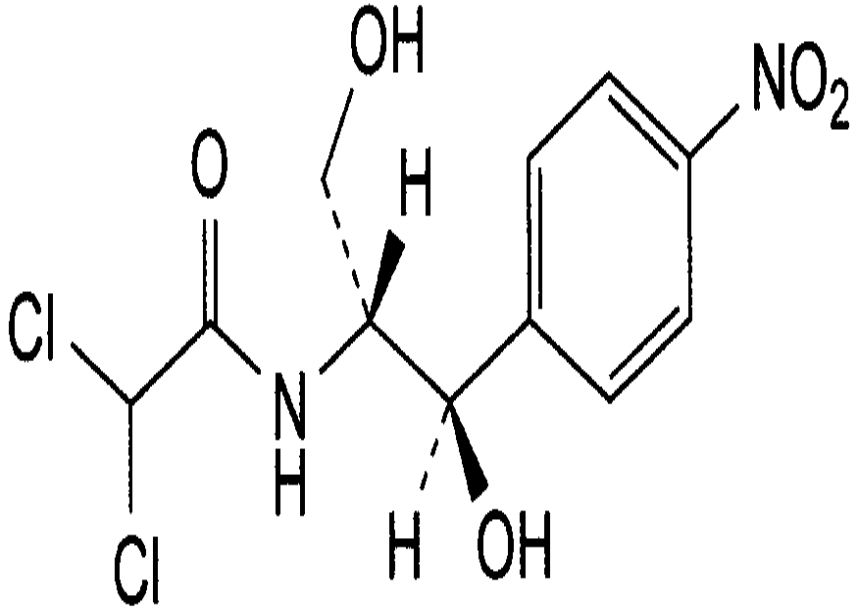
Olsalazine



Mesalamine



Chloramphenicol Palmitate



Chloramphenicol

Bipartite prodrug

It is composed of one carrier (group) attached to the drugs

Such prodrugs have greatly modified lipophilicity due to the attached carrier.

The active drug is released by hydrolytic cleavage either chemically or enzymatically

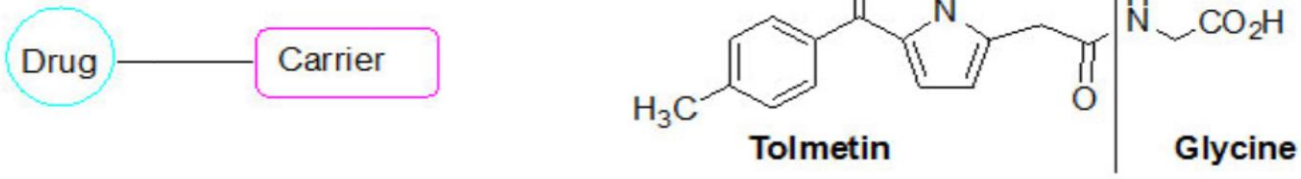
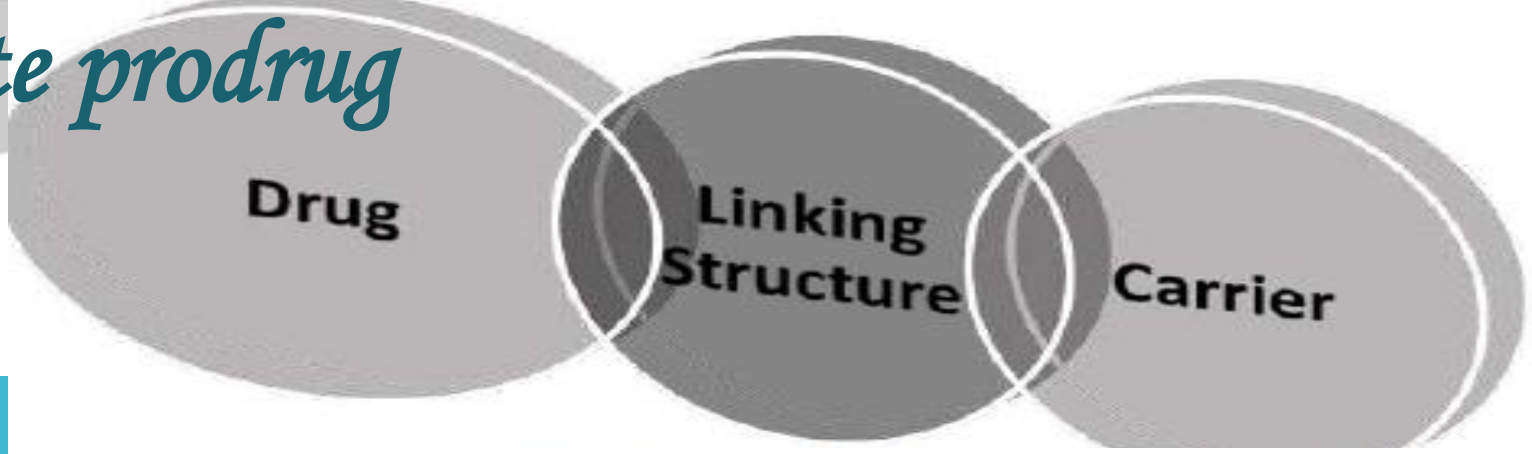


