BALAJI COLLEGE OF PHARMACY

PRODRUGS

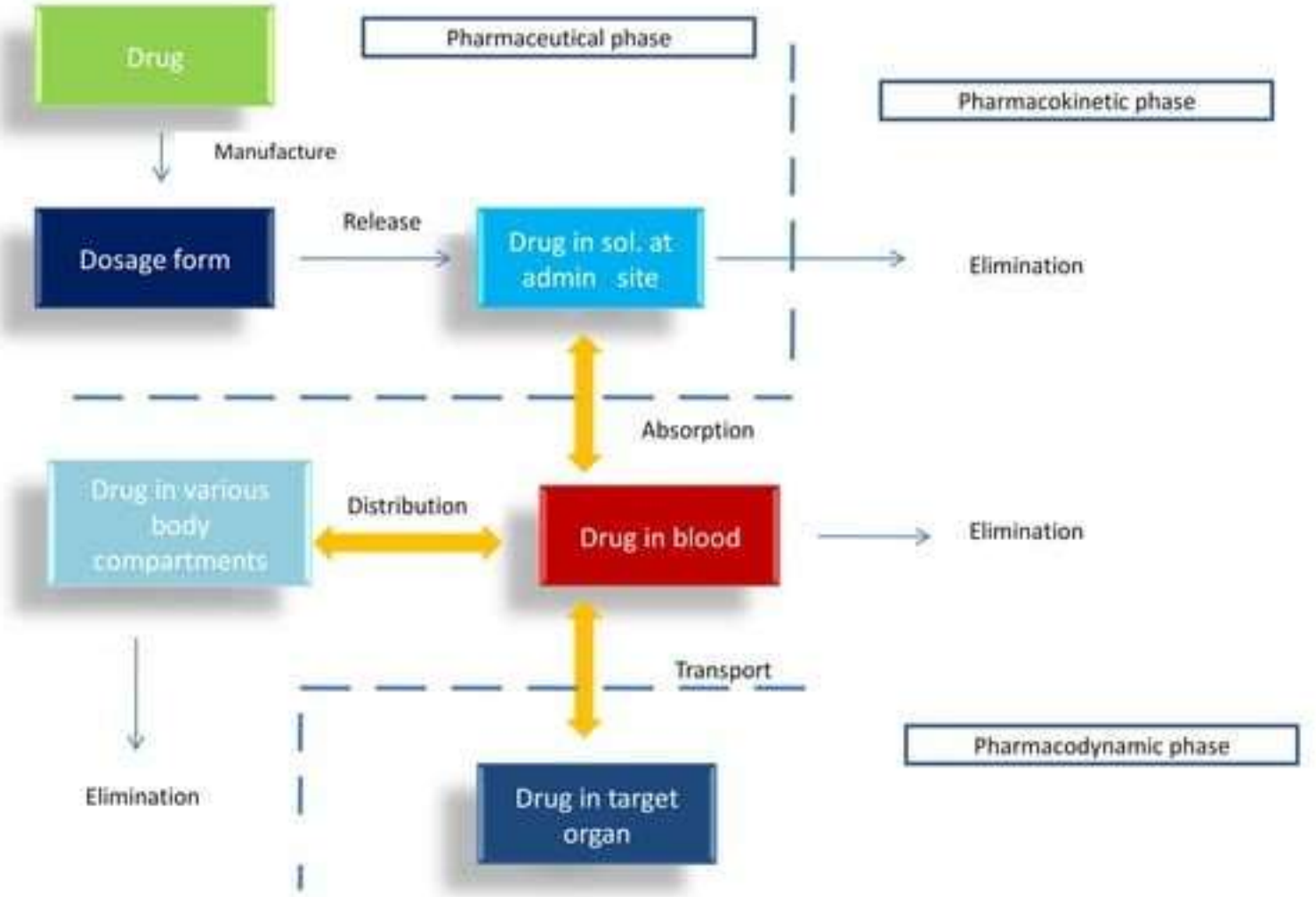
Subject: Medicinal Chemistry
PHARM D III YEAR

Presented by:
S. Sanjeeda Parveen M.Pharm
Asst Professor,
Balaji College of Pharmacy,
Ananthapuramu.

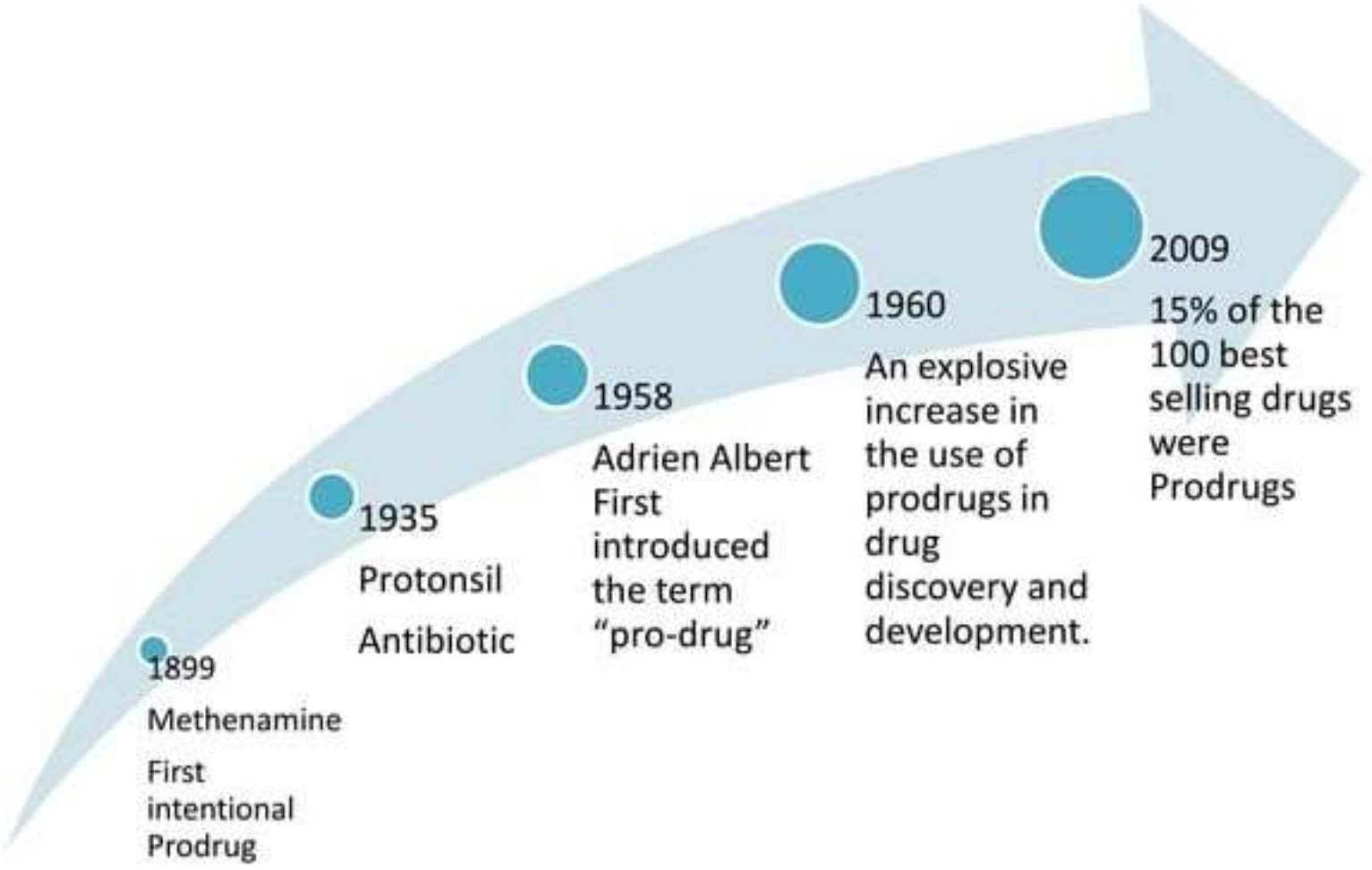
Prodrugs

Basic concept, Prodrugs of functional group, Prodrugs to improve patient acceptability, Drug solubility, Drug absorption and distribution, site specific drug delivery and sustained drug action. Rationale of prodrug design and practical consideration of prodrug design.

BARRIERS TO THE THERAPEUTIC UTILITY OF A DRUG



History and the Present of Prodrug Design



VARIOUS APPROACHES TO ENHANCE THE EFFICACY OF A DRUG:

The therapeutic efficacy can be improved by minimizing or eliminating the undesirable properties while retaining the desirable ones.

- Physical approach
- Chemical approach

CHEMICAL MEANS OF OPTIMIZING THE DRUG THERAPEUTICS

1. Design and development of new drugs.
2. Design of hard and soft drugs.
3. Design of prodrugs.

HARD DRUGS

- Resistant to biotransformation
- Has a long half life
- Design of hard drug involves metabolic stabilization

ADVANTAGES:

- Enhanced duration of action
- Avoids generation of potentially active harmful metabolites
- HOWEVER, less readily eliminated due to lack of metabolism

  Ex: Conversion of tolbutamide to chlorpropamide (Hypoglycemic urea's)

SOFT DRUGS

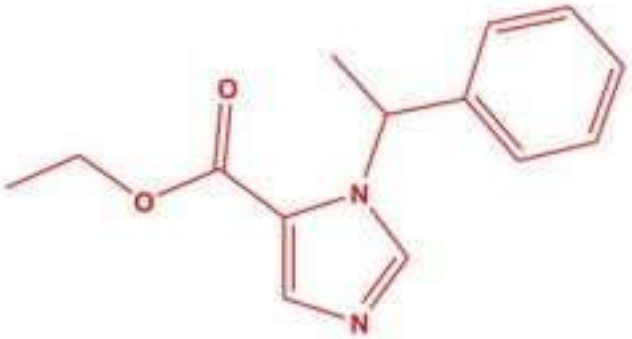
A soft drug is a biologically active compound that is biotransformed *in vivo* in a rapid and predictable manner in to non toxic metabolites.

Design of synthetic soft drug involves introduction of a group or a bond susceptible to rapid metabolic action.

Ex: Natural endogenous compounds such as adrenalin and insulin.

