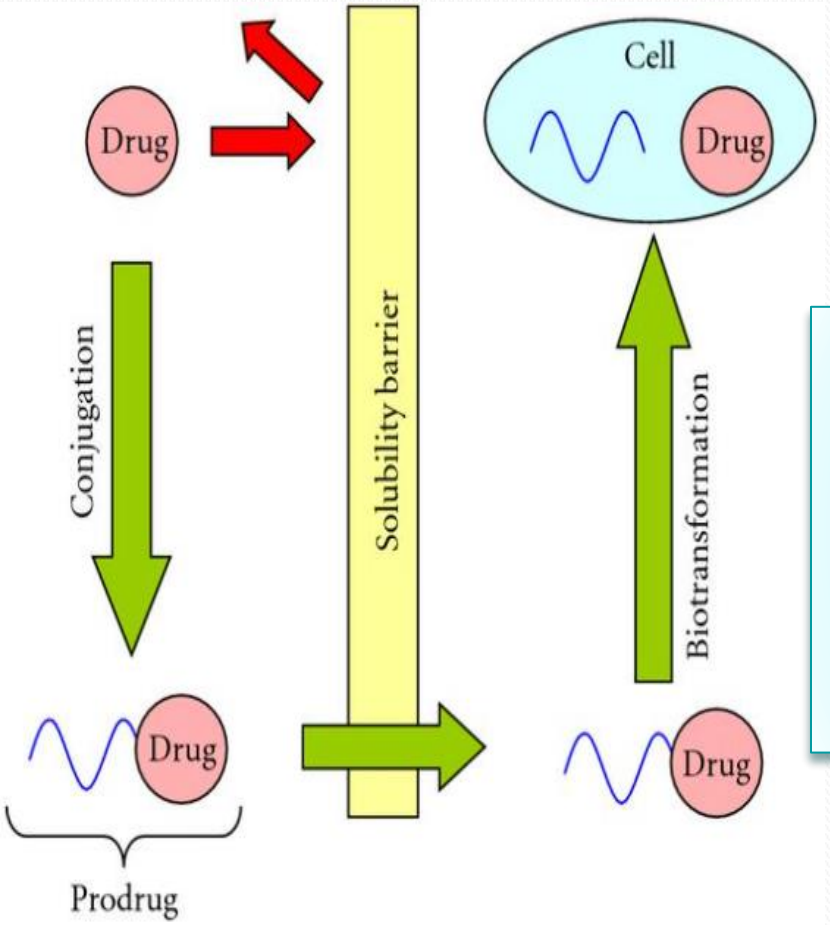
Prodrug Design approaches



Course: Drug Design
Course code: 0510518

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Learning Outcomes

At the end of this lesson students will be able to

- Define and describe various applications of prodrugs.
- Explain different types of prodrugs.
- Describe the carrier-linked prodrugs with examples.
- Define and explain macromolecular drug delivery.
- Describe the importance of mutual prodrugs.
- Explain bioprecursors with suitable examples.

Prodrug

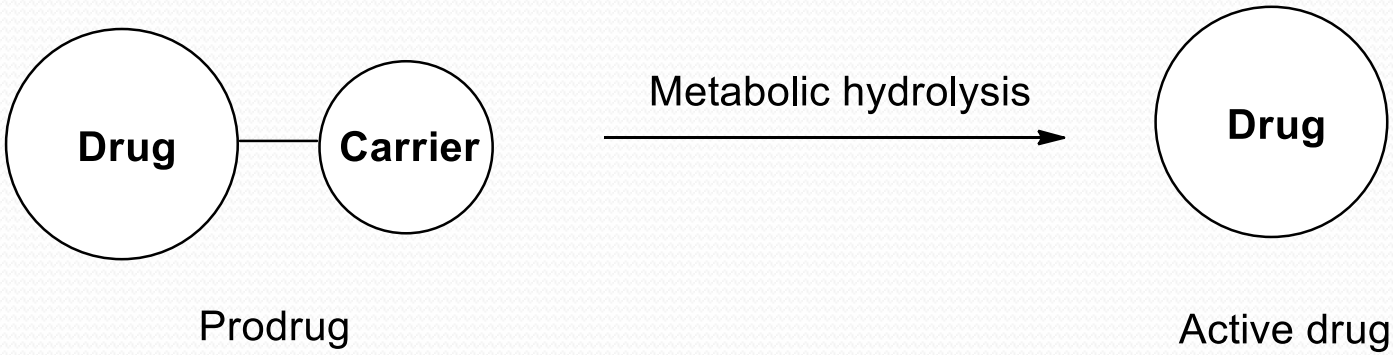
- **Prodrug** is a pharmacologically inactive compound that is converted into an active drug by metabolic transformations.
- A prodrug can also be activated by a non-enzymatic process such as hydrolysis.
- **Prodrug Design** is a lead modification approach that is used to correct some defects in a drug candidate.
- **Soft drug** (antedrug): is pharmacologically active drug and uses metabolism as a means of promoting excretion.

Utility or the useful applications of Prodrugs

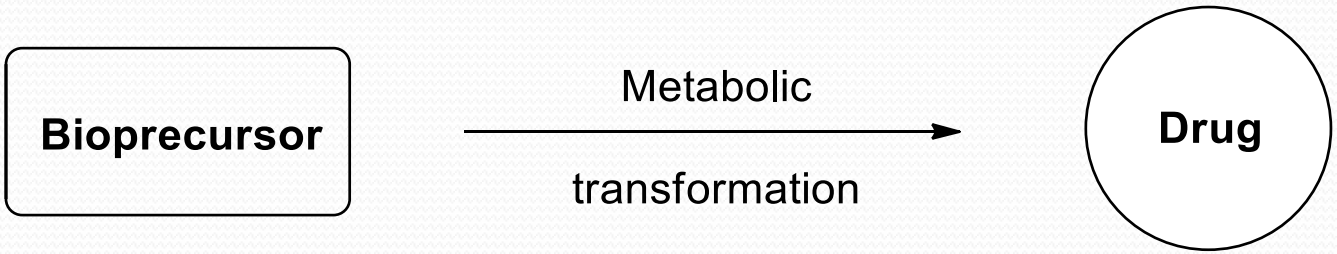
1. Improving aqueous solubility.
2. Improving absorption and distribution.
3. Improving the site-specific delivery.
4. Increasing the stability.
5. To achieve the prolonged release of drug.
6. To minimize the toxicity.
7. To solve formulation problems
8. Improving patient compliance and to overcome:
    - Unpleasant taste or odor,
    - Gastric irritation,
    - Pain at the site of injection.

Types of prodrugs

- Carrier-linked:



- Bioprecursor:



Types of prodrugs

I. Carrier-linked Prodrug

It is a compound that contains an active drug linked to a carrier group that can be removed enzymatically.

Example: Ester in prodrug can be hydrolyzed to an active carboxylic acid containing drug.

They are subdivided into:-

- **Bipartate**: Prodrug having one carrier attached to the drug directly.
- **Tripartate**: carrier moiety connected to a linker group that is connected to the drug
- **Mutual prodrug**: It consists of two synergistic drugs linked together (one drug is a carrier for the other).

Types of prodrugs

II. Bioprecursor Prodrug

- It is a compound that is metabolized by molecular modification into a new active form or which can be metabolized further to the active drug.

- Here oxidation is the main metabolic biotransformation involved in the activation of bioprecursors.

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I. Carrier-linked prodrugs

Ideal drug carrier must:

1. Protect the drug until it is at the site of action.
2. Localize the drug at the site of action.
3. Allow for the drug release by chemically or enzymatically.
4. Minimize host toxicity.
5. Biodegradable, inert and non-immunogenic.
6. Be easily prepared inexpensively.
7. Stable in its dosage form.

Carrier-linkages for various functional groups

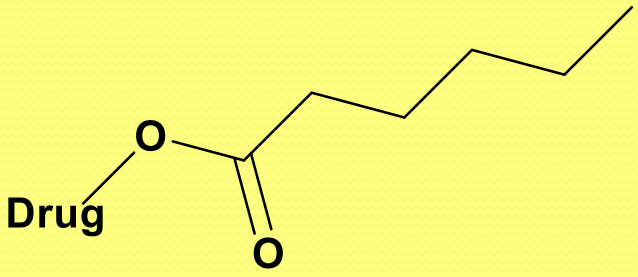
I. Drugs with alcohol and carboxylic acid groups:-

Ester group is the common **carrier group**.

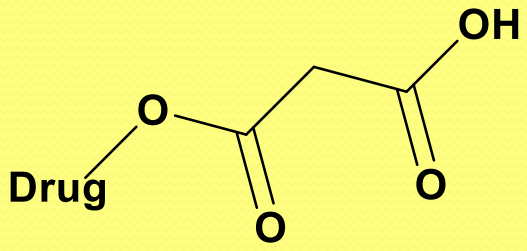
Reasons:-

- Availability of esterase enzyme.
- Possible of increasing or decreasing the lipophilicity of the parent drug.
- A variety of stabilities of ester can be obtained by manipulation of electronic and steric factors.

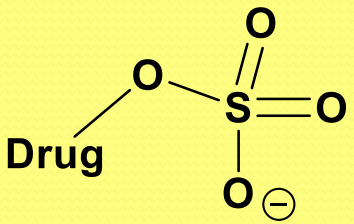
Alcohol containing drugs can be acylated using
(i) Carboxylic acid (to decrease water solubility).
(ii) Carboxylic acid containing amino group (amino acid) or additional carboxylic acid (to increase water solubility).

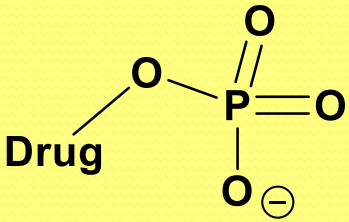


Decreased water solubility



Increased water solubility





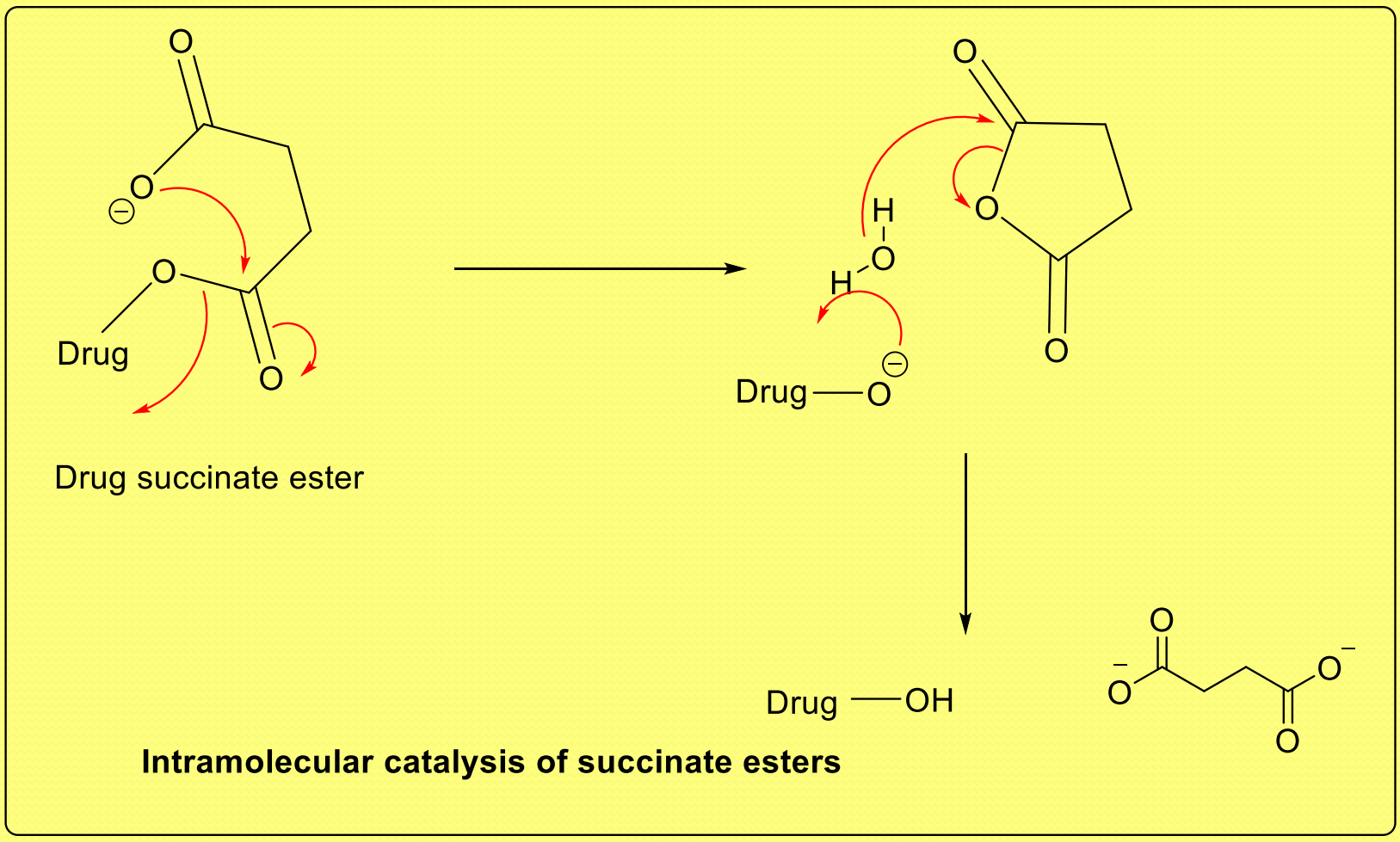
Sulfate and phosphate ester
(increased water solubility

In some cases, esters are not good substrates and hydrolyzed by

(i) Endogenous esterases (or) Sulfatases (or) Phosphatases

So different esters can be used to accelerate **the rate of hydrolysis.**

Example: Succinate ester by intramolecular catalysis.