Figure 6: Bipartite prodrug of tolmetin glycine.

Tripartite prodrug



Tripartite prodrug

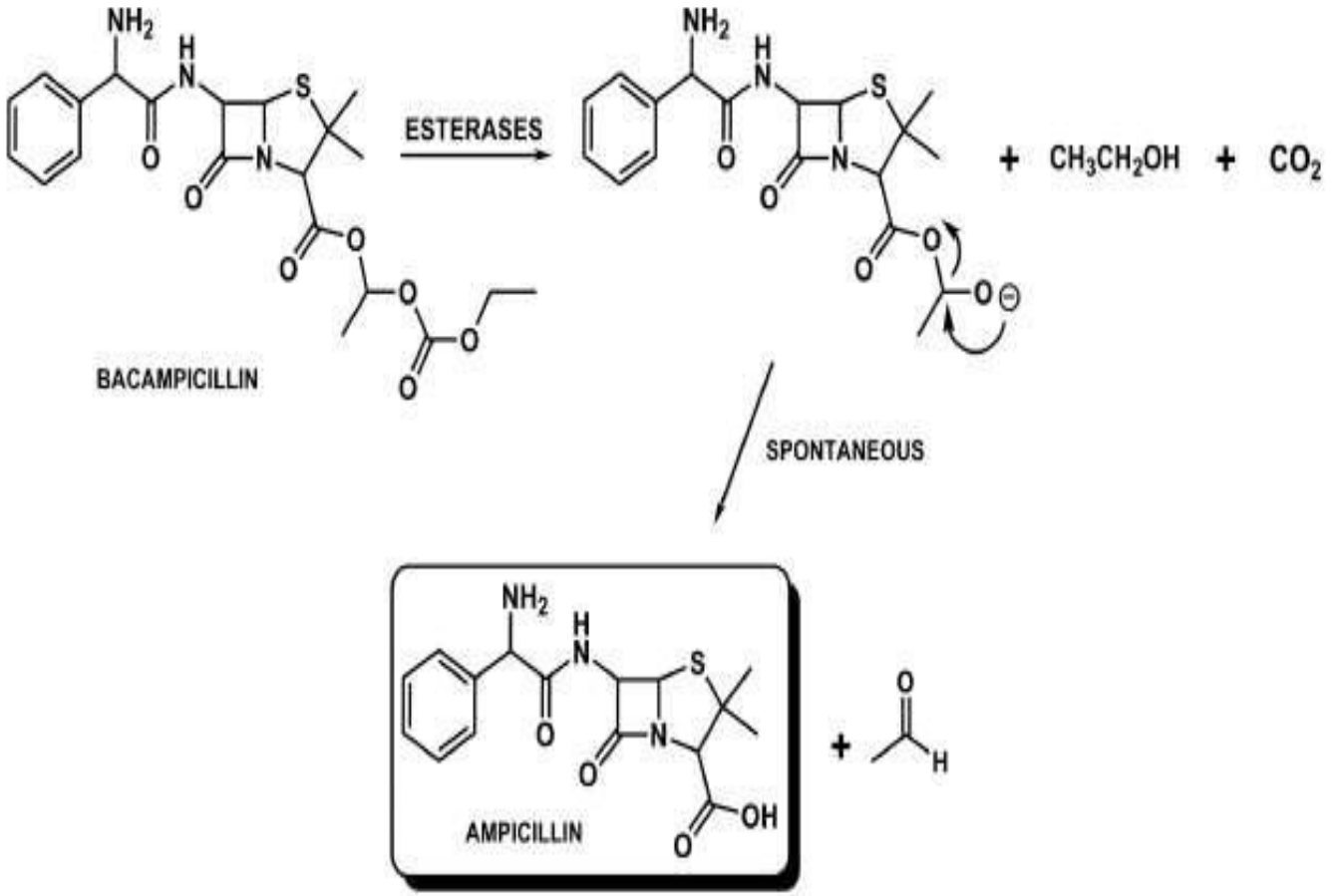