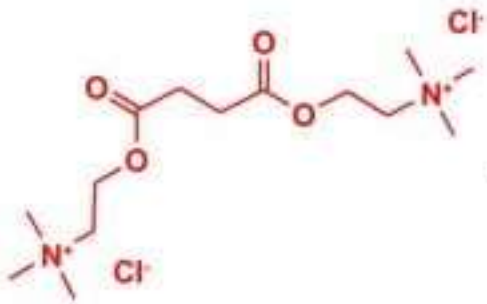
SOFT DRUGS

- Short duration of action prevents possibility of toxicity and increases therapeutic index

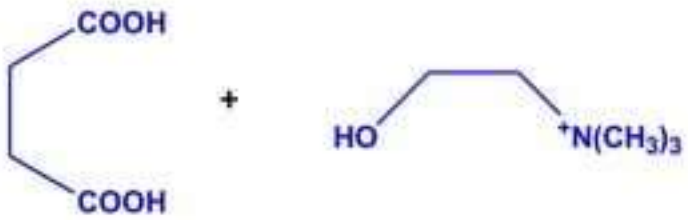


Etomidate (hypnotic)

metabolite



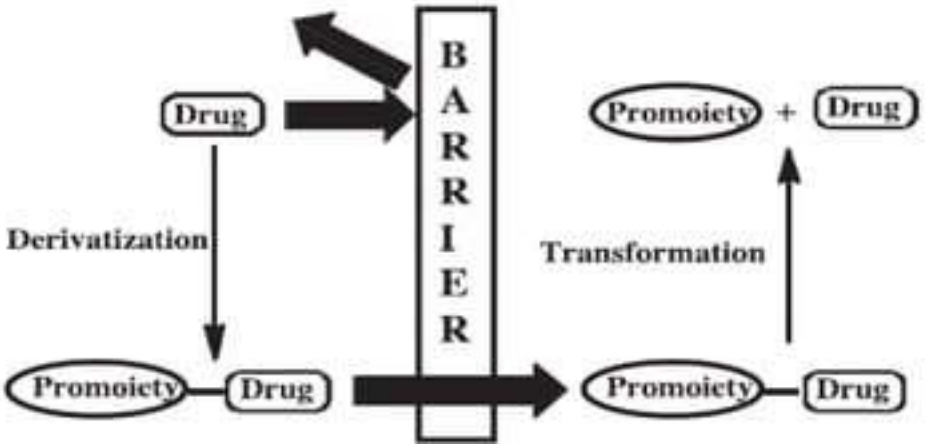
Succinylcholine (neuromuscular blocking agent)



Prodrugs

Prodrugs are pharmacologically inactive derivatives of active drugs that are designed to maximize the amount of active drug that reaches its site of action, through manipulation of physicochemical, biopharmaceutical and pharmacokinetic properties of drug.

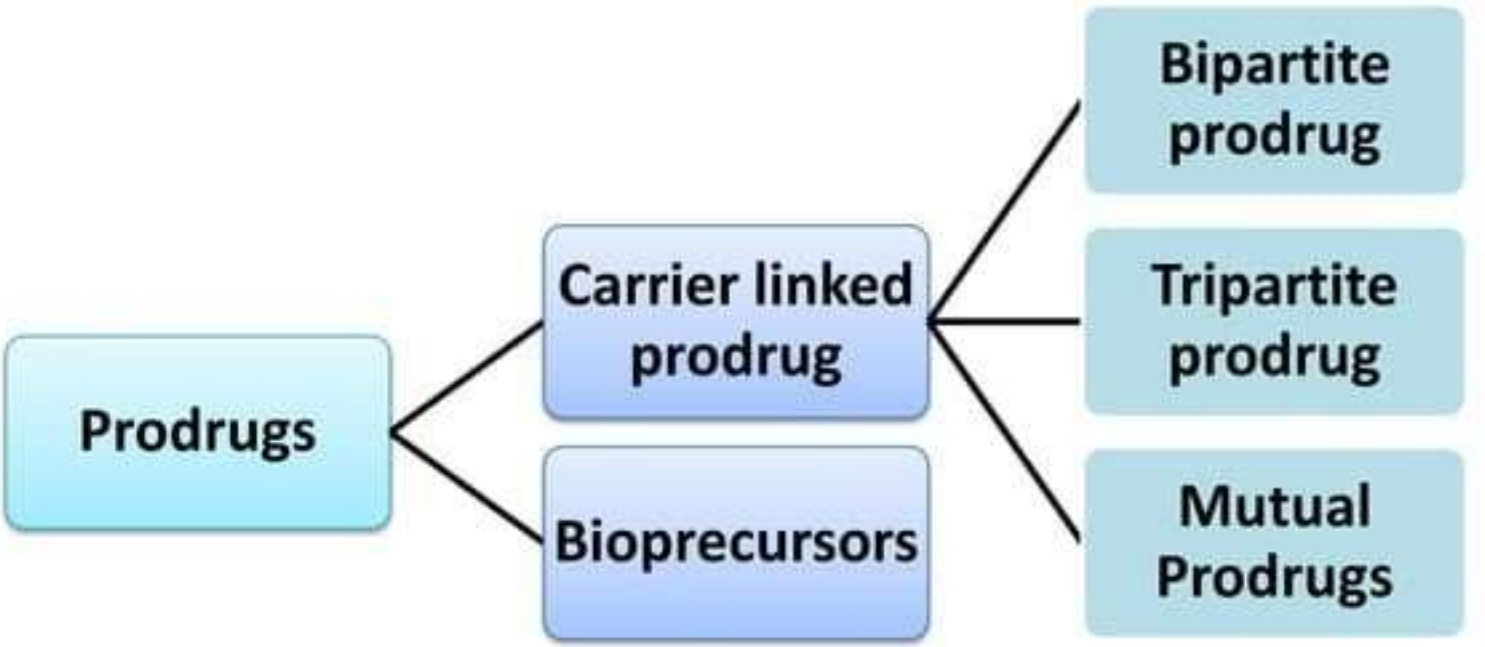
They are converted into active drug within the body through enzymatic or non-enzymatic reactions. Also called drug **latentiation.**



"Drug Latentiation"

Process of purposely designing and synthesizing a molecule that specifically requires "bioactivation" to a pharmacologically active substance

Classification of Prodrugs



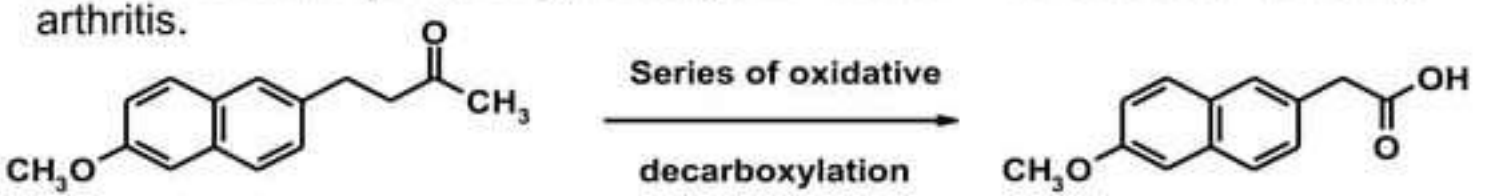
CLASSIFICATION OF PRODRUGS:

1.Carrier linked prodrugs:

Active drug is covalently linked to an inert carrier or transporter moiety. They have enhanced lipophilicity due to attached carrier. The active drug is released by hydrolytic cleavage, either chemically or enzymatically.

2.Bioprecursors:

These are inert molecules obtained by chemical modification of the drug but do not contain a carrier. Such a molecule has the same lipophilicity as the parent drug and is bioactivated generally by redox biotransformation, only enzymatically. Ex: NSAID – nabumetone (relafen) - arthritis.

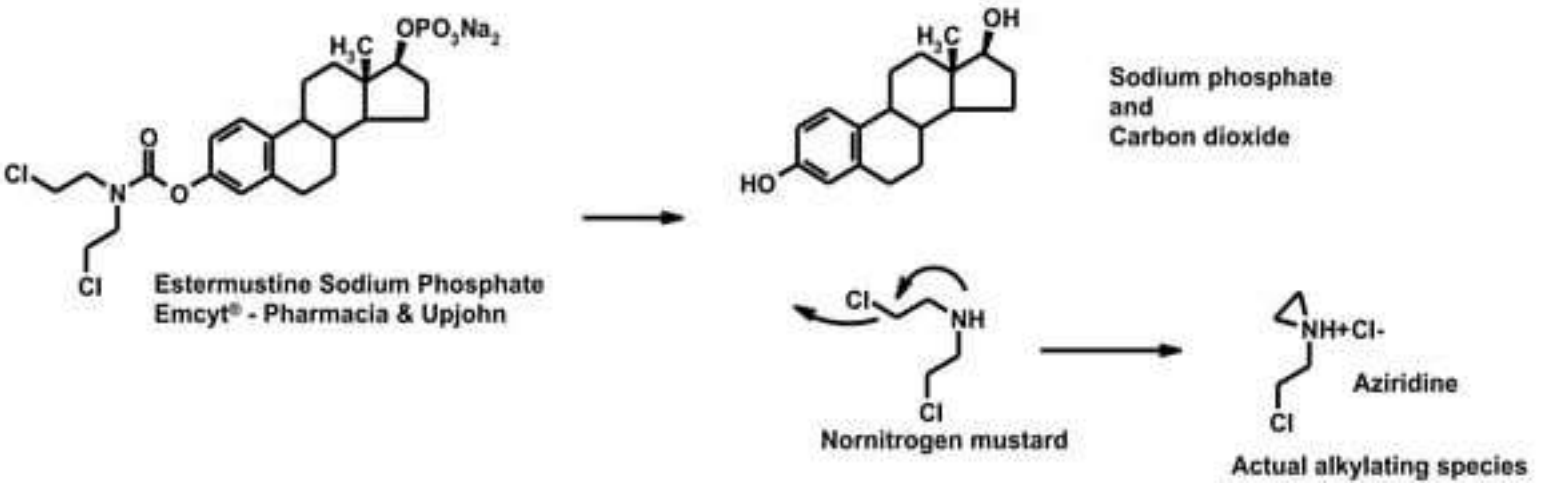


Active form of the drug that inhibits Prostaglandin biosynthesis by cyclooxygenase

3. Mutual prodrugs:

The prodrug comprises of two pharmacologically active agents coupled together to form a single molecule such that each acts as the carrier for the other.

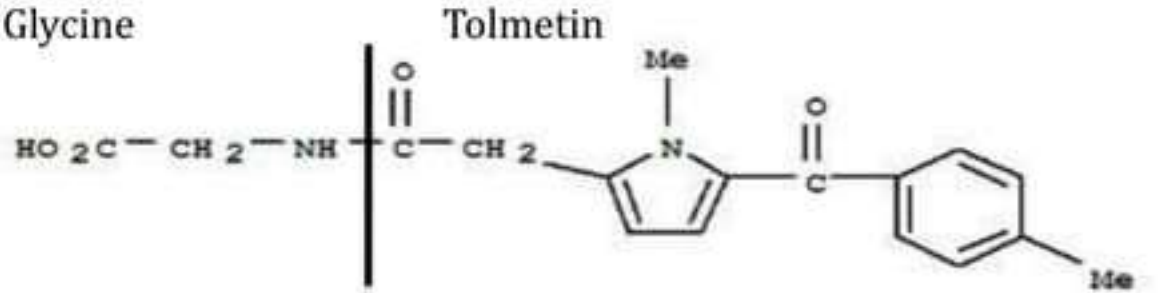
Ex: Benorylate is mutual prodrug of NSAIDs aspirin and paracetamol.
Ex: Emcyt is a mutual prodrug containing estramustine and nornitrogen mustard linked to each other.