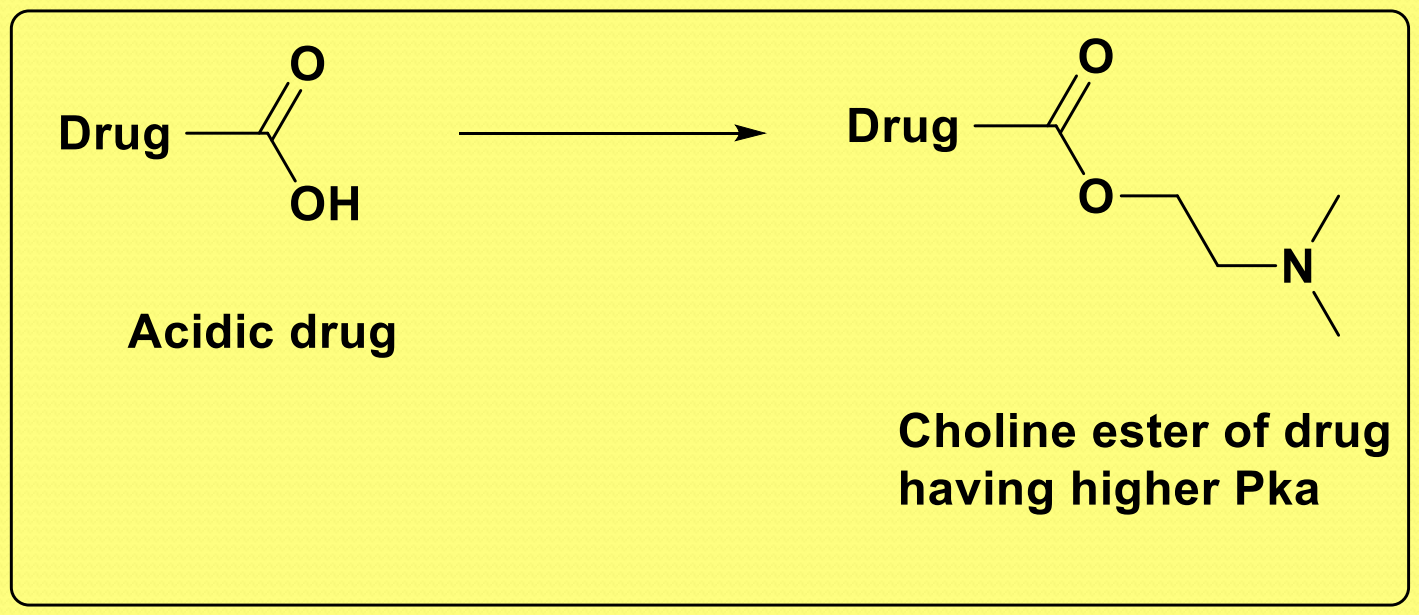


Intramolecular catalysis of succinate esters

Carboxylic acid containing drugs can be esterified using alcohol.

pKa of carboxylic acid can be **increased** by conversion to:

(i) Choline ester
(ii) Amino ester
(iii) 3-phthalidyl ester



II. Drugs with amine moiety:-

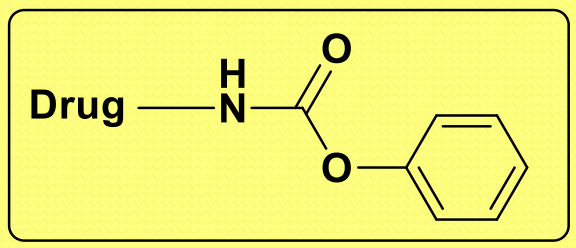
N-acylation of amine moiety to amide **is NOT** commonly used.

Reasons:-

- Amides are stable towards metabolic hydrolysis.
- Amides are less basic.
- Amides of amino acids are more susceptible to enzymatic cleavage.

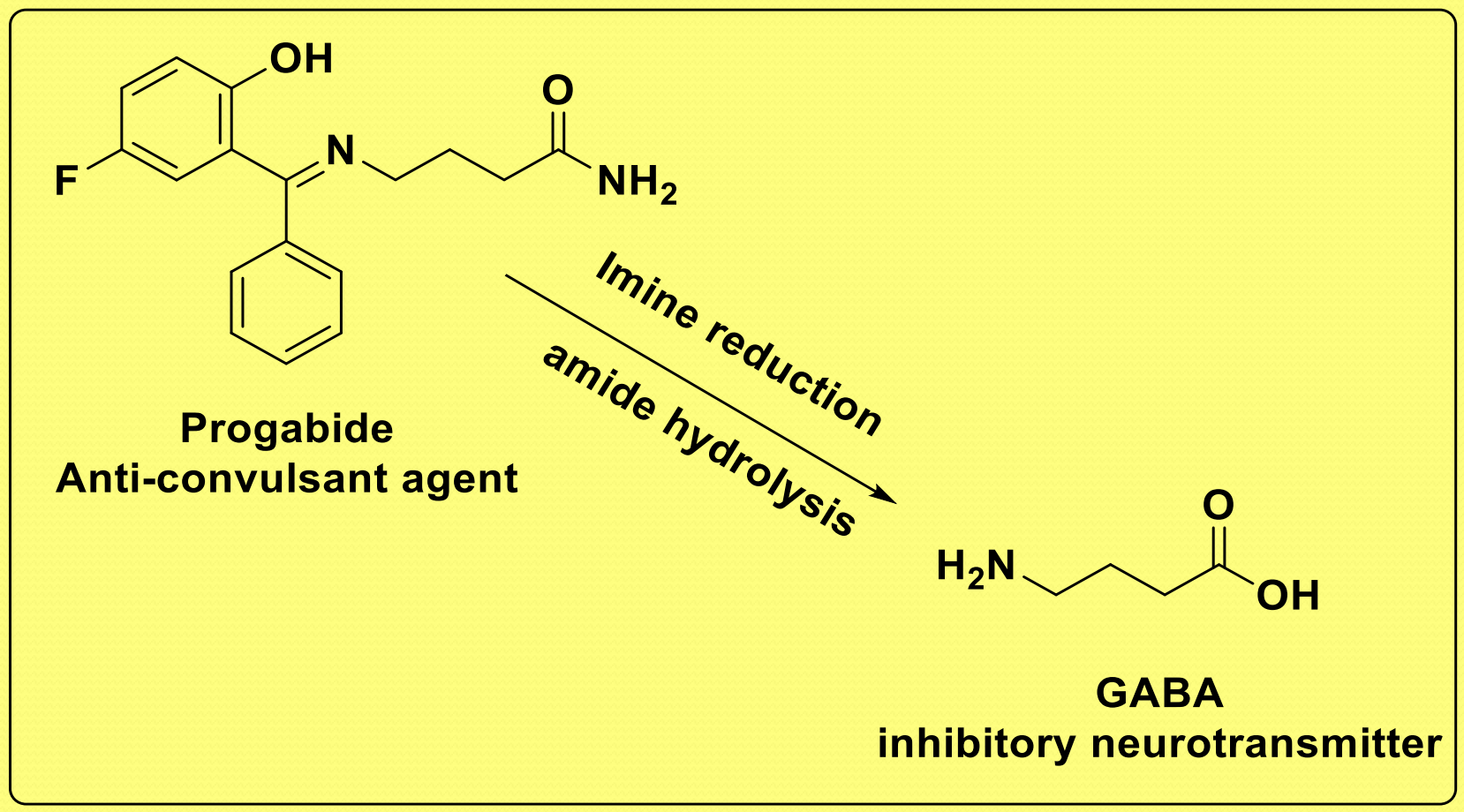
Example:-

Phenyl carbamate (rapidly cleaved by plasma enzymes)



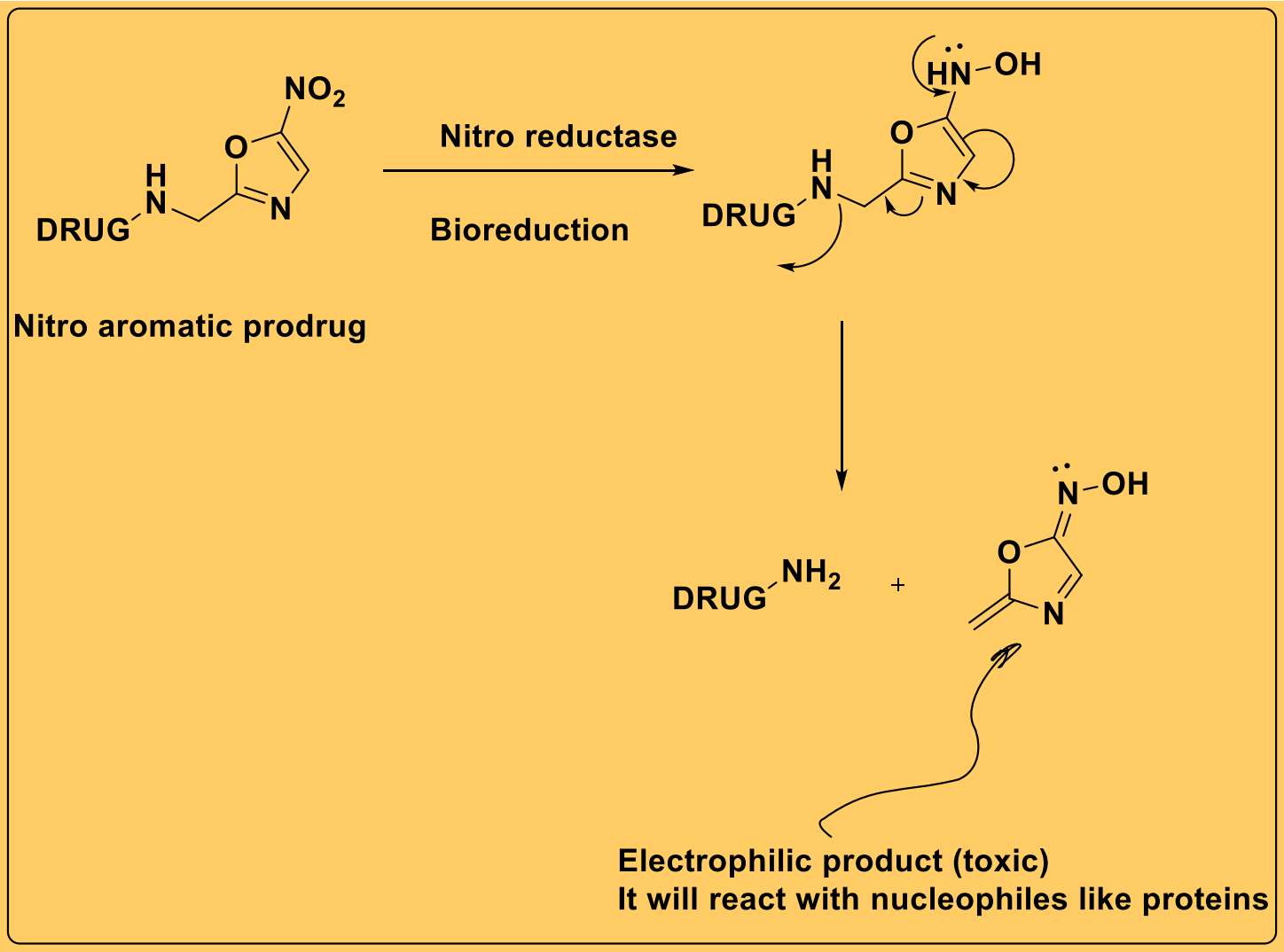
Approach to decrease pKa of **amine moiety** to increase the lipophilicity is the conversion to **imine moiety.**