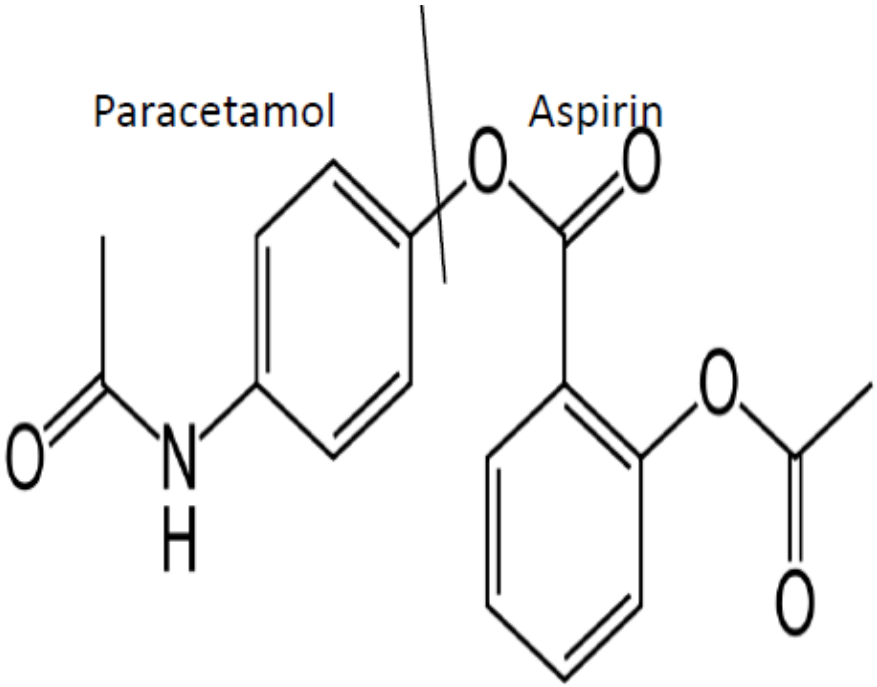
FIGURE 20 - Bacampicillin structure and its conversion into ampicillin.