It can be further subdivided into

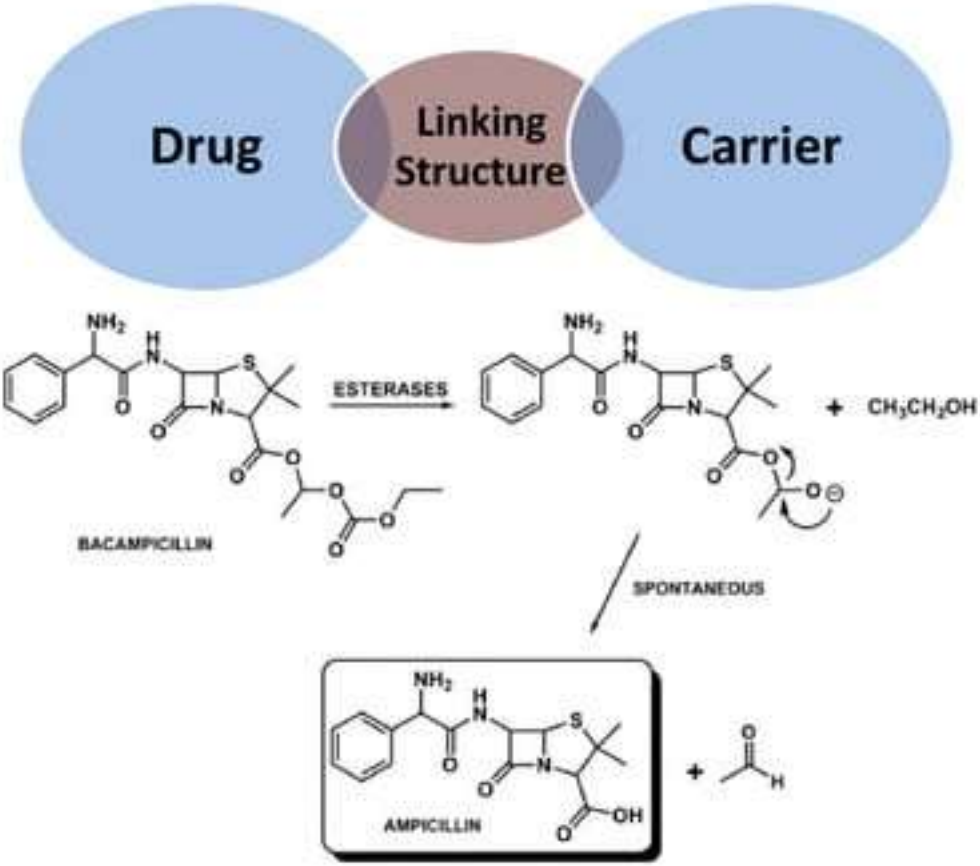
1. Bipartite prodrug

- 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.
- E.g. Tolmetin-glycine prodrug (NSAID).



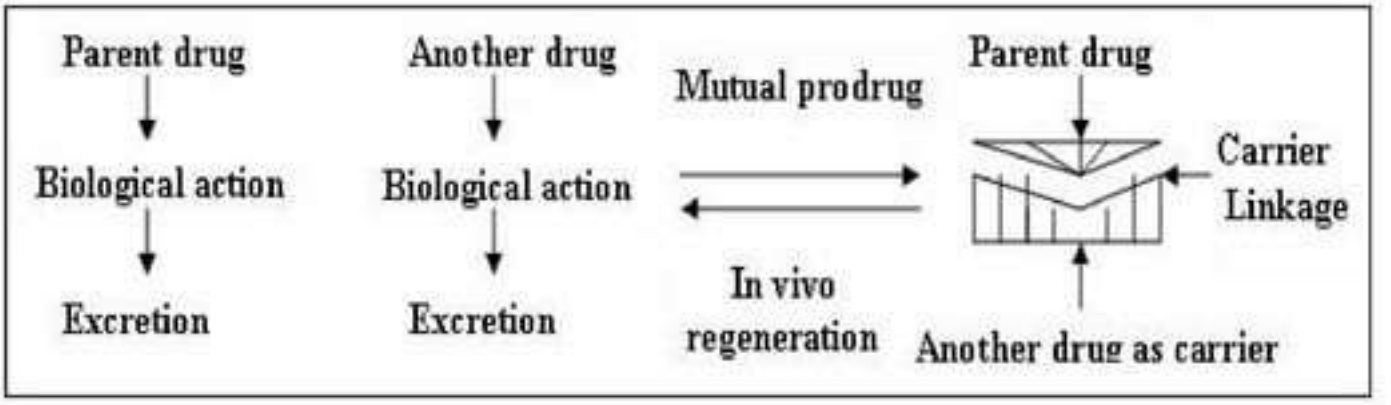
2. Tripartite prodrug-

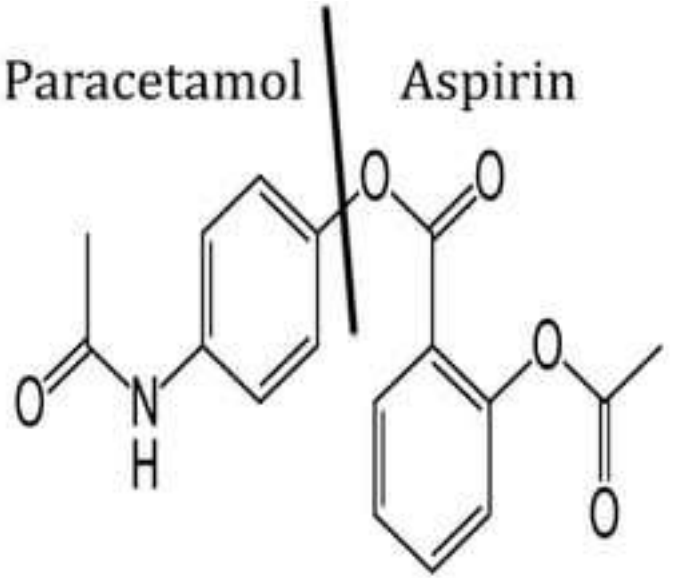
The carrier group is attached via linker to drug.



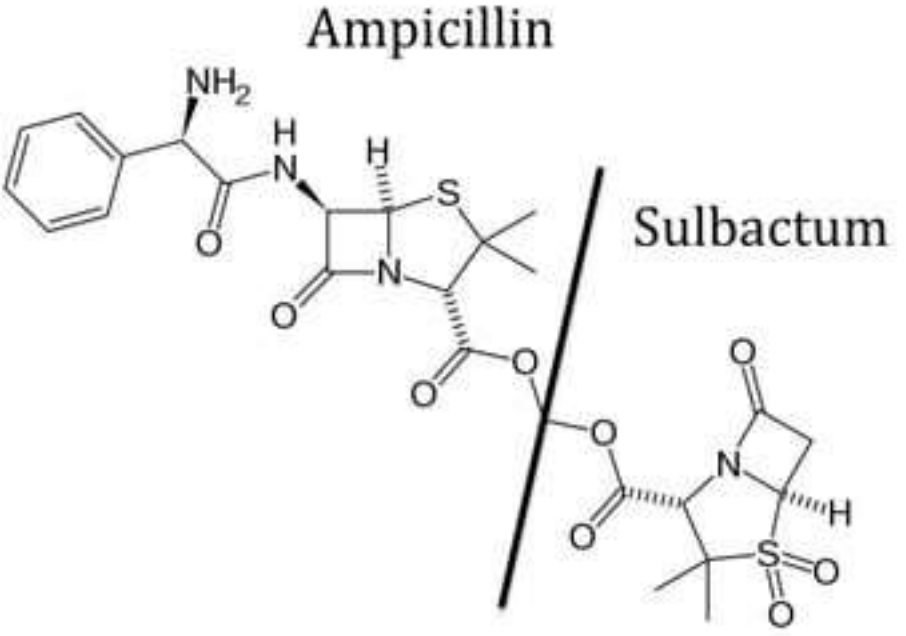
3. Mutual Prodrugs

- 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 is a mutual prodrug aspirin and paracetamol.
- Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum.





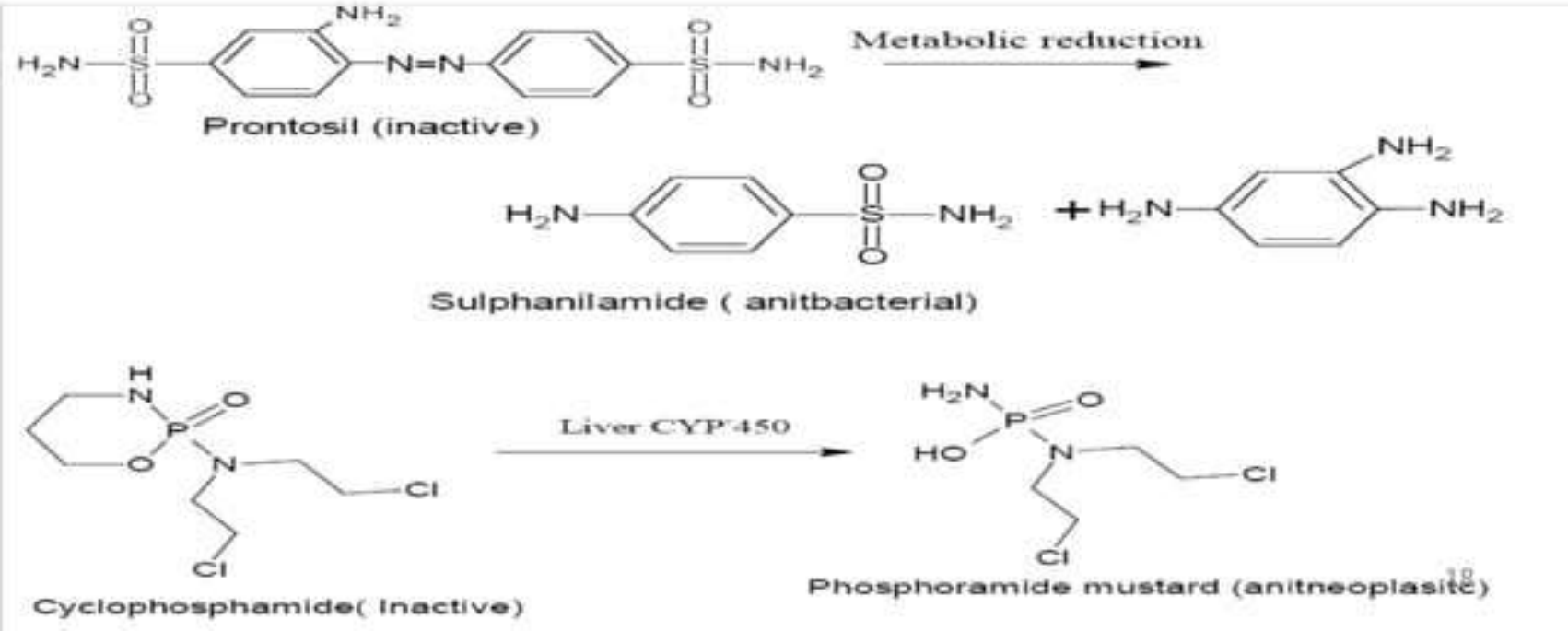
Benorylate/Benorilate



Sultamicillin

B) Bioprecursors

- Bio- precursor prodrugs produce their effects after in vivo chemical modification of their inactive form.
- Bioprecursor prodrugs rely on oxidative or reductive activation reactions unlike the hydrolytic activation of carrier-linked prodrugs.
- They metabolized into a new compound that may itself be active or further metabolized to an active metabolite