Example:- **Progabide**



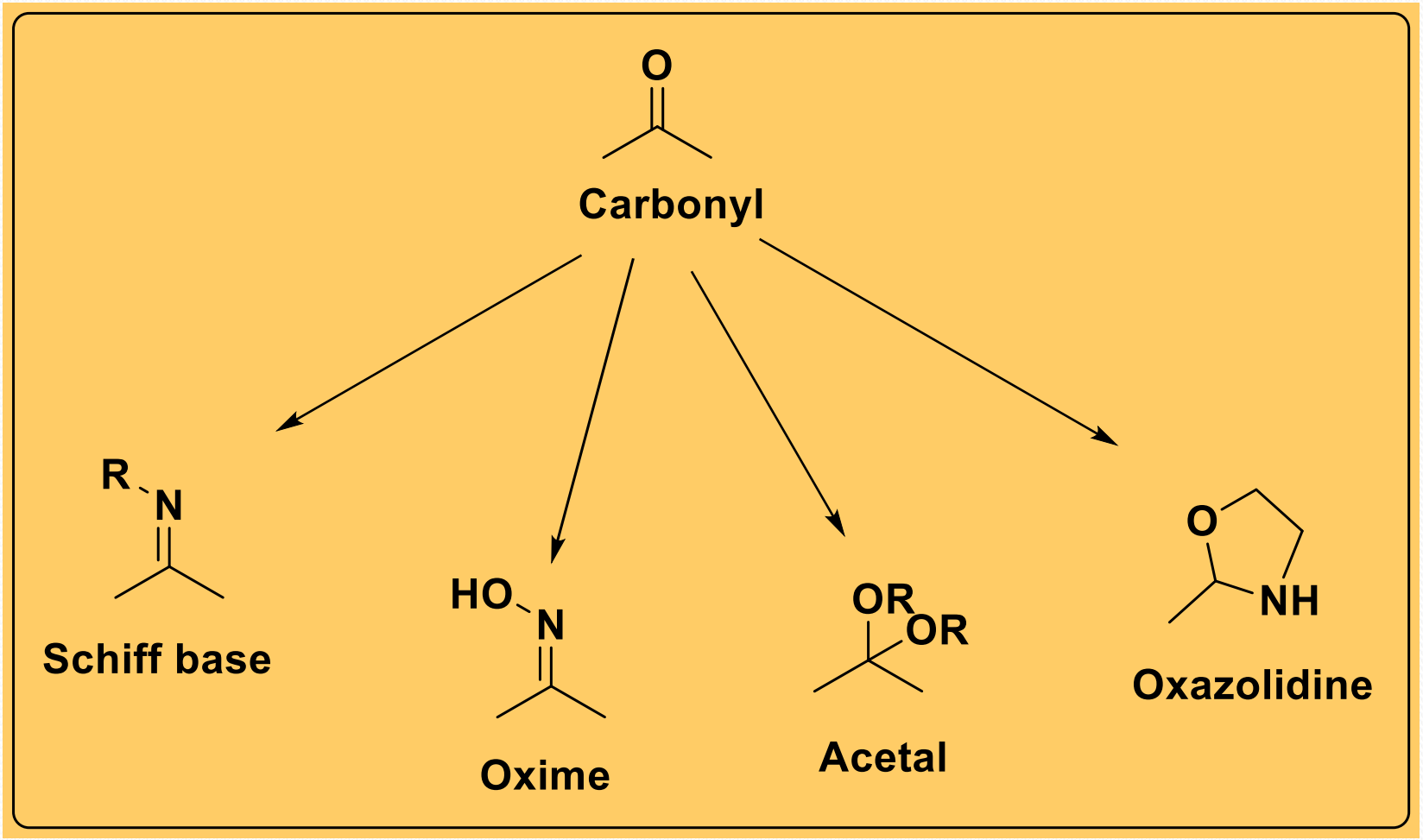
Most of solid tumours are hypoxic(low oxygen), reductive activation mechanism is also important.

Example:- **Reduction of nitro aromatic prodrugs.**



III. Drugs with carbonyl (C=O) moiety:-

The prodrug forms of carbonyl (C=O) groups of aldehydes and ketones are:-



Examples of Carrier-linked Bipartate Prodrugs

I. Prodrugs for increased water solubility

Poorly water soluble Corticosteroidal drugs are **Predinisolone** and **Methylpredinisolone**

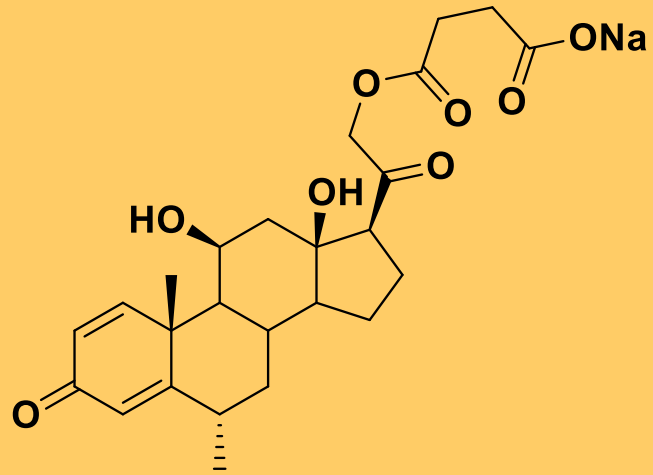
Factors to be considered:-

(i) The ester must be stable enough in aqueous solution (long half-life).

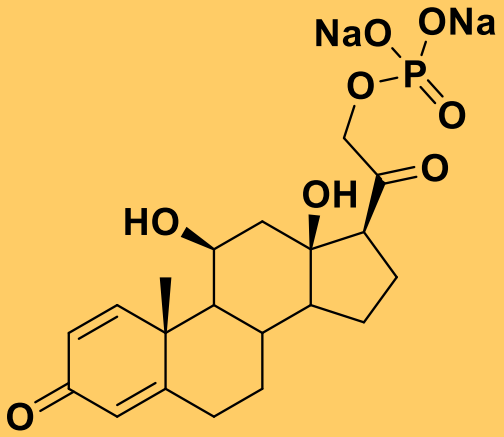
(ii) The ester must be hydrolysed *in vivo* so that it can release the drug (short half-life).

So, solubilizing group must be selected carefully to obtain optimal conditions.

Example-1: Predinisolone Drug



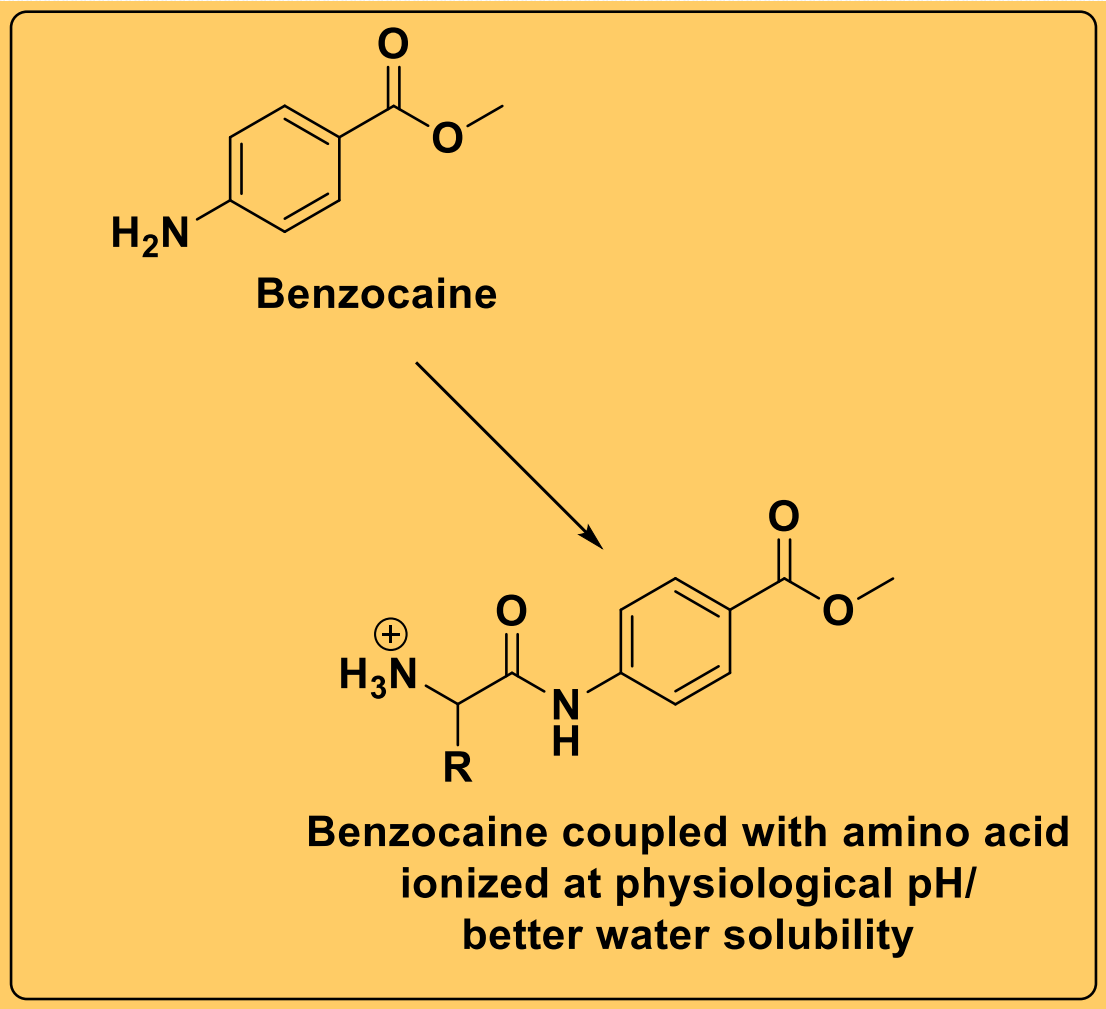
Methylprednisolone sodium succinate (Solu-Medrol)
Low *in vitro* stability due to intramolecular catalysis
So, lyophilized powder must be reconstitued with water then given to the patient within 48 hours.



Prednisolone phosphate
Hydrolysed by Phosphatase

- Esters with anionic solubilizing agent are poorly hydrolyzed while with cationic solubilizing groups will be easily hydrolyzed.

Example-2: Benzocaine Drug

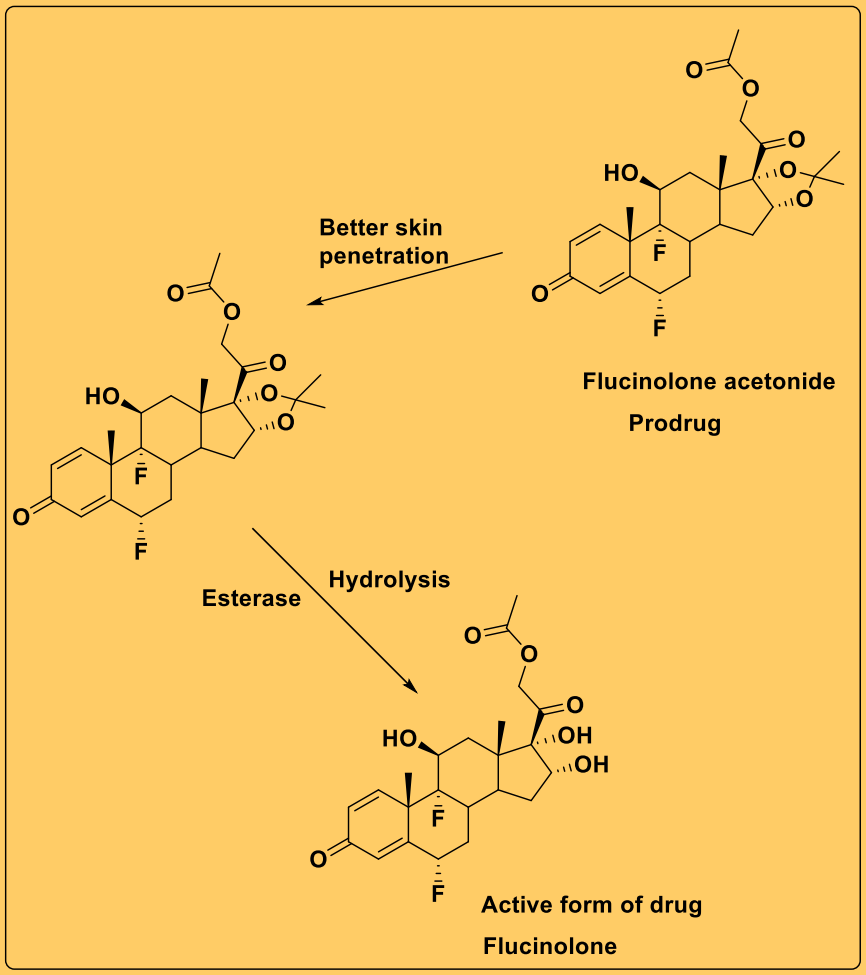


Benzocaine is a local anesthetic drug (more lipophilic) and converted to water soluble amide prodrug.

Amidase enzyme in human serum hydrolyze this amide.