Mutual Prodrugs

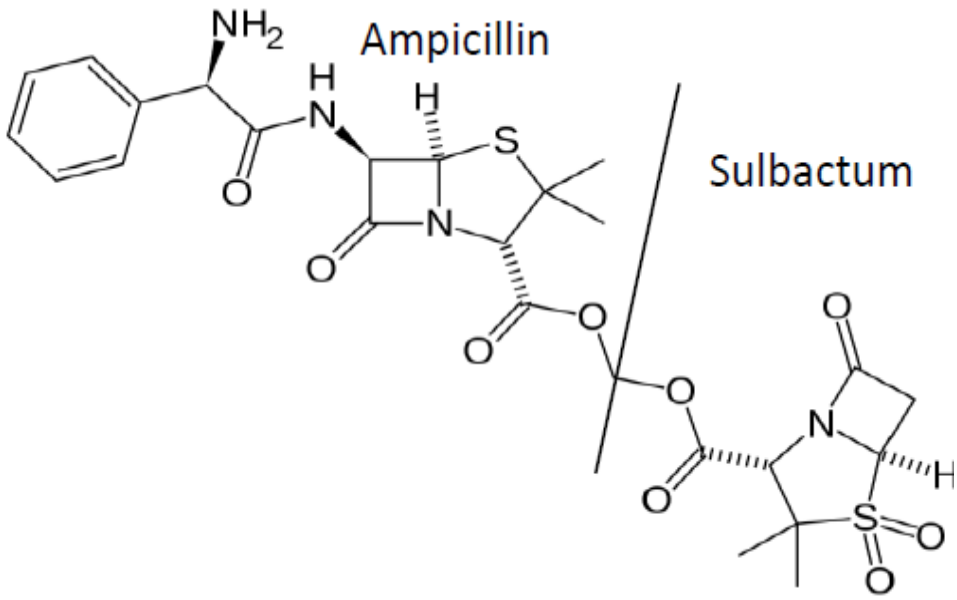
Mutual Prodrugs

A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa

A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked



Benorylate



Sultamicillin

Bioprecursors

Bioprecursors

A compound that is metabolized into an active drug, usually by Phase I reactions; eg **acetanilide.**

Do not contain a carrier or promoiety

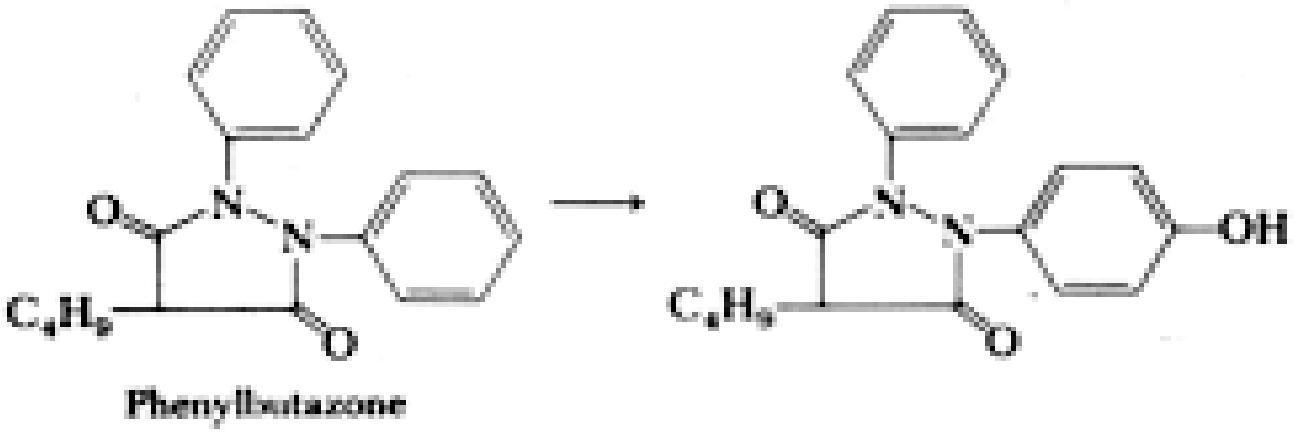
Eg: phenylbutazone. Phenylbutazone gets metabolized to hoxyphenylbutazone