Strategies for the design of prodrugs:

1. Carriers:

- Carrier is an inert molecule or the promoiety attached to the active drug moiety through a metabolically labile linkage.
- The carrier imparts some desirable property to the drug such as increased lipid or water solubility.
- Carriers that help in directing the active moiety to the target site is called as specifier.

Specifiers:

Targeting unit part of the prodrug which directs the active moiety to the target site.

- Antibody Directed Enzyme Prodrug Therapy
- Gene Directed Enzyme Prodrug Therapy
- Polymer Directed Enzyme Prodrug Therapy/ Macromolecule Directed Prodrug Therapy

linkers:

A releasable linker or spacer is incorporated between the specifier/carrier and the parent drug.

Reasons for the application of linkers:

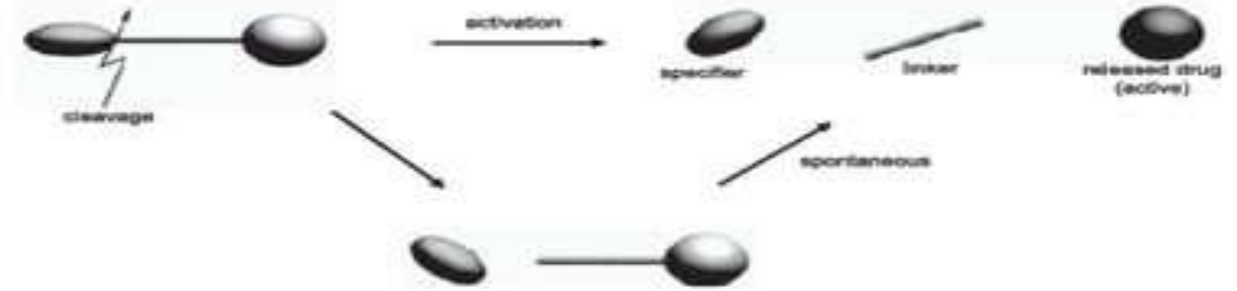
1. Incorporation of appropriate linkage between the promoiety and the active drug.
2. Facilitation of enzymatic action on carrier linked prodrugs.

Classification of linkers:

- Electronic cascade linkers (Cleavage occurs by mesomeric effect)
- Cyclization linkers (cleavage occurs by cyclisation)

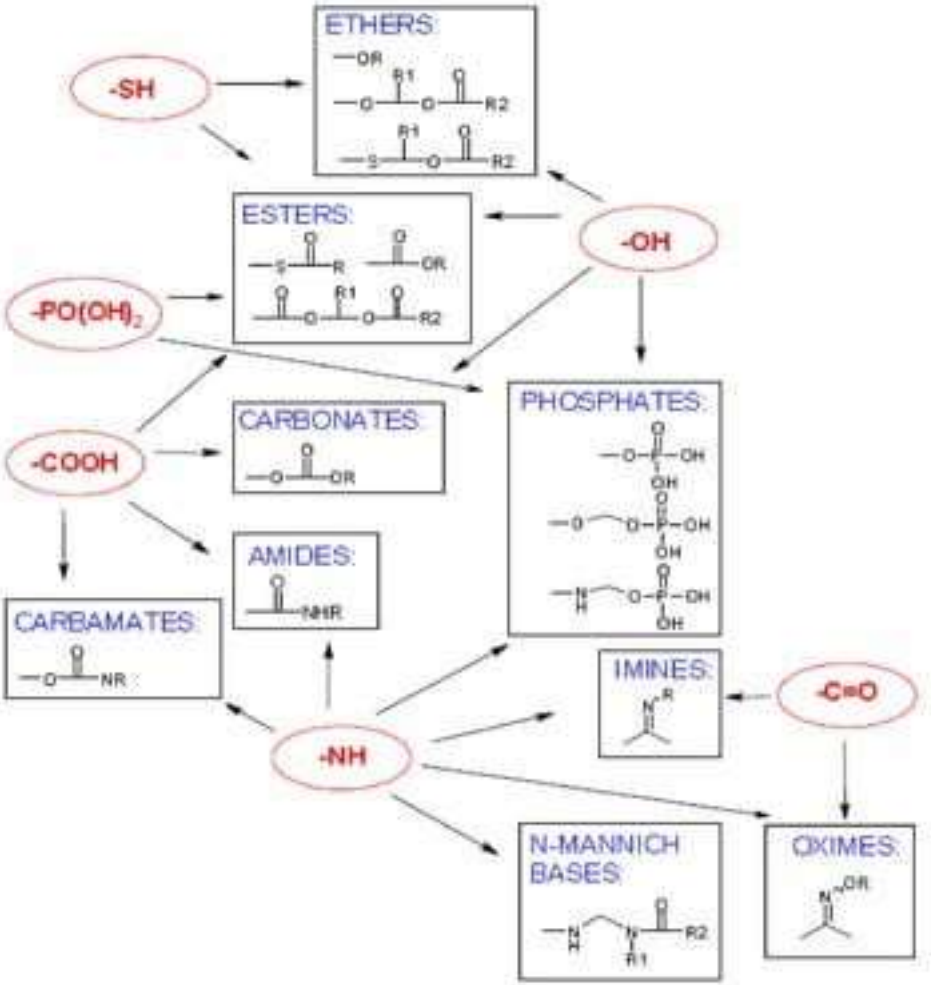
  Doxorubicin (anticancer) attached with β-glucuronide was inert towards clevage by β-glucuronidase

Simple Drug-Linker-specifier:



Multiple drug release:

Functional groups amenable to prodrug design



Prodrug linkage and enzymes involved in the hydrolysis of linkage:

Prodrug linkage	**Hydrolyzing enzymes**
Ester	Esterase
Short and medium chain	Cholinesterases
Aliphatic	Ester hydrolase , Lipase, Cholesterol Esterase, Acetylcholinesterase, Aldehyde oxidase, Carboxypeptidase
Long chain aliphatic carbonate	Pancreatic lipase,Pancreatin,Lipase, Carboxypeptidase, Cholinesterase
Phosphate, Organic	Acid phosphatase, Alkaline Phosphatase
Sulfate, organic	Steroid sulfatase

Prodrug Linkage	Hydrolyzing Enzyme
Amide	Amidase
Amino acid	Proteolytic enzymes, Trypsin, Carboxypeptidase A and B,
Azo	Azo reductase
Carbamate	Carbamidase
Phosphamide	Phosphoramidases
β-Glucuronide	β-Glucuronidase
N-Acetylglucosaminide	α- N-Acetylglucosaminidase
β-Glucoside	β-Glucosidase

APPLICATIONS OF PRODRUGS:

1.Prodrugs to improve patient acceptability

2.Enhancing Drug solubility

3. Enhancing Drug absorption and distribution

4.Site specific drug delivery

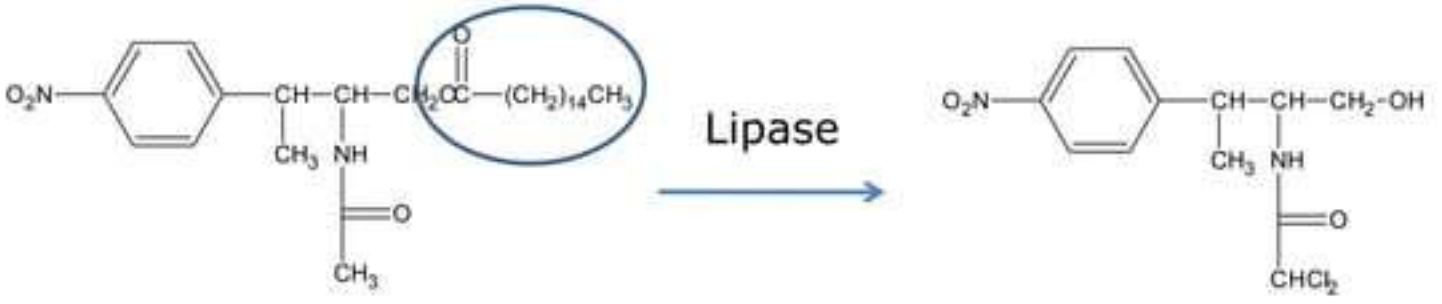
5. Sustained drug action

1. Pharmaceutical applications/Prodrugs to improve patient acceptability :

a).Improvement of taste:

- Bitter taste of the drug
- Unsuitable for preparation of suspension.
- Reduce the solubility of the drug in the saliva.