II. Prodrugs for improved Absorption and Distribution

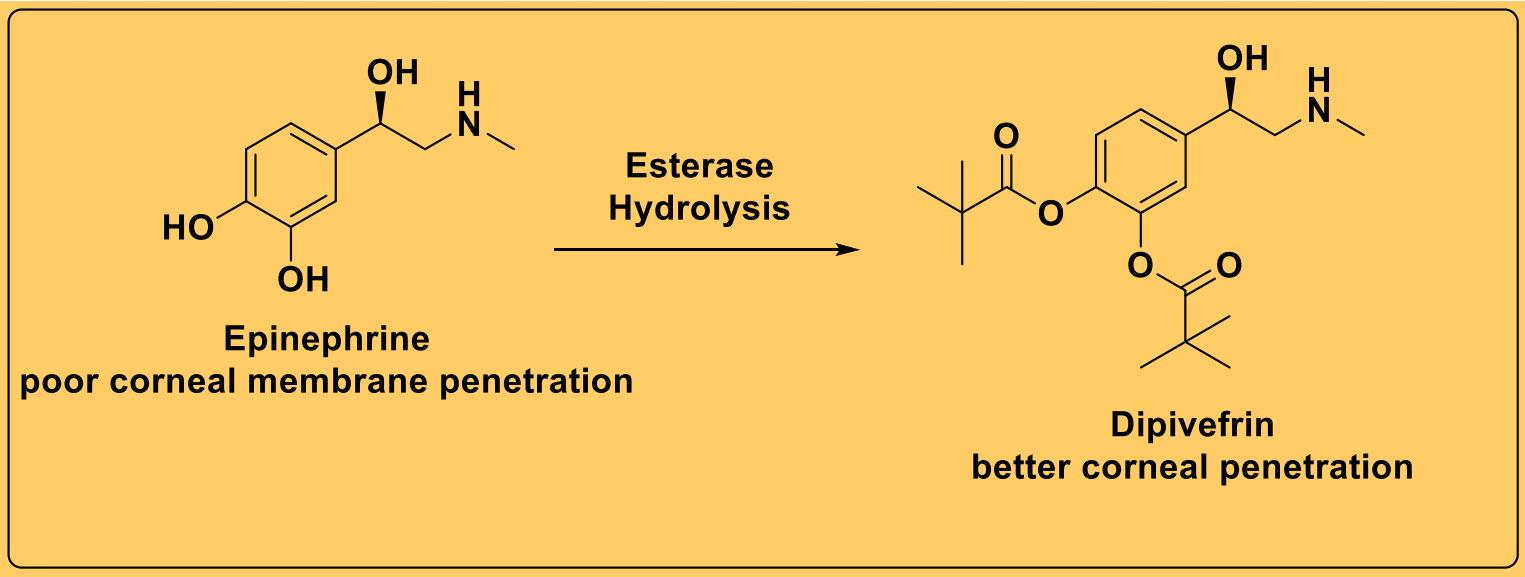
Example-1: Flucinolone Drug



Steroids having low skin absorption due to hydroxyl groups (-OH) which interact with skin/binding-site of keratin. Corticosteroids like **Flucinolone** can be used for skin allergy and inflammation. They have lower skin permeability.

So to increase the skin permeability, the **prodrug Flucinolone acetonide** was formulated.

Example-2: Epinephrine Drug



Epinephrine is an antiglaucoma drug (poor corneal membrane penetration in eyes) and converted prodrug Dipivefrin (better corneal penetration) which can be hydrolyzed by the enzyme esterases.

III. Prodrugs for Site-specificity

- **Factors affecting** the delivery of drugs to Brain through Blood-Brain Barrier (**BBB**):
  - BBB is lipid-like protective barrier that prevents the entry of hydrophilic drugs to brain
  - BBB has active enzyme systems that protect the brain.

So, for better penetration though BBB, the drugs must have adequate **Molecular size** and **Lipophilicity**.

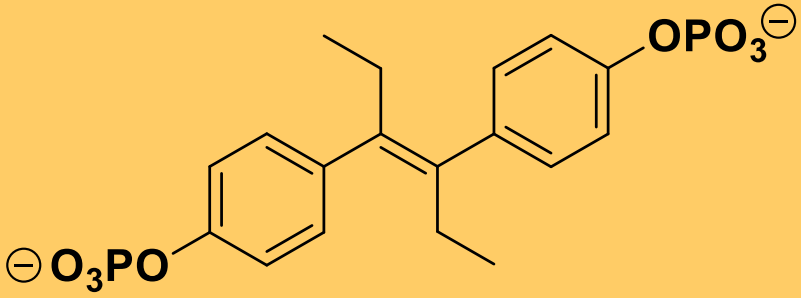
Example-1: GABA Drug

GABA is polar, anticonvulsant drug which cannot penetrate BBB.

So, Progabide a prodrug of GABA is used which can penetrate BBB due to high lipolphilicity.

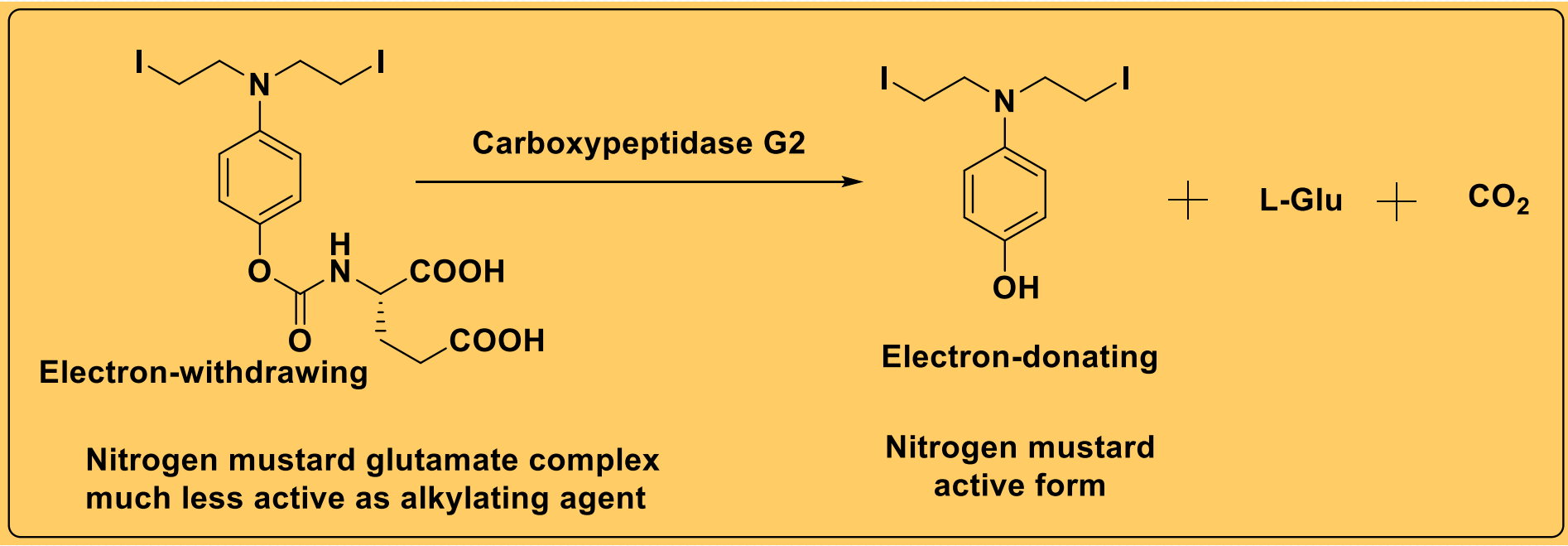
Example-2: Diethylstibestrol Drug

- Tumor cells have elevated amount of phosphatase and amidase.
- Diethylstilbestrol diphosphate prodrug was designed for the site-specific delivery of Diethylstilbestrol to prostatic carcinoma tissue.



Diethylstilbosterol diphosphate
Will be hydrolysed more in tumor cells by the available phosphatase

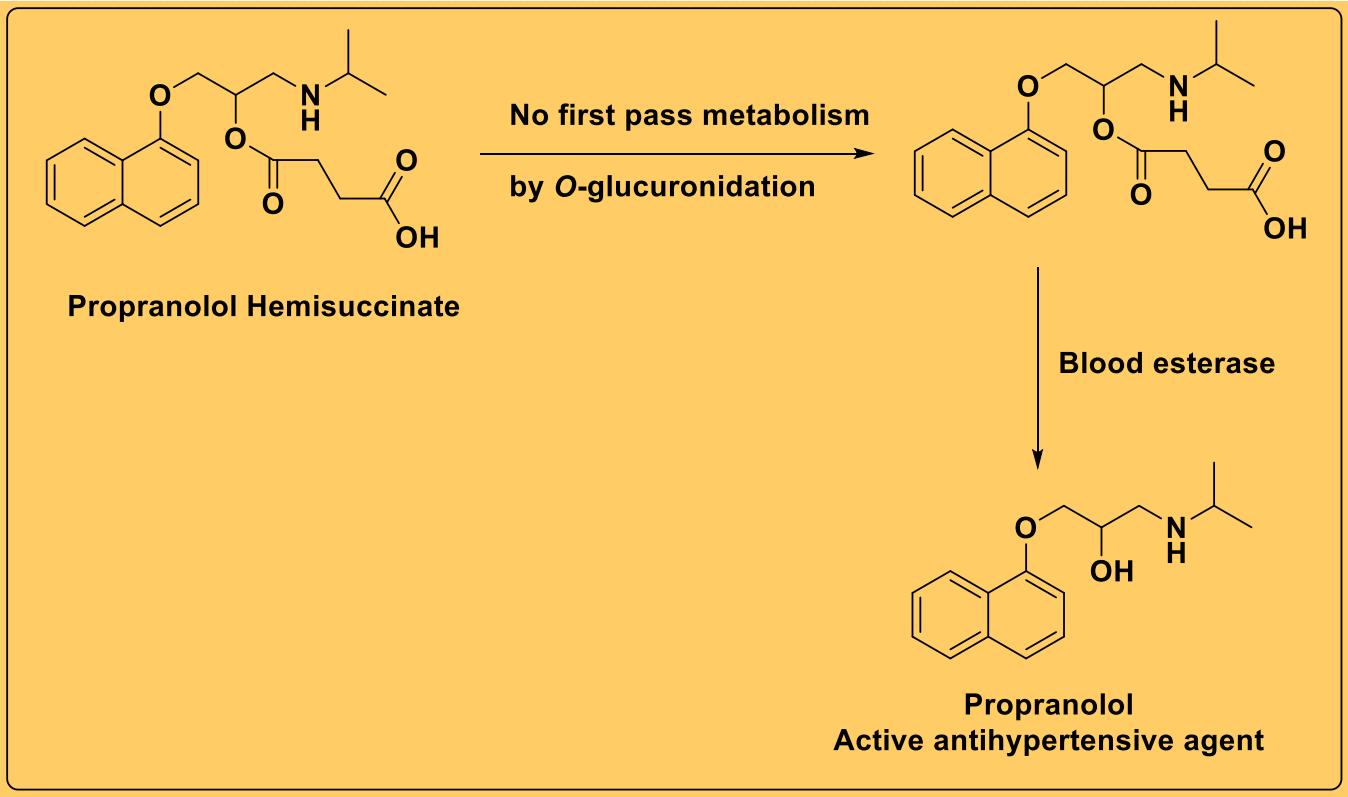
Example: Nitrogen mustard activation by the enzyme Carboxypeptidase G2.



Humanized monoclonal antibody conjugated to the bacterial enzyme carboxypeptidase G2 for the delivery of nitrogen mustard as a conjugate with glutamate.