that is responsible for the anti inflammatory activity of the parent drug

phenylbutazone

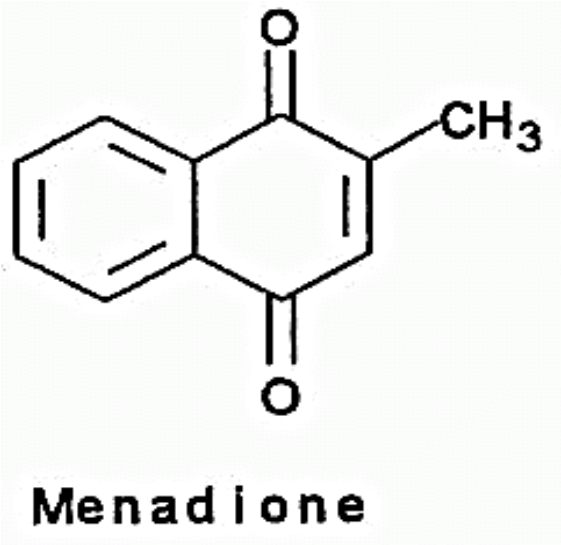
1.Oxidation

a. Aromatic hydroxylation

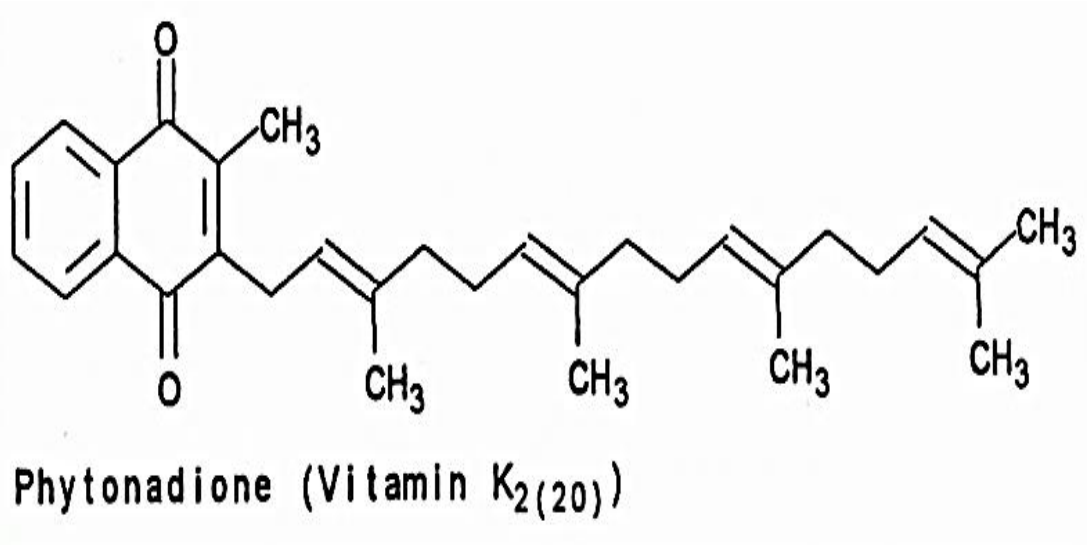


Phenylbutazone

Metabolic precursor



Menadione



Phytonadione (Vitamin $K_{2(20)}$)

Menadione can be converted to active vitamin K2, after alkylation in vivo

Polymeric Prodrugs

Polymeric Prodrugs

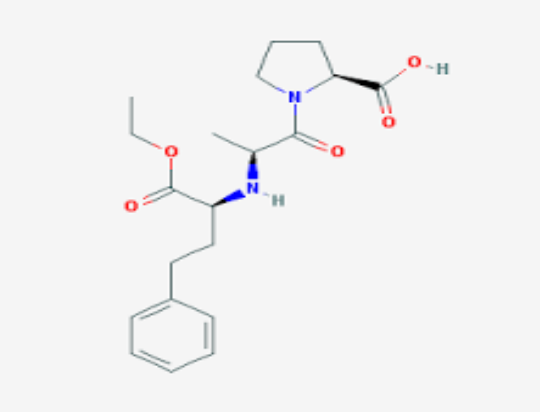
Also known as macromolecular prodrug, the drug is incorporated into the polymer system by formation of covalent bond between drug and polymer.