PARENT DRUG	PRODRUG WITH IMPROVED TASTE
chloramphenicol	Palmitate ester
clindamycin	Palmitate ester
sulfisoxazole	Diacetate ester



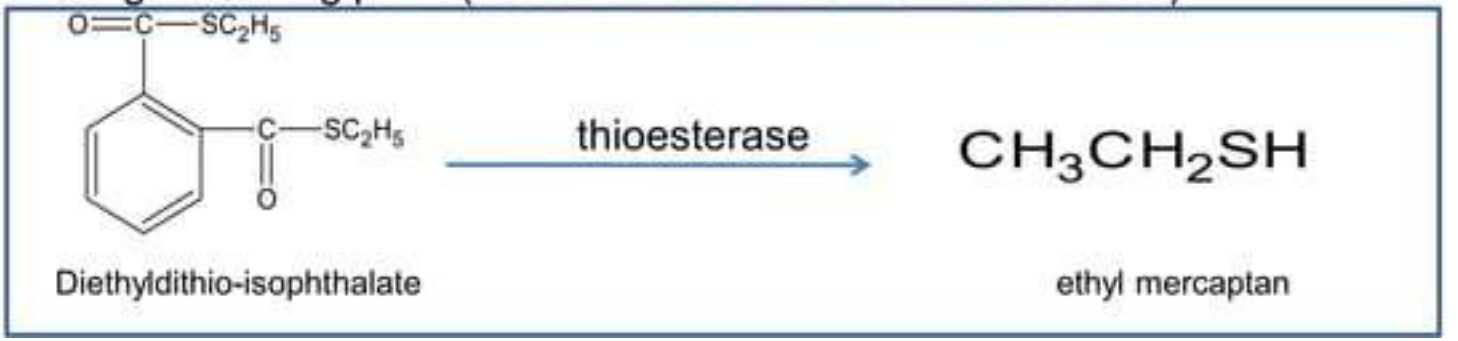
Chloramphenicol palmitate

chloramphenicol

b) Improvement of odour:

•The odor of the compound depends upon its vapor pressure.

Ex: ethyl mercaptan is a foul smelling liquid of b.p. 35 C. It is converted into its phthalate ester, diethyldithio-isophthalate ester which is odorless and has higher boiling point.(Used in the treatment ofTuberculosis)



c). Reduction of gastric irritation:

- Increased stimulation of acid secretion.
- Interference with the protective mucosal layer.

parent drug	prodrugs
Salicylic acid	Aspirin
Diethyl stilbestrol	Fosfestrol
Phenyl butazone	N-methyl piperazine salt
Oleandrin	Oleandrine acetate

d). Reduction of pain on injection

- Drug precipitates or penetrates into the surrounding tissues.
- The solution is strongly acidic, alkaline or alcoholic.

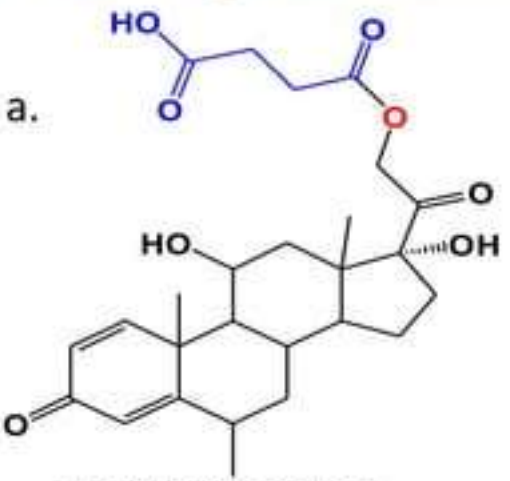
2.Enhancement of solubility and dissolution rate:

- Dissolution is the rate limiting step in the absorption of drug.
- Parenteral and ophthalmic formulations of such agents required.

Parent drug	Prodrugs with enhanced hydrophilicity
Chloramphenicol	Sodium succinate ester
Tocopherols	Sodium succinate ester
Testosterone	Phosphate ester
Diazepam	L-lysine ester

1. Prodrugs for Increased Water Solubility

a.

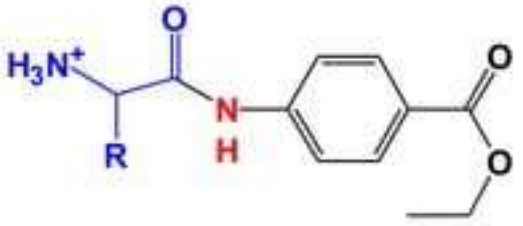


methylprednisolone
succinate ester

esterases

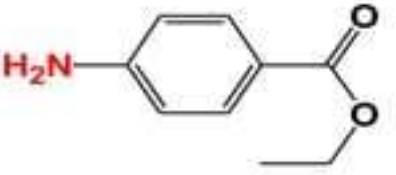
R = H prednisolone (corticosteroid)
R = CH_3 methyl prednisolone

b.



amino acid amide of benzocaine

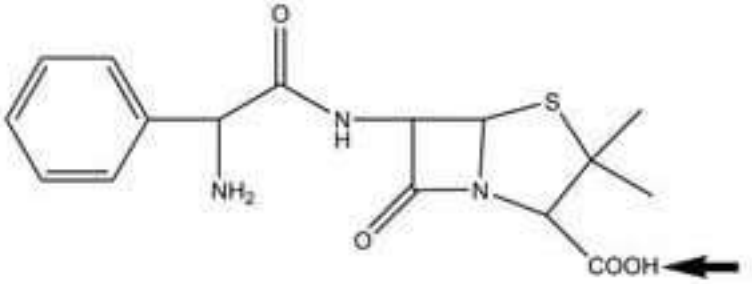
amidases



Benzocaine (local anesthetic)

- 3. Prodrugs for improved Absorption and Distribution

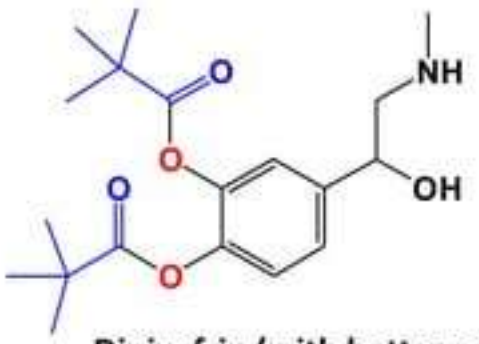
- Ampicillin when administered orally only about 40% of dose is absorbed. Therefore, ampicillin when presented in the form of its esters has increased absorption.
- Eg: Pivampicilline and Becampicillin



becampicillin

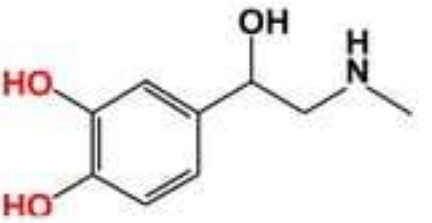
Prodrugs for improved Absorption and Distribution

a.



Dipivefrin (with better corneal penetration

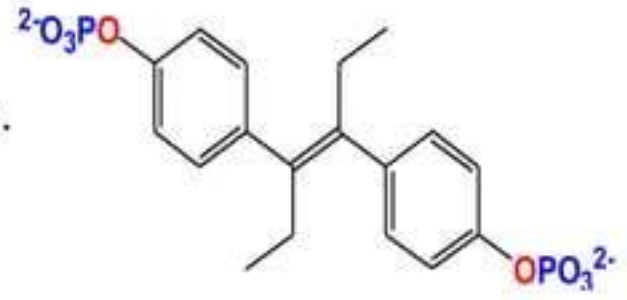
esterase



Epinephrine (anti-glaucoma)

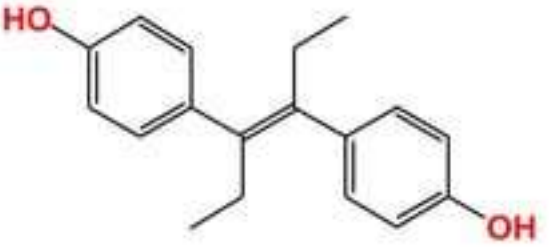
4. Prodrugs for Site Specificity

a.

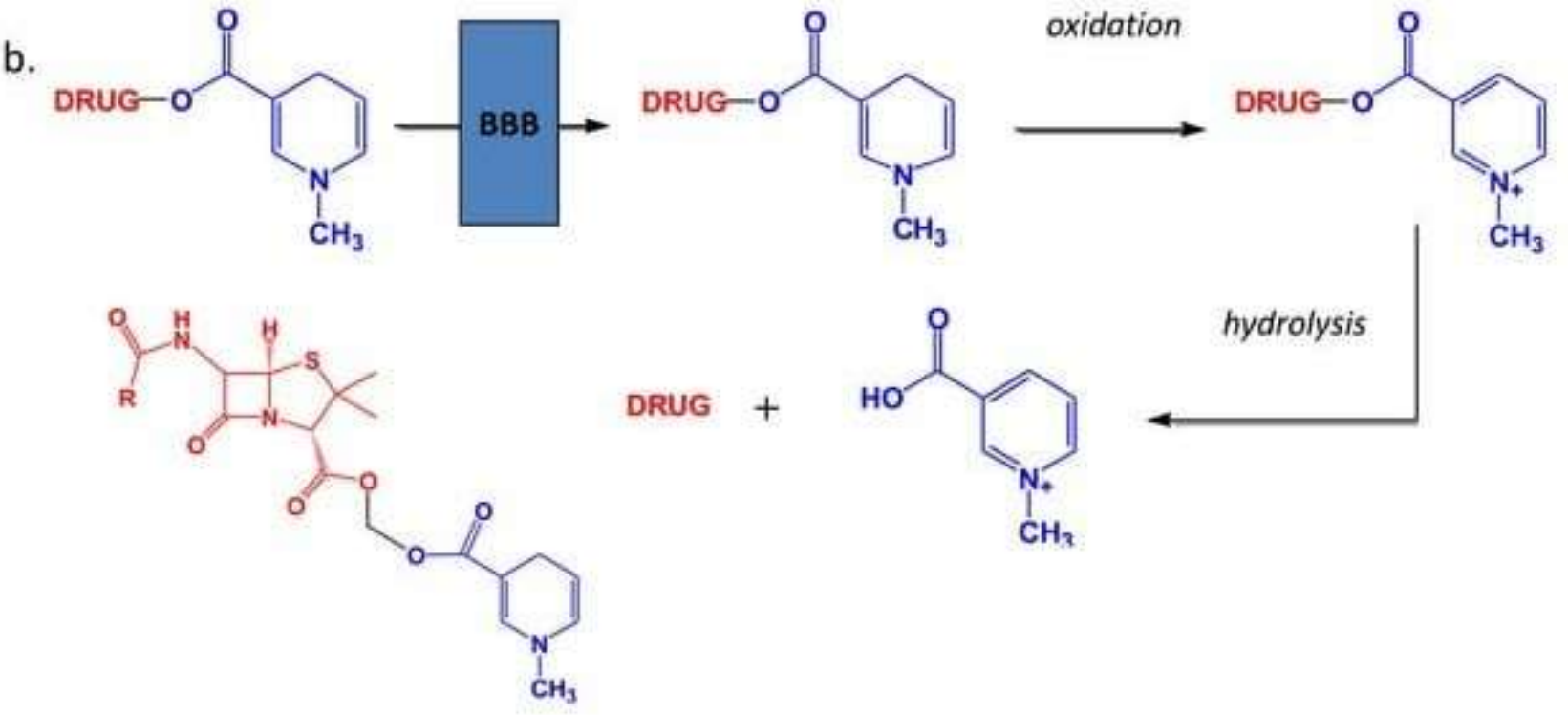


diethlystilbestrol diphosphate

phosphatase



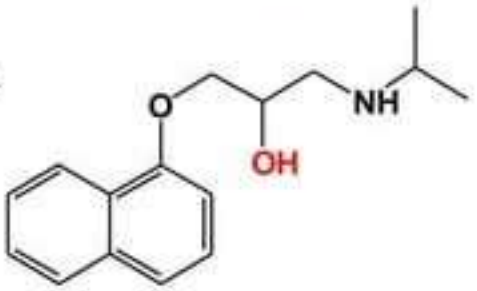
Diethlystilbestrol
(breast cancer treatment)