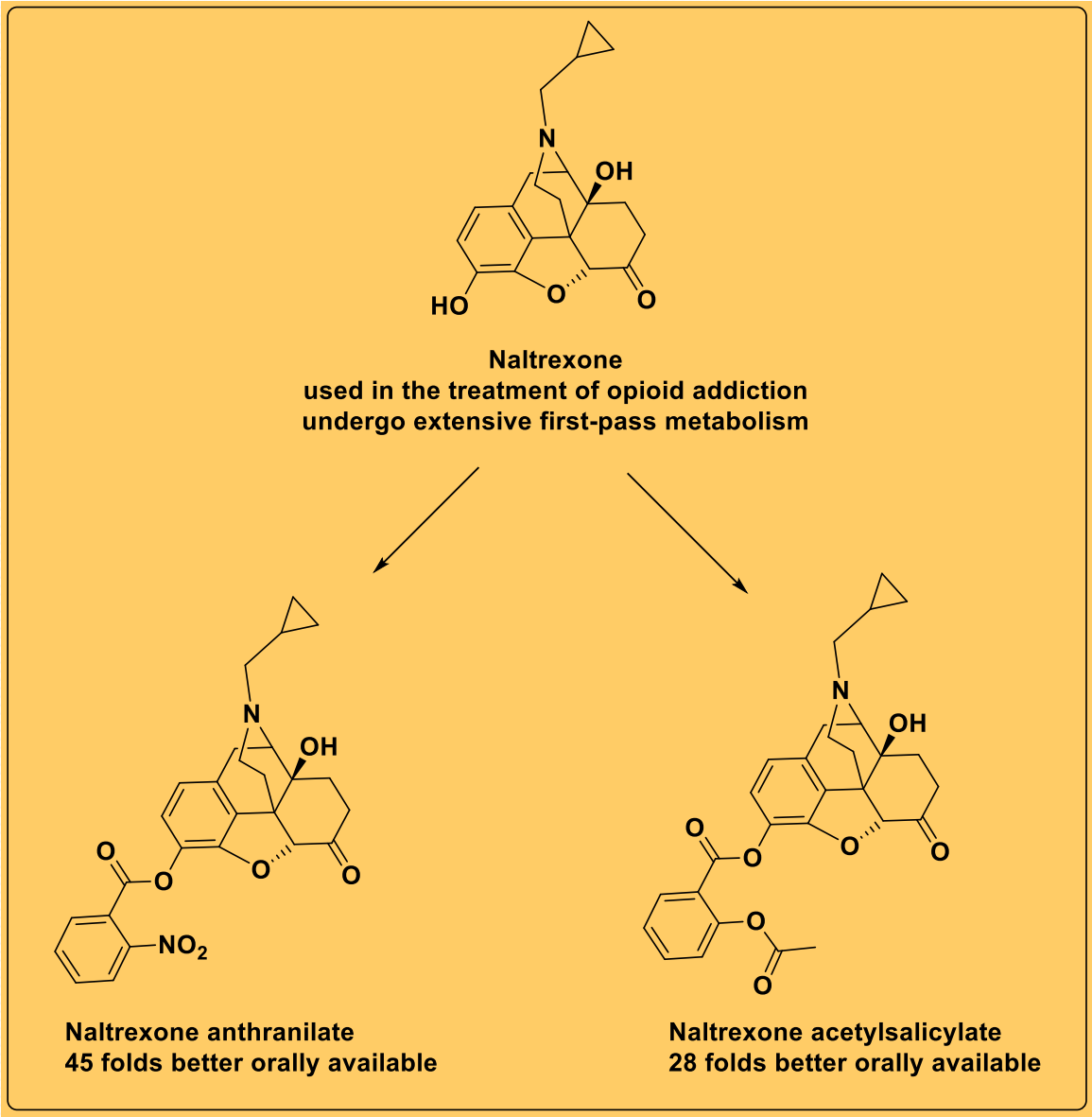
IV. Prodrugs for Stability

Example-1: Propranolol (Antihypertensive Drug)



- Due to first-pass effect, propranolol has low oral bioavailability.
- O-glucuronide of propranolol is the major metabolite.
- The hemisuccinate ester of propranolol (prodrug) is metabolically stable, can be administered orally and blocks the glucuronide formation.

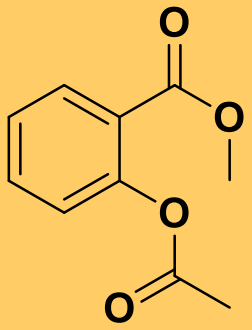
Example-2: Naltrexone (treatment of opioid addiction)



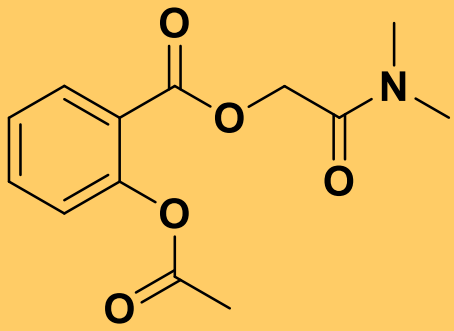
V. Prodrugs to minimize toxicity

Example: Aspirin (NSAID)

- ✓ Side effects of Aspirin: Gastric irritation and ulcerogenicity.
- ✓ Reason: Accumulation of the acid in gastric mucosal cells.
- ✓ Solution: Esterification of Aspirin.



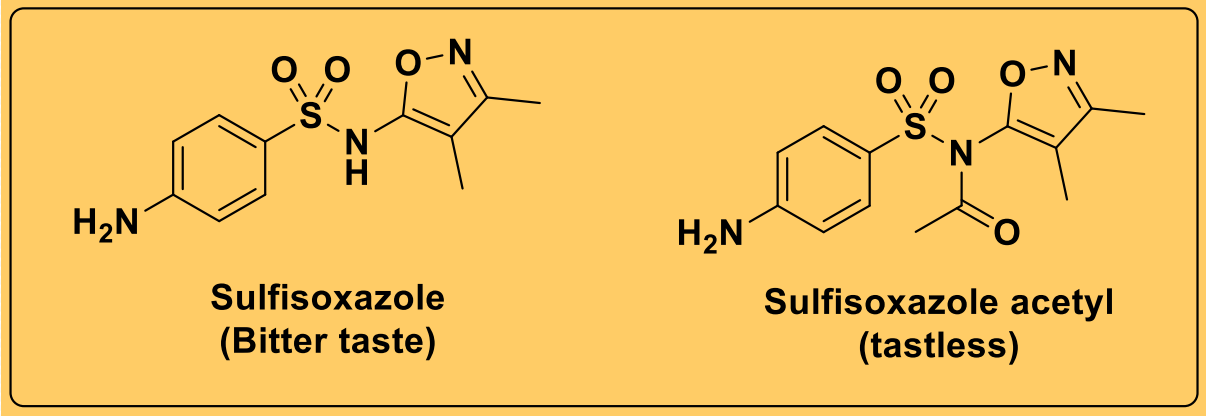
Acetyl ester of Aspirin
Sensitive to enzymatic hydrolysis
Becomes less active



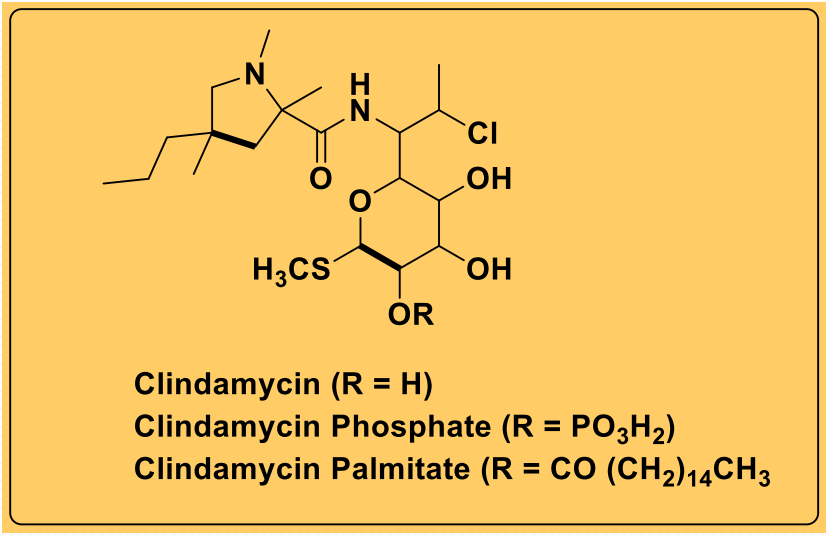
N,N-disubstituted 2-hydroxyacetamide of Aspirin
Chemically stable but hydrolysed by pseudocholineesterase in plasma

VI. Prodrugs to encourage patient acceptance

Example-1: Sulfisoxazole (Antibacterial Sulfa Drug)



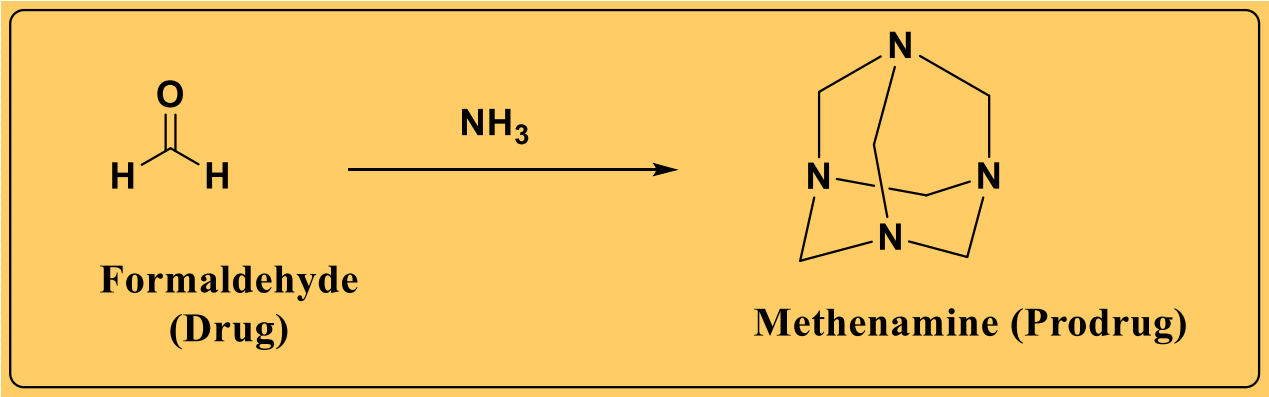
Example-2: Clindamycin (Antibiotic Drug)



- Clindamycin generates pain on injection and bitter taste orally.
- **Prodrug** Clindamycin Phosphate generates **no pain.**
- **Prodrug** Clindamycin Palmitate gives **no bitter taste.**

VII. Prodrugs to eliminate formulation problems

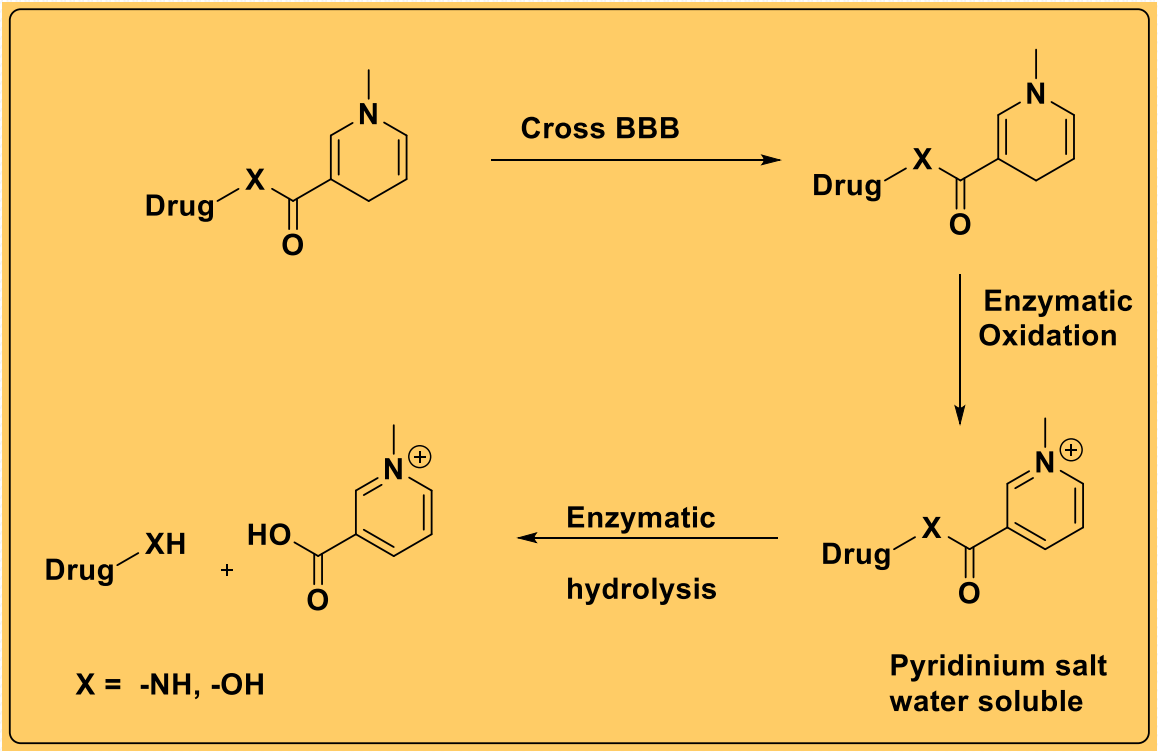
Example: Formaldehyde (Urinary antiseptic, Disinfectant)



- Highly concentrated Formaldehyde solution is toxic.
- Reaction of formaldehyde with ammonia produces a stable Methenamine (prodrug).
- pH of urine inside the urinary bladder is acidic, so methenamine hydrolyzed to release formaldehyde.
- To prevent the hydrolysis of the prodrug methenamine in the acidic environment of stomach, the enteric coated tablets are formulated.