Doxorubicin coupled poly-(N-(2 hydroxypropyl) methacrylamide)

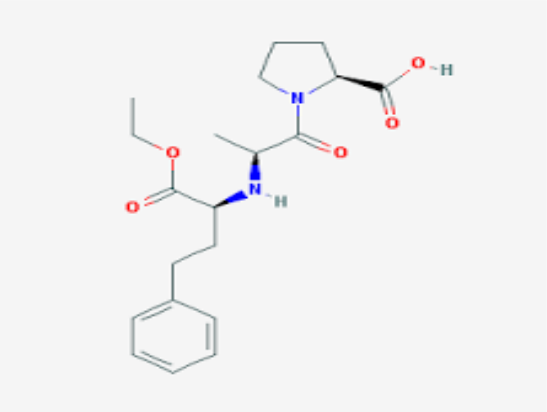
Prodrugs of functional groups:

- Occasionally, the prodrug approach is used to enhance the absorption of a drug that is poorly absorbed from the gastrointestinal tract

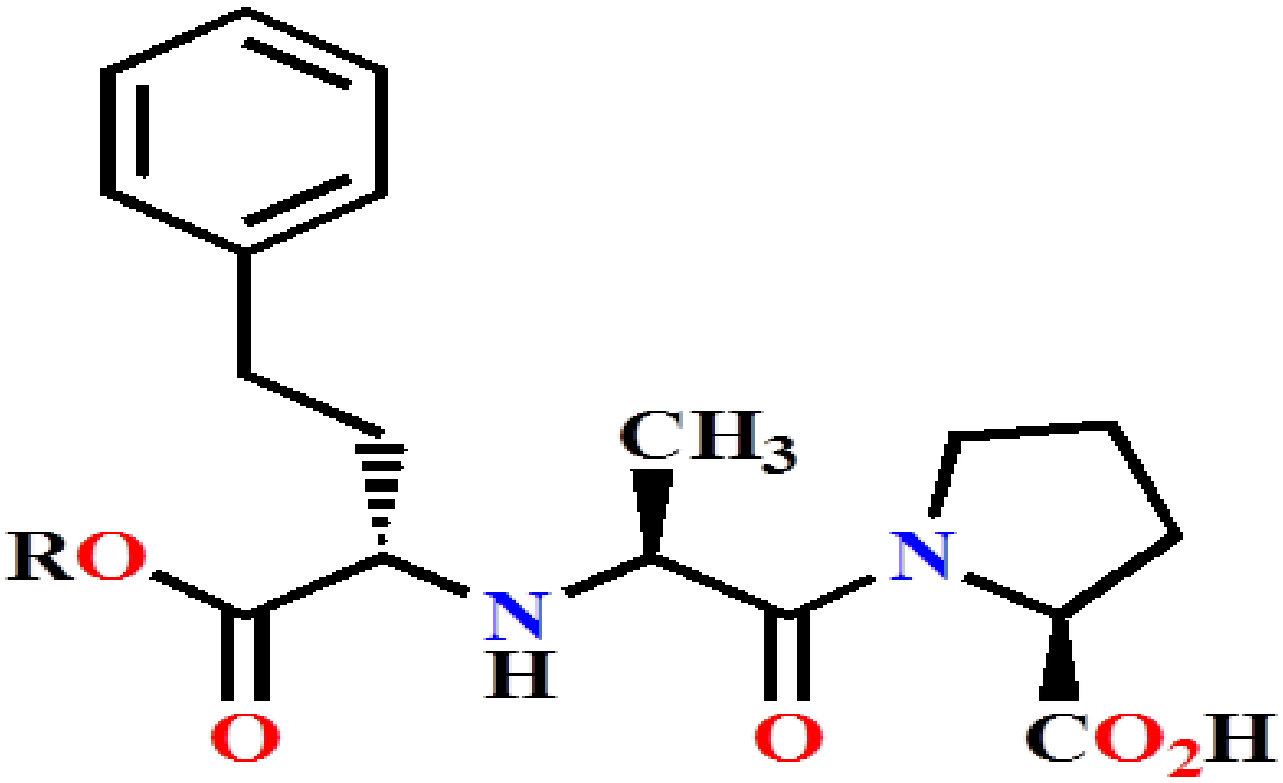
Prodrugs of functional groups:



Enalapril is the ethyl ester of enalaprilic acid, an active inhibitor of angiotensinconverting enzyme (ACE)



The ester prodrug is much more readily absorbed orally than the pharmacologically active carboxylic acid



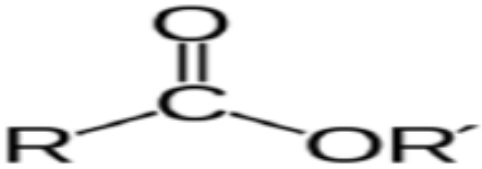
R=Et Enalapril
R=H Enalaprilit

Types of prodrugs:

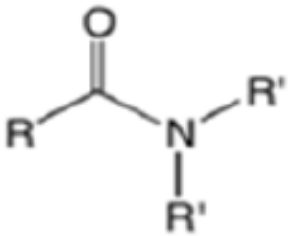
• Various prodrugs for compounds containing different functional groups are listed below:

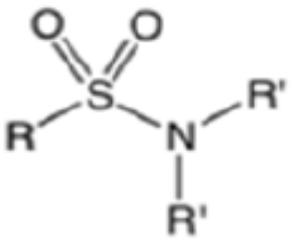
1. Esters.
2. Prodrug for Amides, Imides and Other Acidic Compounds.
3. Prodrugs for Amines
4. Prodrugs with Carbonyl Group

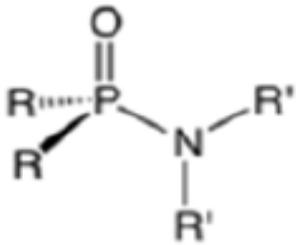
- Esters:



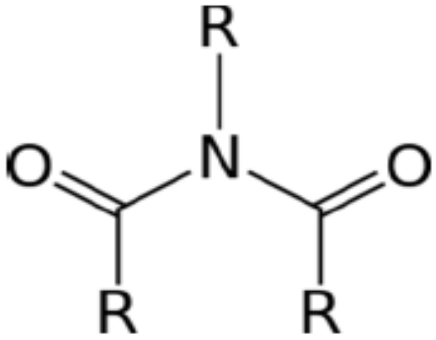
- Amides:



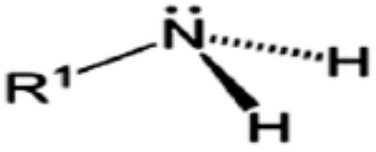
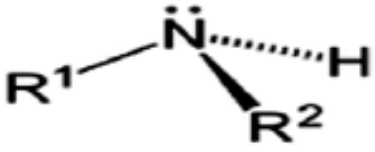
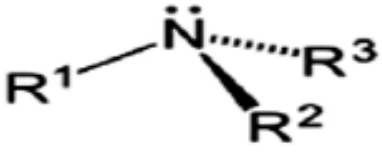




- Imides:



- Amines:

Primary amine	Secondary amine	Tertiary amine
		

References:

• Wilson and Gisvold’s Textbook of Organic Medicinal And Pharmaceutical Chemistry,12th Edition.


Thank You