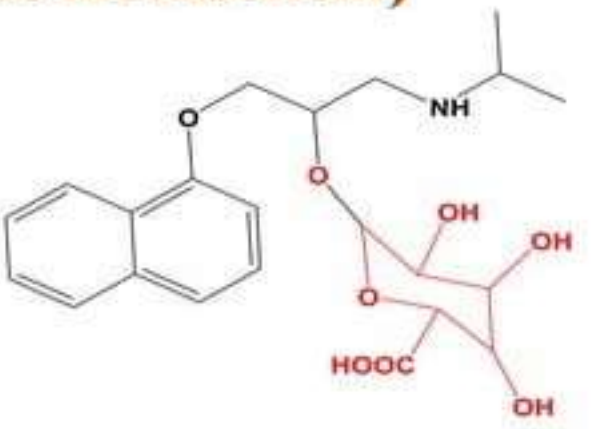
β-lactam antibiotic delivery to brain
In the treatment of meningitis

4. Prodrugs for Stability (first-pass metabolism)

a.



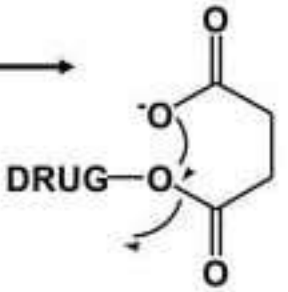
glucuronidation

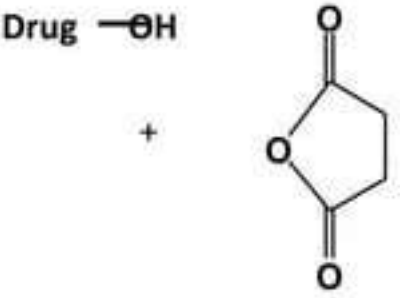


propranolol (antihypertensive)

propranolol O-glucuronide

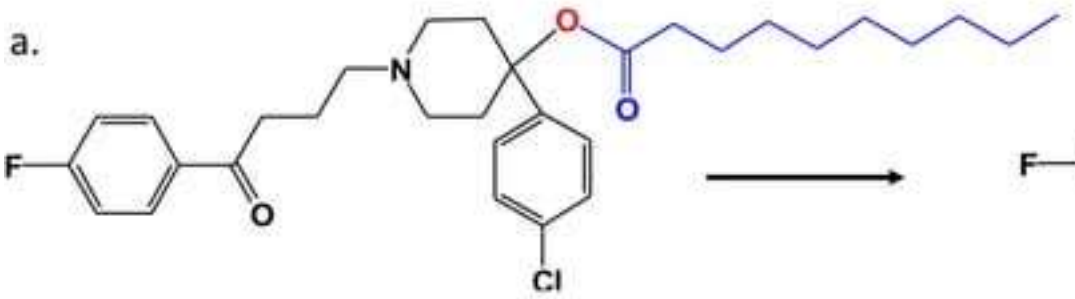
propranolol hemisuccinate



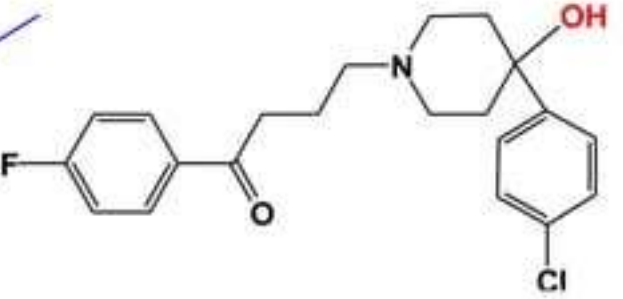


5. Prodrugs for Slow and Prolonged Release

a.

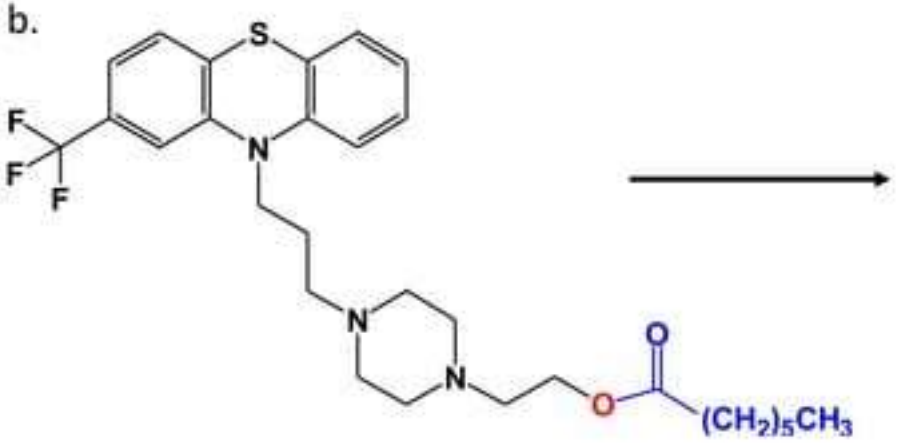


haloperidol decanoate (activity ~ 1 month i.m.)

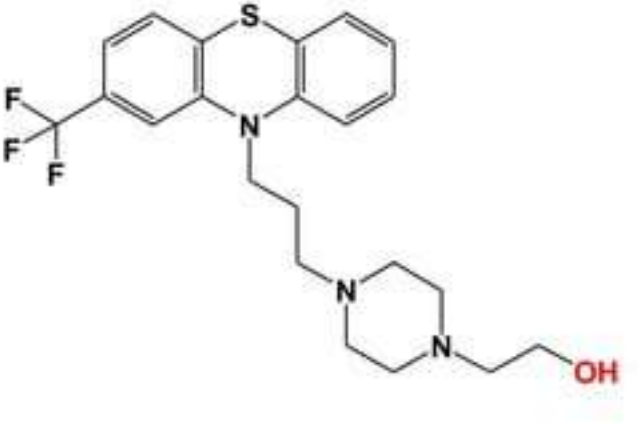


haloperidol (tranquilizer)
(peak plasma ~ 2-6 hr oral)

b.



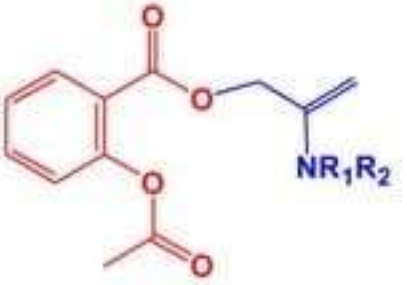
fluphenazine enanthate
(duration of activity ~ 1 month)



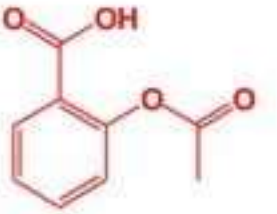
fluphenazine (antipsychotic)
(duration of activity 6-8 hrs)

6. Prodrugs to minimize toxicity

a.



ester derivative of aspirin (without gastric irritation)



clindamycin (R = H)
clindamycin phosphate ($R = PO_3H_2$)
clindamycin palmitate ($R = CO(CH_2)_{14}CH_3$)

aspirin (anti-inflammatory)

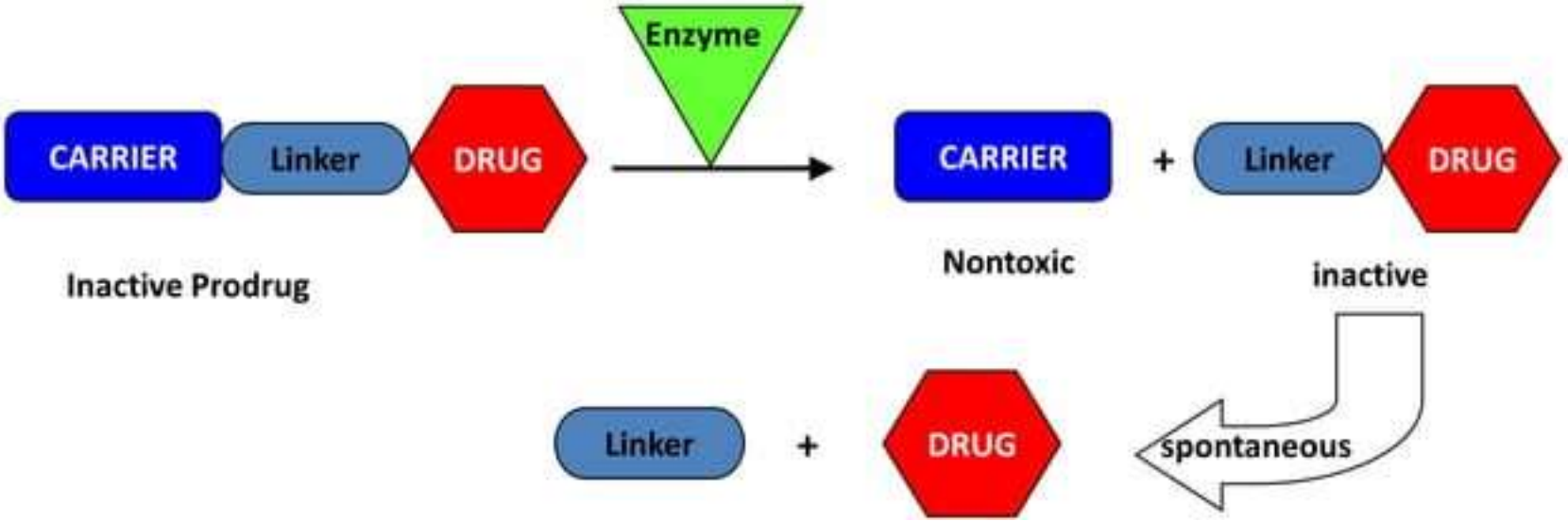
Antibody-directed enzyme prodrug therapy (ADEPT)

- The principle of ADEPT is to use an antibody directed at a tumor-associated antigen which localizes the enzyme in the vicinity of the tumor.
- A non-toxic prodrug, a substrate for the enzyme, is then given intravenously and converted to a cytotoxic drug only at the tumor site where the enzyme is localized, resulting in tumor cell death.