Dihydropyridine as a carrier for CNS targeting (Bipartate)

Reversible redox drug delivery system

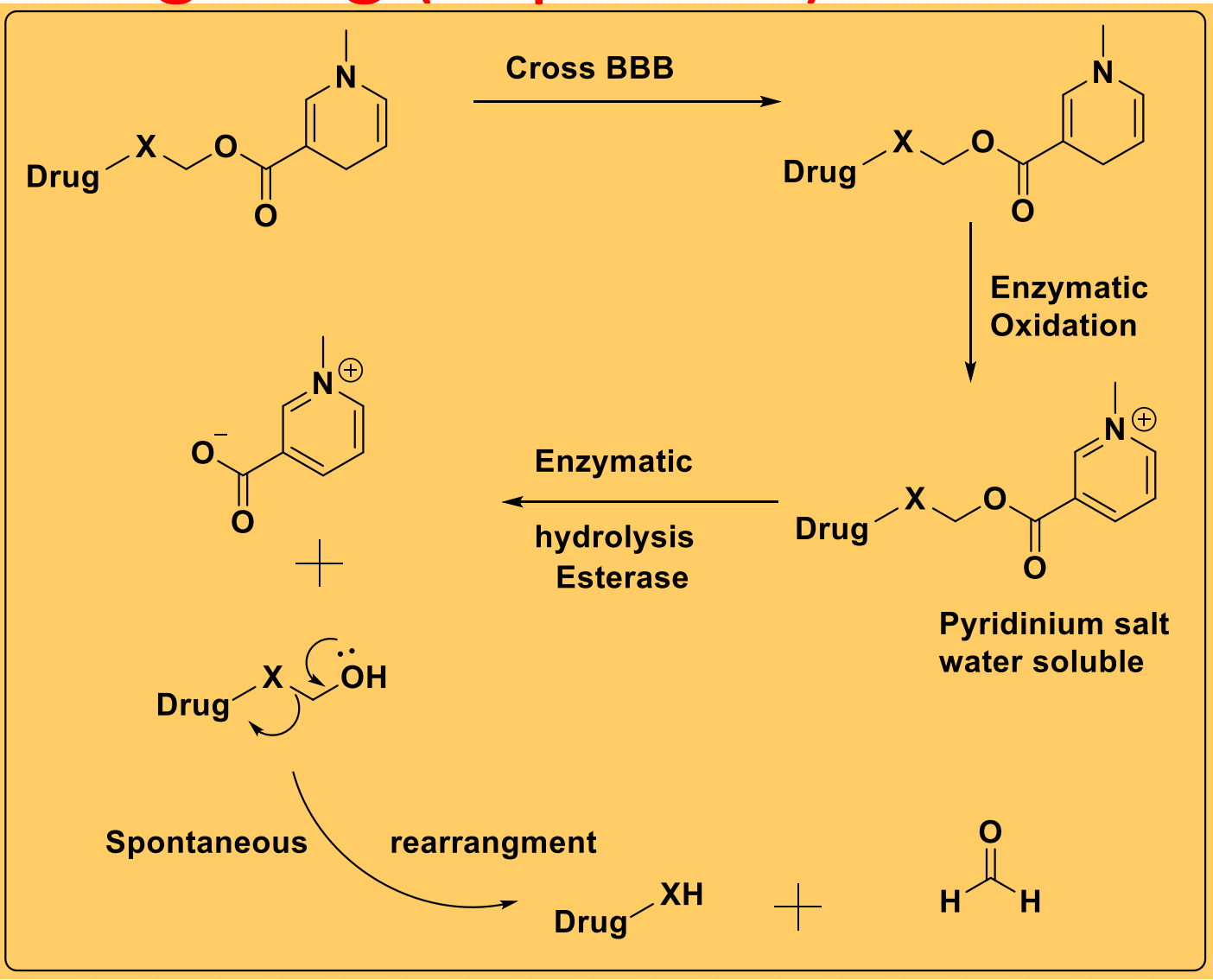


N-methyl nicotinic acid.
Non-toxic and actively transported out from brain.

The lipophilic carrier Dihydropyridine is attached to hydrophilic drug. The nitrogen in the Dihydropyridine is conjugated into carbonyl thereby it is less reactive to nucleophiles, more stable for hydrolysis.

Inside the brain, the carrier is converted into hydrophilic species. So, no conjugation to carbonyl and pyridinium ion now activates the carbonyl group for nucleophilic attack.

Dihydropyridine as a carrier for CNS targeting (Tripartate)



Oxidation of dihydro-pyridine to pyridinium ion prevents the drug from escaping out from the brain because it becomes charged.

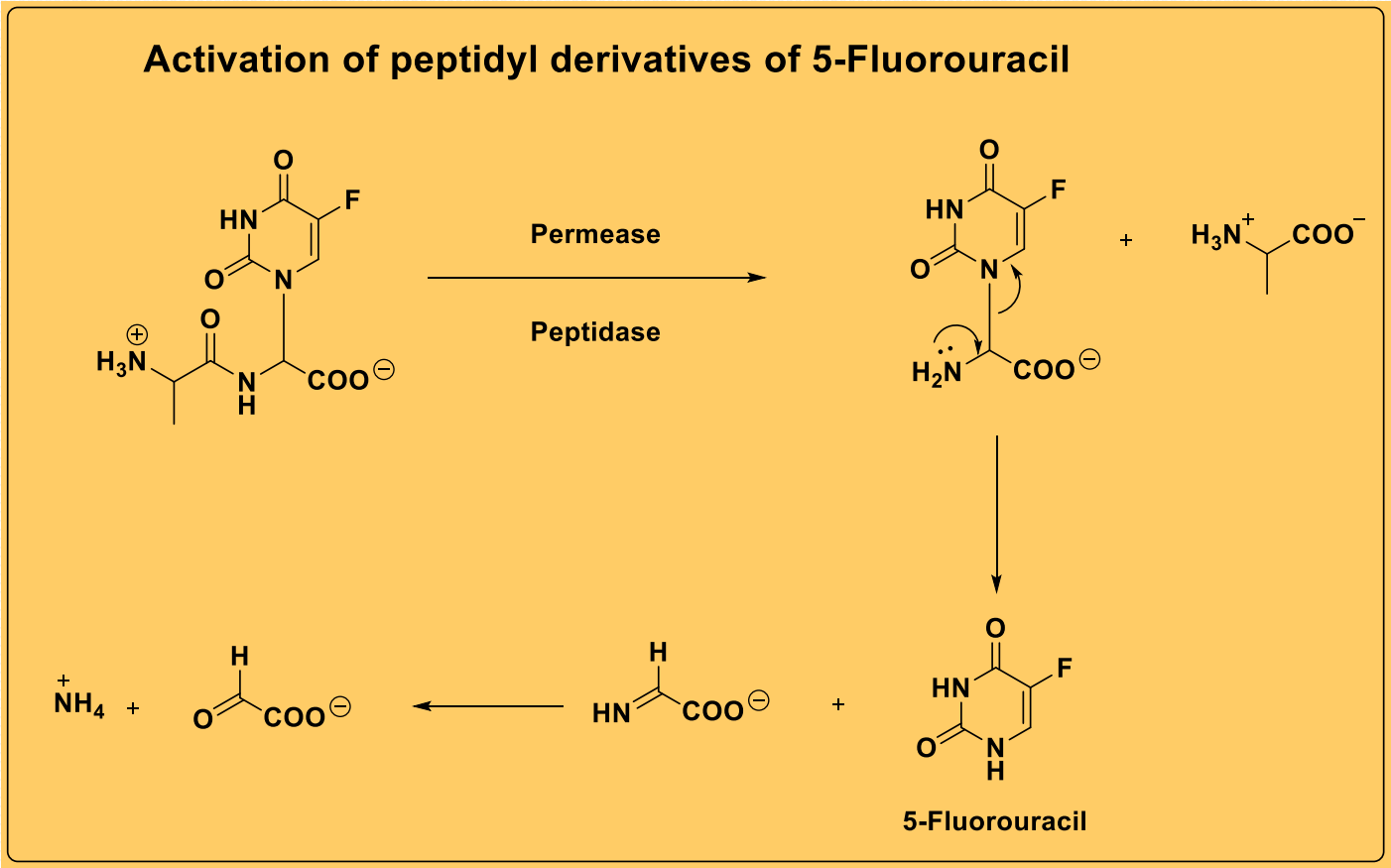
It can have better water solubility.

Then the drug-pyridinium complex will be hydrolyzed to release the active drug and the non toxic *N*-methyl nicotinic acid.

Example-1: β lactam antibiotics for the treatment of bacterial meningitis

- β lactam antibiotics are hydrophilic, can reach brain very slowly.
- They are actively transported out from the brain.
- Also, cerebrospinal fluid (CSF) contains less than 0.1% of the immunocompetent leuckocytes when compared to the blood.
- It has no immunoglobulins. So antibody generation is not significant against the bacterial strains.
- Thus, β lactam antibiotics are not effective in the treatment of brain infections.
- Therefore, β lactam antibiotics are converted into their tripartite prodrugs for the delivery in high concentrations in the brain.

Example-2: 5-fluorouracil for treatment of skin infections



- Due to low lipophilicity, 5-fluorouracil has low bioavailability. So peptidyl derivative of 5-fluorouracil was prepared that showed 5 times better skin penetration and rapid metabolism.
- Microbes have specialized transport system for the uptake of peptides (permeases) and these have side-chain specificity. L, L stereochemistry on peptidyl prodrug was active.

Mutual prodrugs

- Applied when it is necessary for two synergistic drugs to be at the same time at the same site.

- Mutual prodrug is a bipartate or tripartate prodrug in which the carrier is the synergistic drug with the drug to which it is linked.

Examples of **Bipartate mutual prodrugs**:-

- Combination of **amoxicillin** and **potassium clavulanate**
- Combination of **pivampicillin** and **penicillanic acid sulfone**

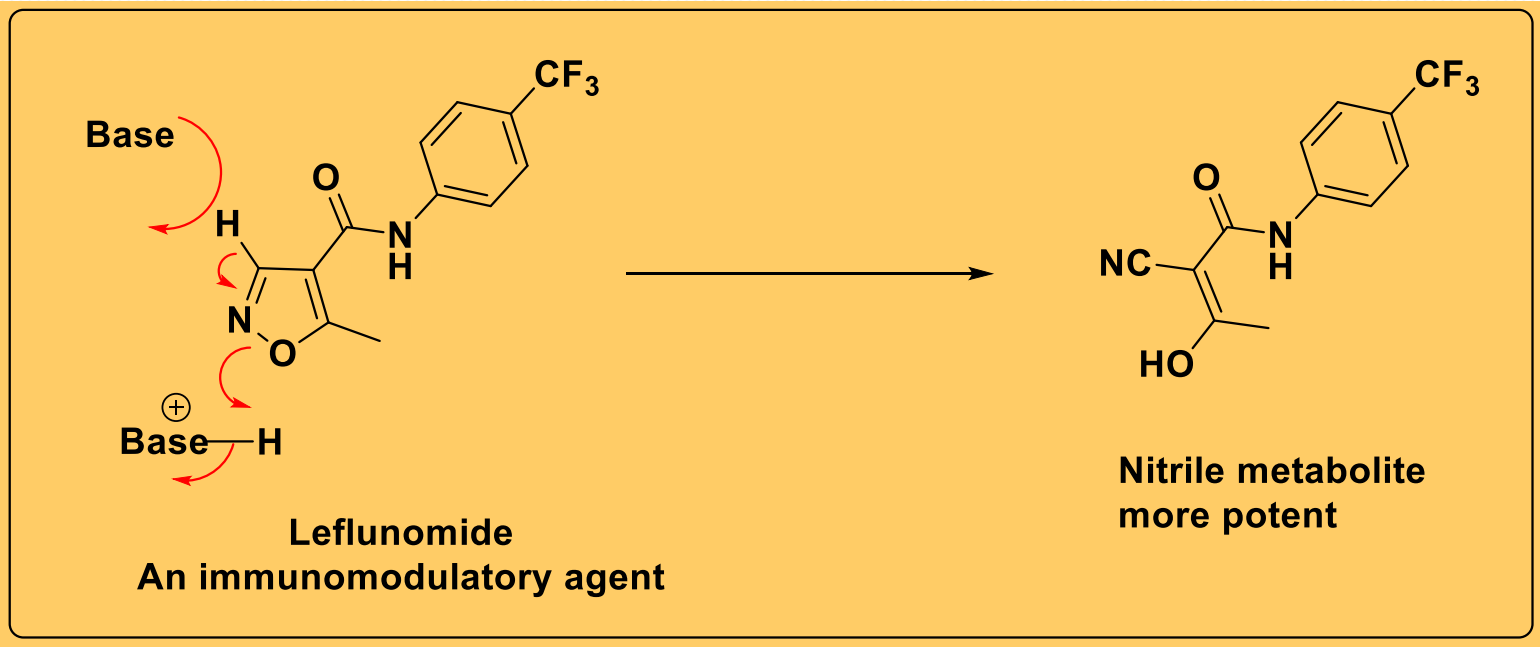
Bioprecursor prodrugs

- **History**: Prontosil (azo prodrug, active *in vivo*) reduced to sulphanilamide (amine sulfa drug).
- Bioprecursor prodrugs mostly use either oxidative or reductive activation reactions.

  But carrier-linked prodrugs depends on hydrolysis reactions.
- **The main activation pathways** are:

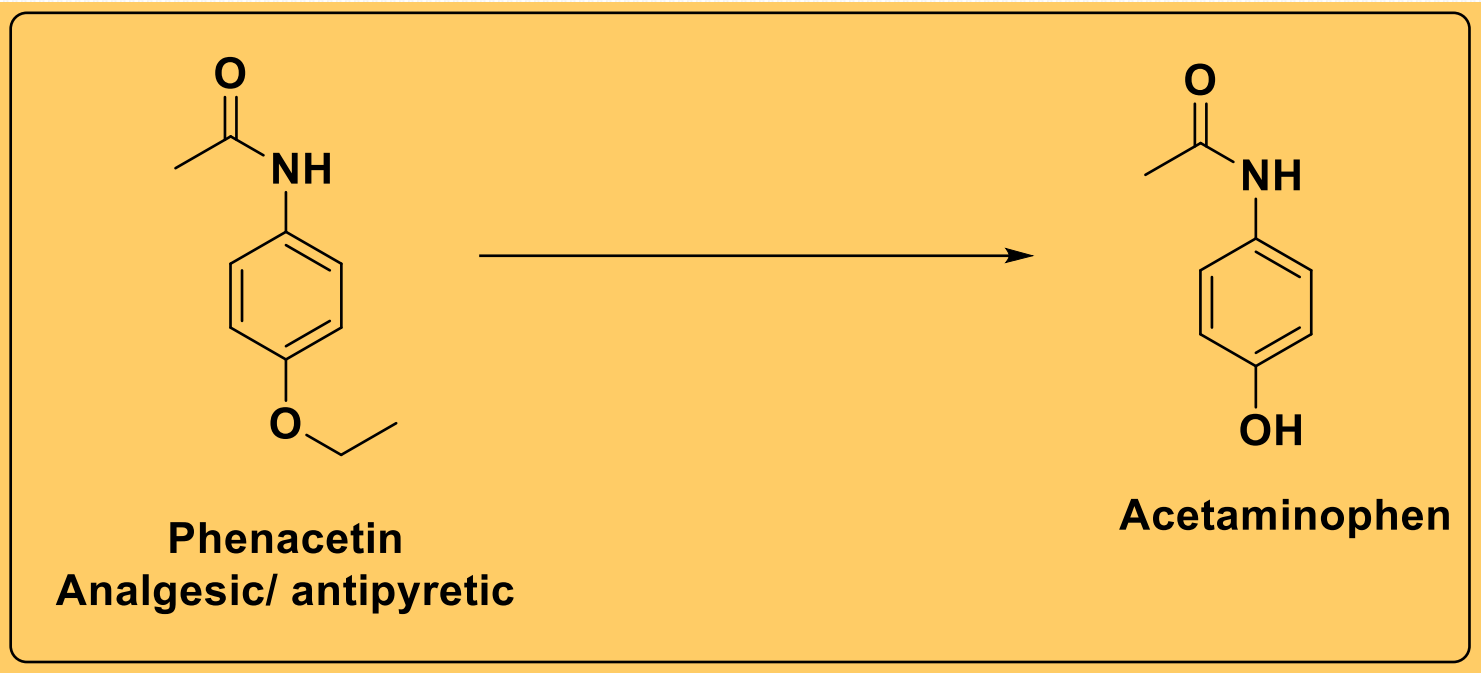
  - Proton activation
  - Hydrolytic activation
  - Elimination activation
  - Oxidative activation
  - Reductive activation
  - Nucleotide activation
  - Phosphorylation activation
  - Sulfation activation
  - Decarboxylation activation

Bioprecursor by *Elimination activation*

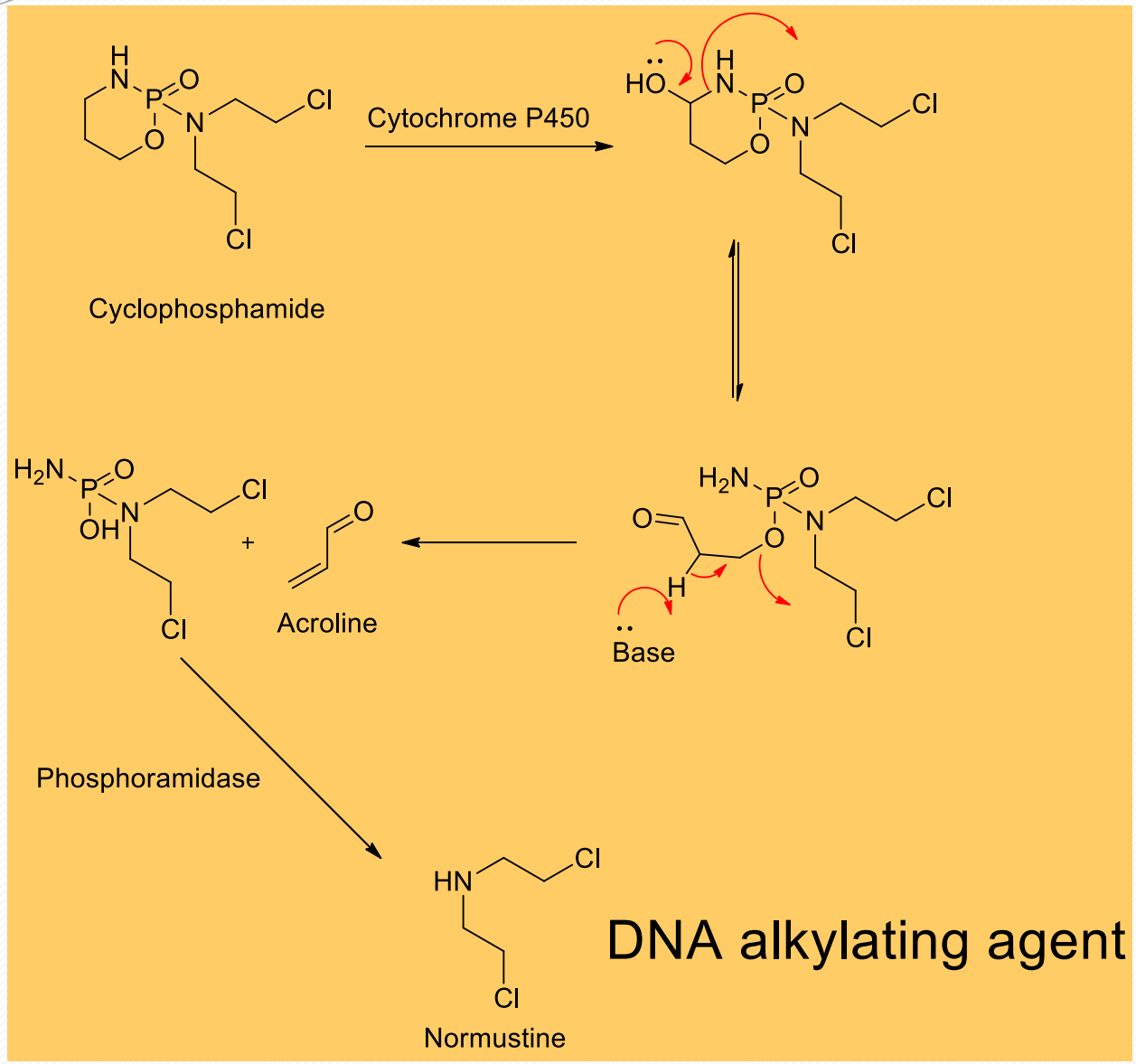


- Leflunomide inhibits the pyrimidine biosynthesis by blocking enzyme **Dihydroorate dehydrogenase**, but less potent.
- Isoxazole ring undergoes elimination to nitrile.
- This **nitrile metabolite** is highly **potent** inhibitor than parent drug Leflunomide.

Bioprecursor by *O-de*alkylation



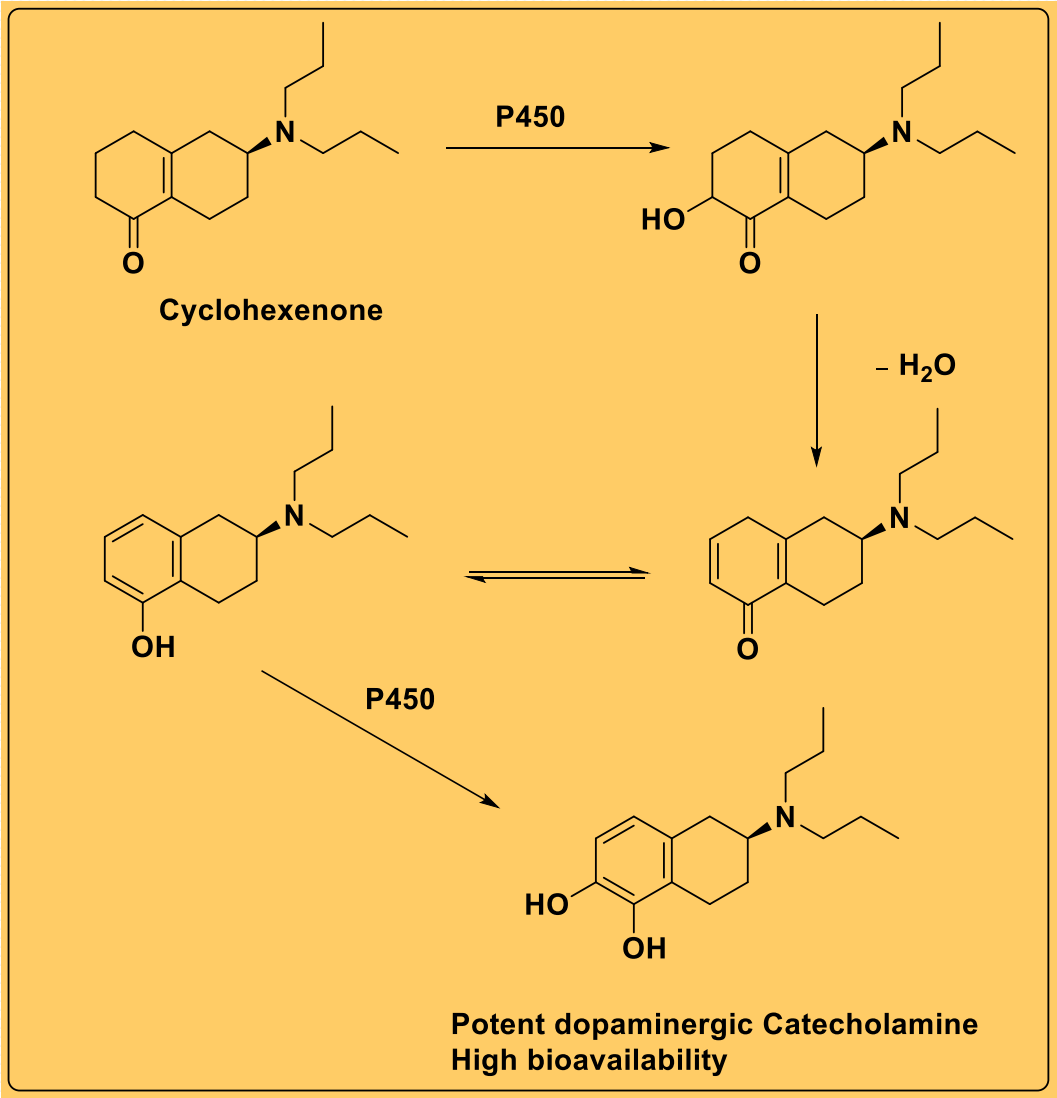
Bioprecursor by *Oxidative deamination*



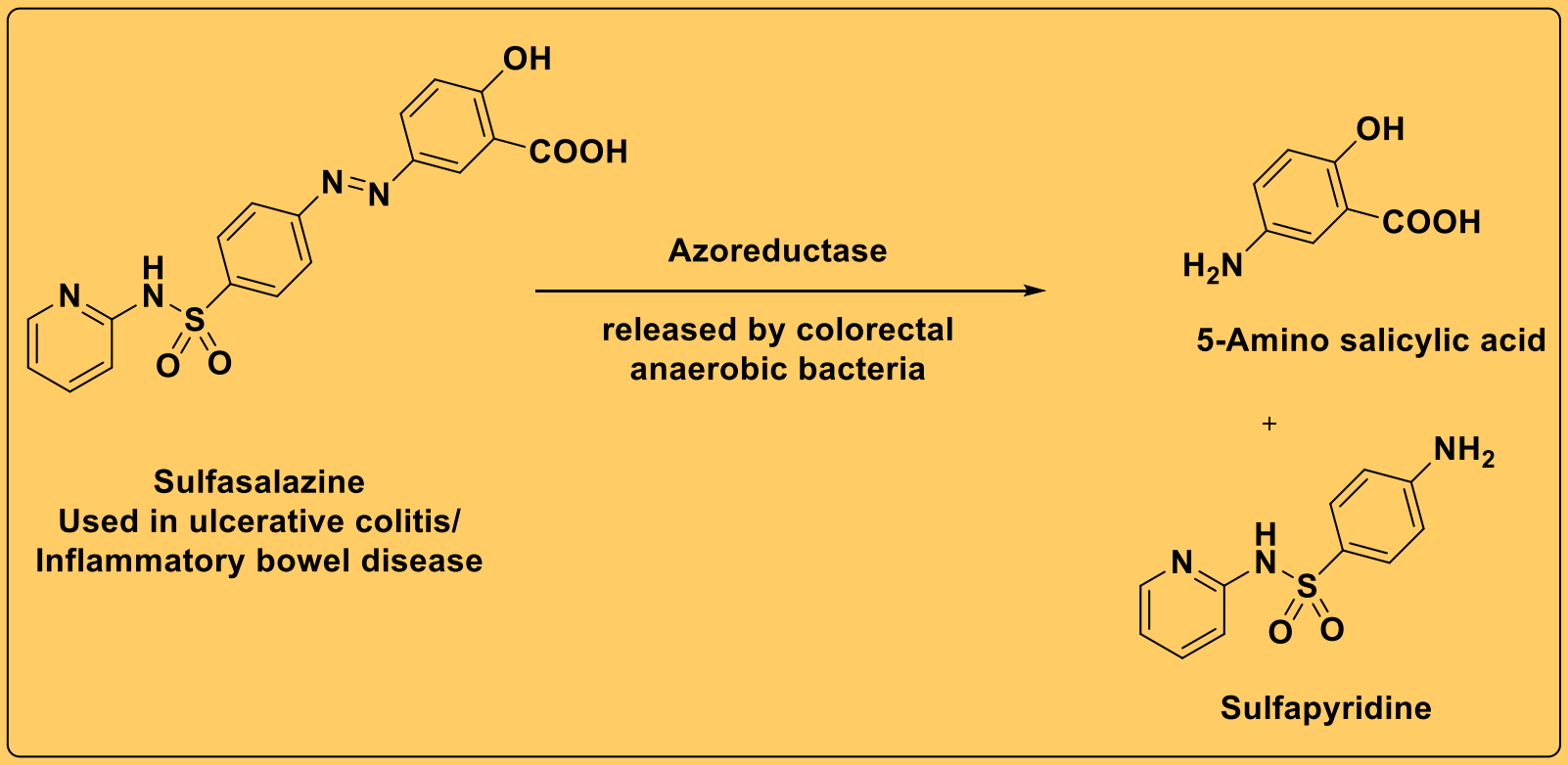
Phosphoramidases are present in cancer cells at higher levels.