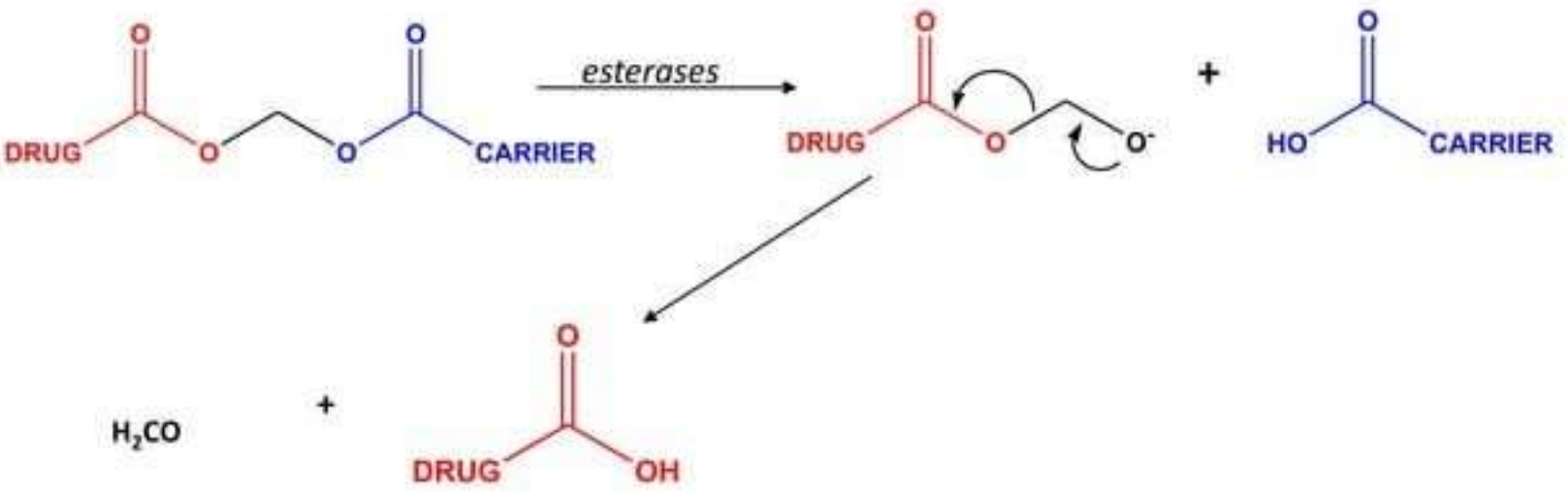
Antibody	Prodrug	Drug	Tumor target
L6	Mitomycin C phosphate	Mitomycin C	Lung adenocarcinoma
BW413	Etoposide phosphate	Etoposide	Colon carcinoma
L6	Doxorubicin phosphate	Doxorubicin	Lung adenocarcinoma

TRIPARTATE PRODRUGS

- The **carrier** is not linked directly to the **drug** but instead through a **linker**
- Allows for decreased steric hindrance during enzymatic cleavage that may occur with bipartate prodrugs
- **Carrier** is enzymatically cleaved from **Linker**
- **Linker** spontaneously cleaves from **Drug**



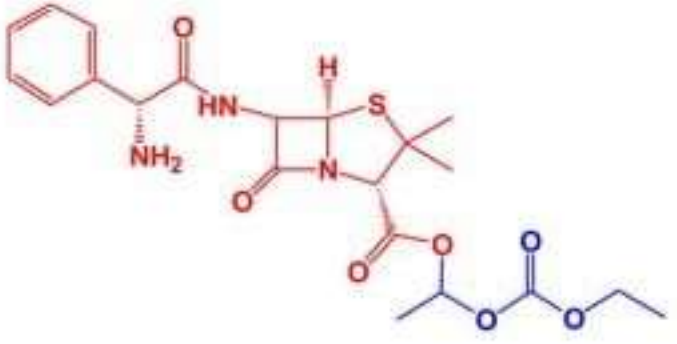
TRI PARTATE PRODRUGS – Double Prodrugs



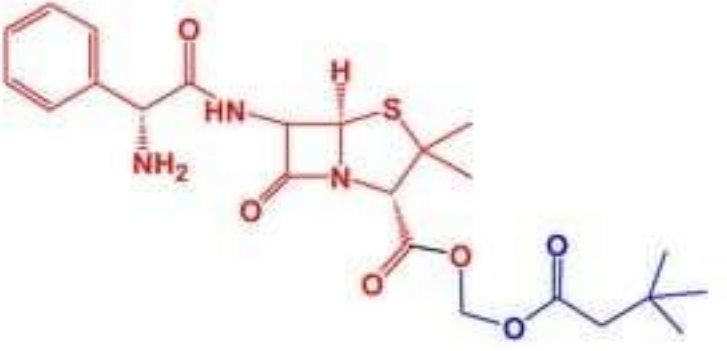
Examples of Carrier-linked Tripartate Prodrugs

a.

ampicillin (antibiotic)



bacampicillin

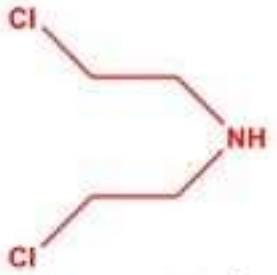


pivampicillin

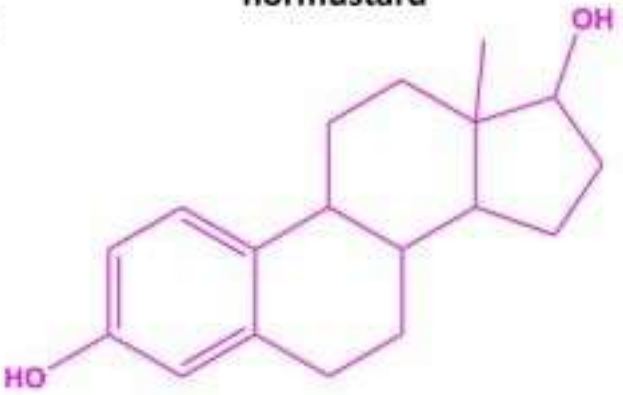
MUTUAL PRODRUGS

- Useful when 2 synergistic drugs need to be administered at the same site at the same time
- Mutual prodrug is bipartate or tripartate where a synergistic drug acts as the carrier

estramustine (prostatic cancer treatment)



normustard



estradiol

- Used for metastatic carcinoma of the prostate
- Promoiety also a drug!
- 17-alphaestradiol slow prostate cell growth
- Nornitrogen mustard is a weak alkylating agent

BIOPRECURSOR PRODRUGS

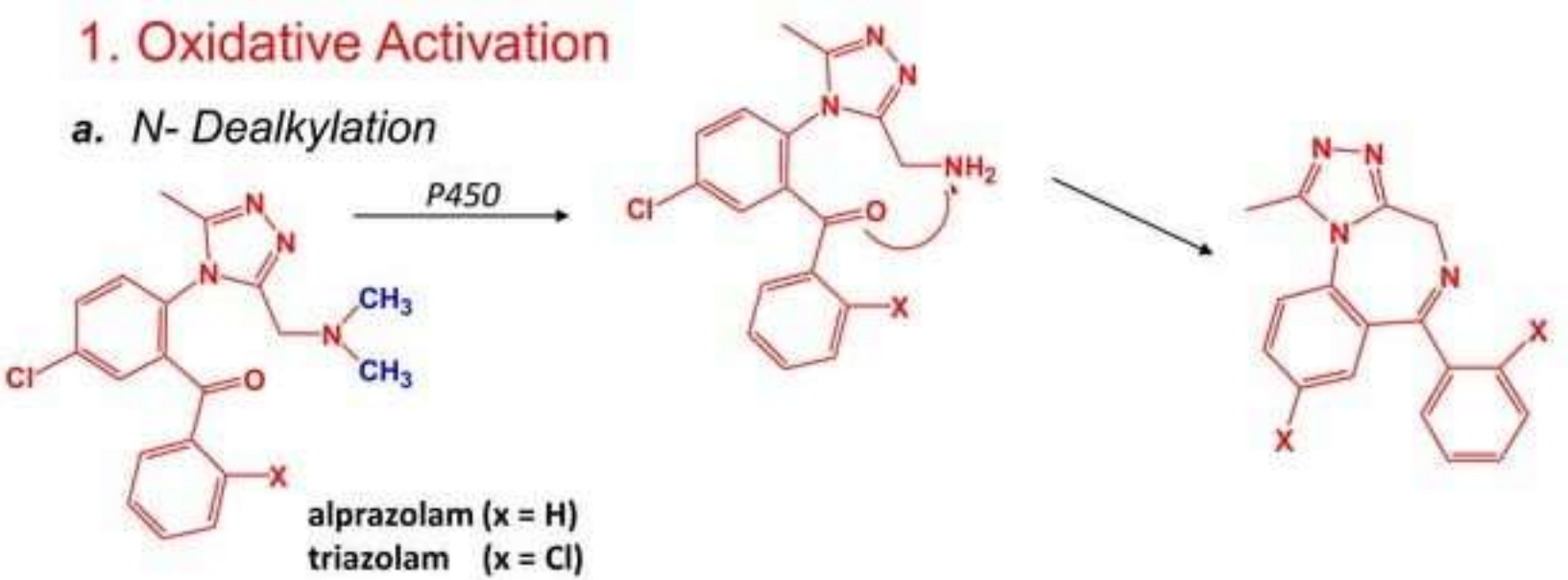
Bioprecursor prodrugs rely on oxidative or reductive activation reaction unlike the hydrolytic activation of carrier-linked prodrugs

Metabolic Activation of Bioprecursor Prodrugs:

1. Oxidative Activation
    - *N*- and *O*-Dealkylation
    - Oxidative Deamination
    - N-Oxidation
    - Epoxidation
2. Reductive Activation
    - Azo Reduction
    - Sulfoxide Reduction
    - Disulfide Reduction
    - Bioreductive Alkylation
    - Nitro Reduction
3. Nucleotide Activation
4. Phosphorylation Activation
5. Decarboxylation Activation