Cyclophosphamide is a prodrug that requires activation by Oxidative Deamination mechanism.

Bioprecursor by *Aromatic hydroxylation*

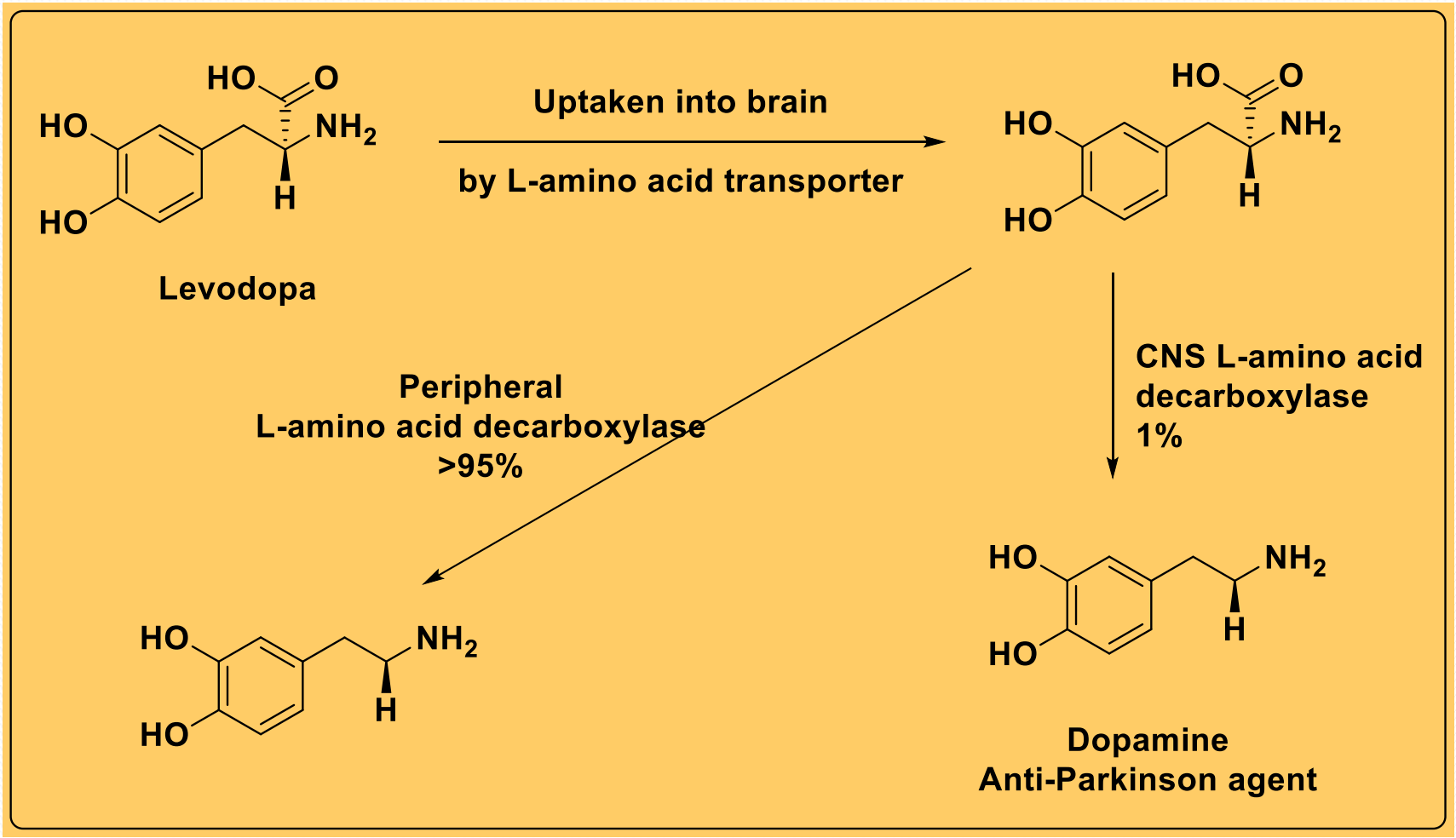


Bioprecursor by *Reduction*



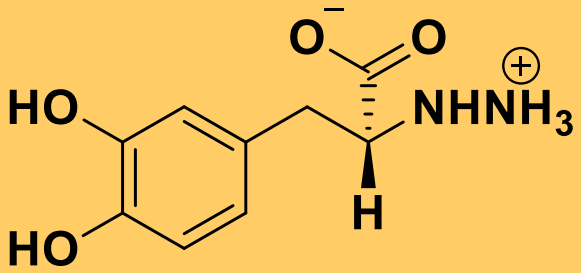
Sulfasalazine
Used in ulcerative colitis/
Inflammatory bowel disease

Bioprecursor by *Decarboxylation*

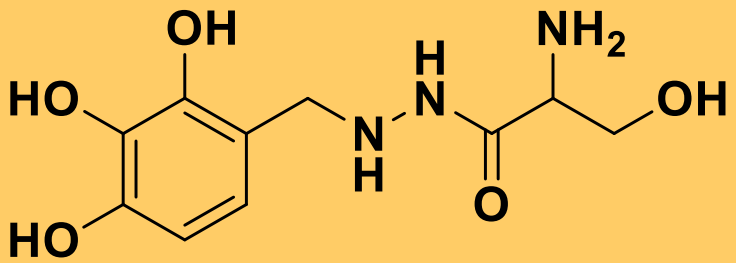


- Parkinson's disease is due to the deficiency of dopamine.
- Exogenous dopamine cannot cross BBB.
- So, Levodopa can be given and transported into the brain where it is decarboxylated by the enzyme dopa decarboxylase (Aromatic L-amino acid decarboxylase).
- This enzyme also present outside the CNS.
- More than 95% of the administered Levodopa undergoes first-pass metabolism by liver.
- Possibly 1% of levodopa only reaching the CNS making less effective.
- In order to prevent this, Peripheral dopa decarboxylase (Aromatic L-amino acid decarboxylase) must be inhibited.
- So, levodopa can reach CNS safely at higher concentration.

- Peripheral dopa decarboxylase (Aromatic L-amino acid decarboxylase) inhibitor such as **Carbidopa** can be combined with levodopa for better treatment.
- Carbidopa is a charged molecule, cannot cross BBB and used in **United States**.
- Another Peripheral dopa decarboxylase (Aromatic L-amino acid decarboxylase) inhibitor **Benserazide** is used in **Europe** and **Canada**.

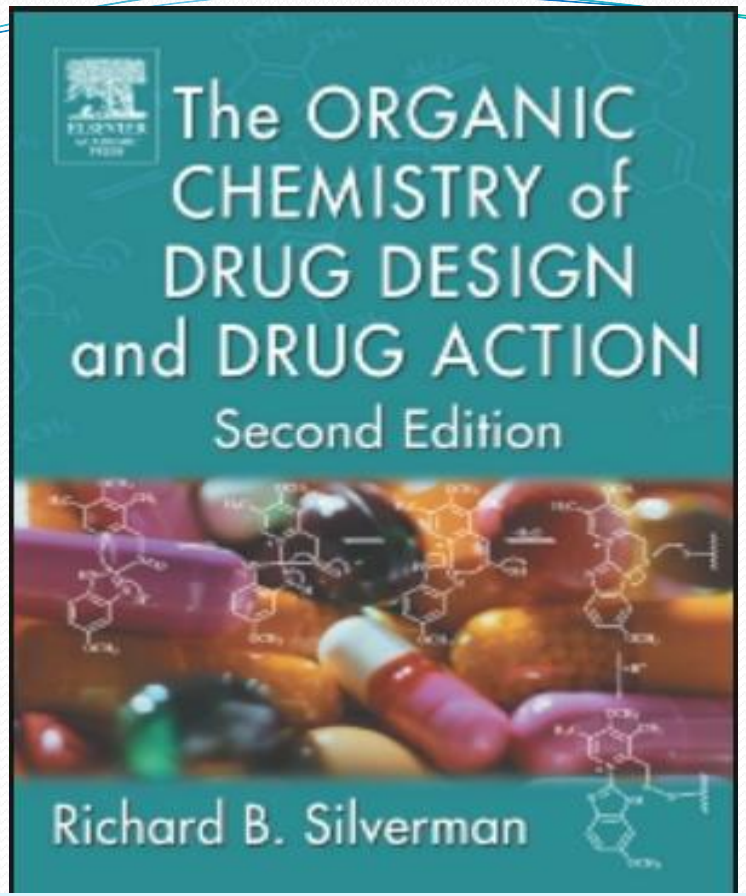


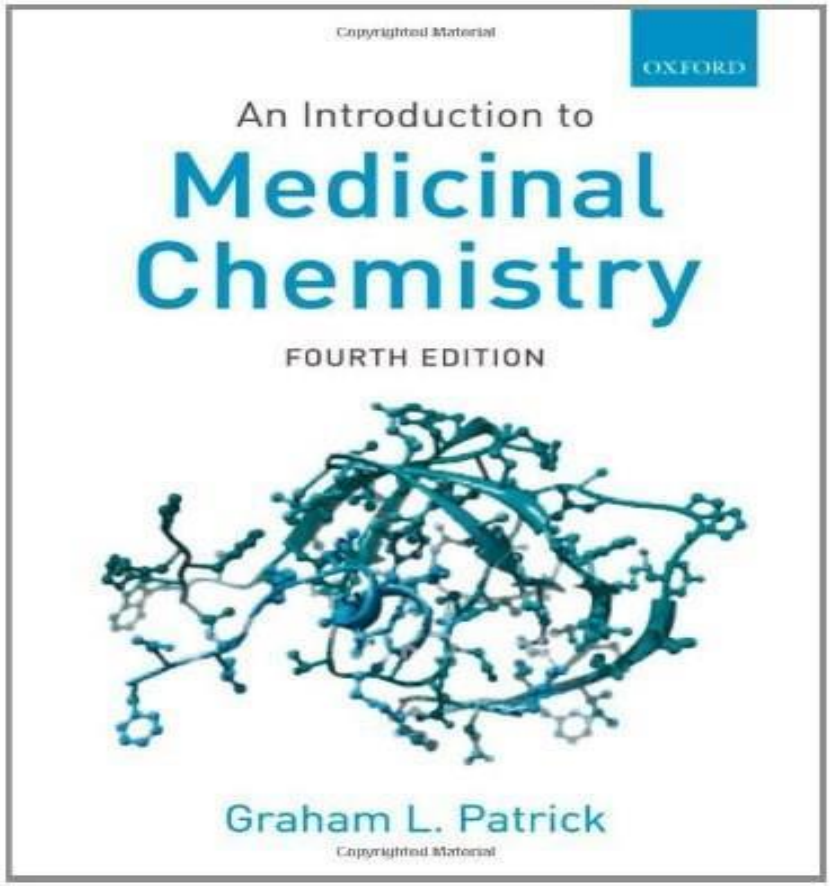
Carbidopa



Benserazide

Recommended Books





1. The organic chemistry of drug design by Richard B. Silverman. Second edition, Elsevier, 2004.

2. An introduction to Medicinal Chemistry by Graham L. Patrick. Fourth edition, Oxford, 2009.


Thank
You