1. Oxidative Activation

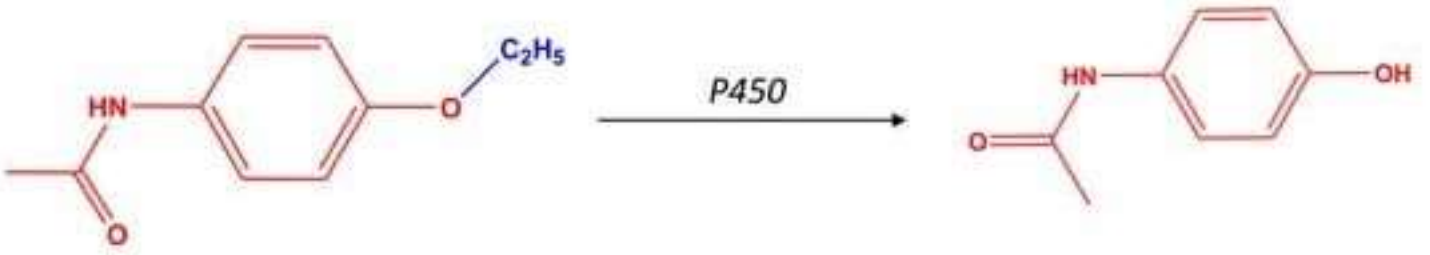
a. N- Dealkylation



alprazolam (x = H)
triazolam (x = Cl)

benzodiazepine (anxiolytic & sedative)

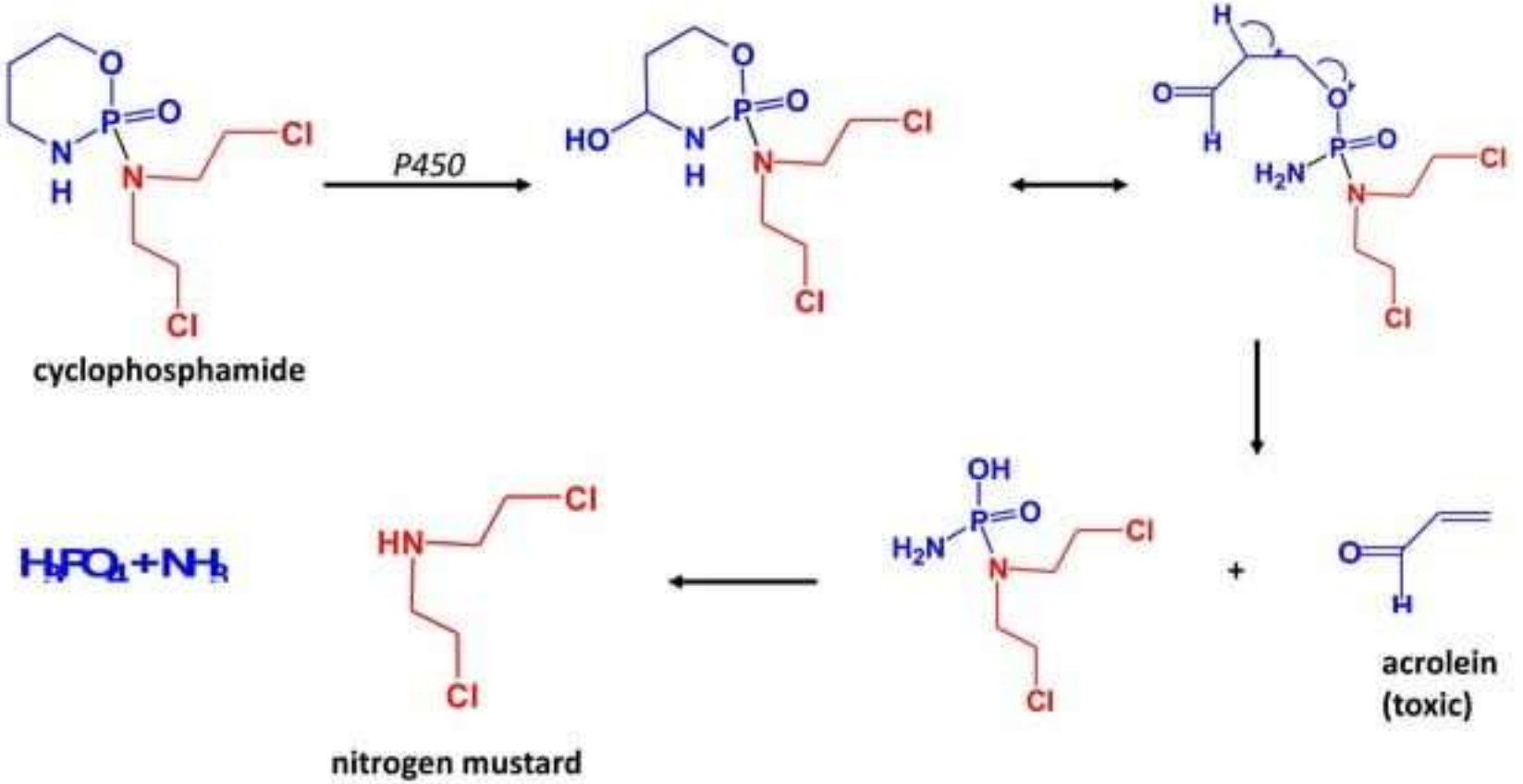
b. O- Dealkylation



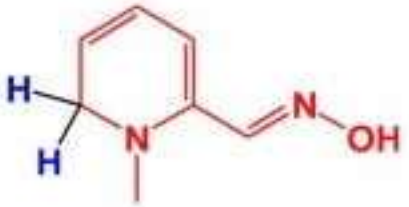
phenacetin

acetaminophen

c. Oxidative deamination



d. N-Oxidation



5, 6 dihydropyridine bioprecursor

pralidoxime (acetylcholine esterase activator)

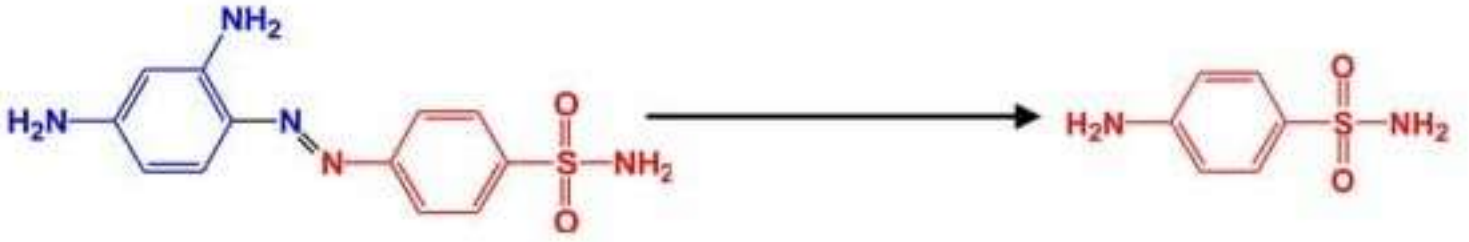
e. Epoxidation

carbamazepine (anticonvulsant)

carbamazepine 10, 11-oxide

2. Reductive Activation

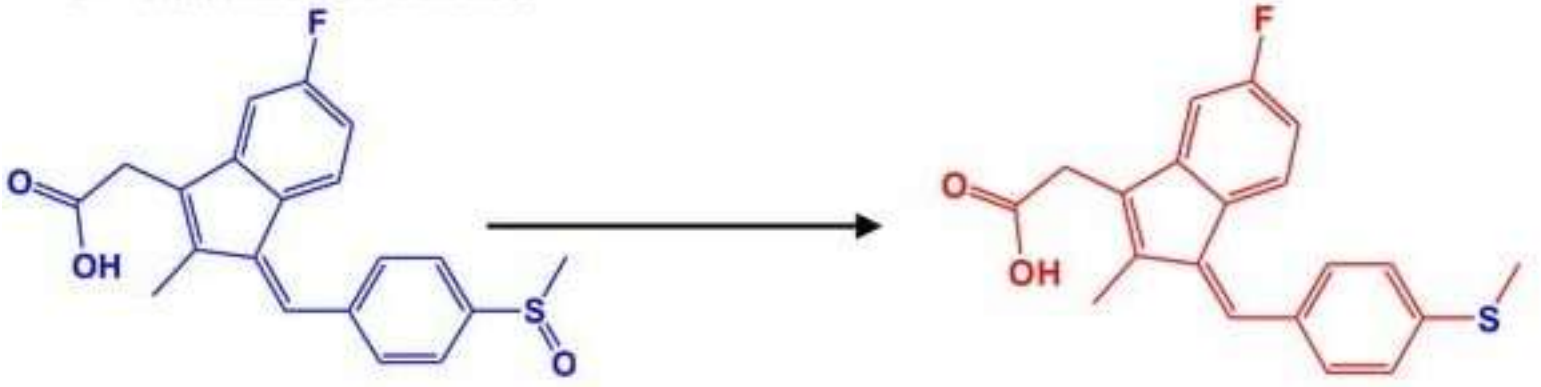
a. Azo reduction



prontosil

sulfanilamide

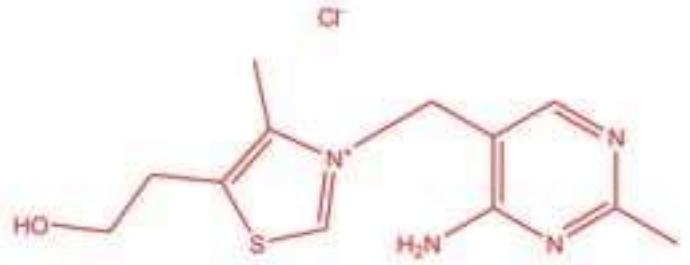
b. Sulfoxide reduction



Sulindac (NSAID)

sulfide derivative

c. Disulfide reduction

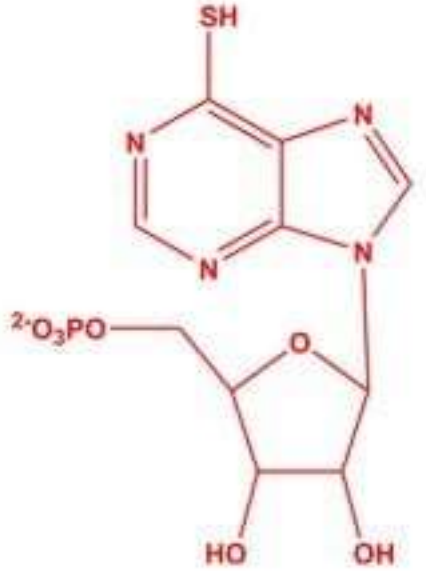


thiamine tetrahydrofurfuryl disulfide

Thiamine B1

3. Nucleotide Activation

6-mercaptopurine



inhibits purine synthesis

4. Phosphorylation Activation

ganciclovir

substrate for DNA polymerase

5. Decarboxylation Activation

levodopa

dopamine