Organic Pharmaceutical Chemistry IV

Lec3: Rational For the Use of Prodrugs

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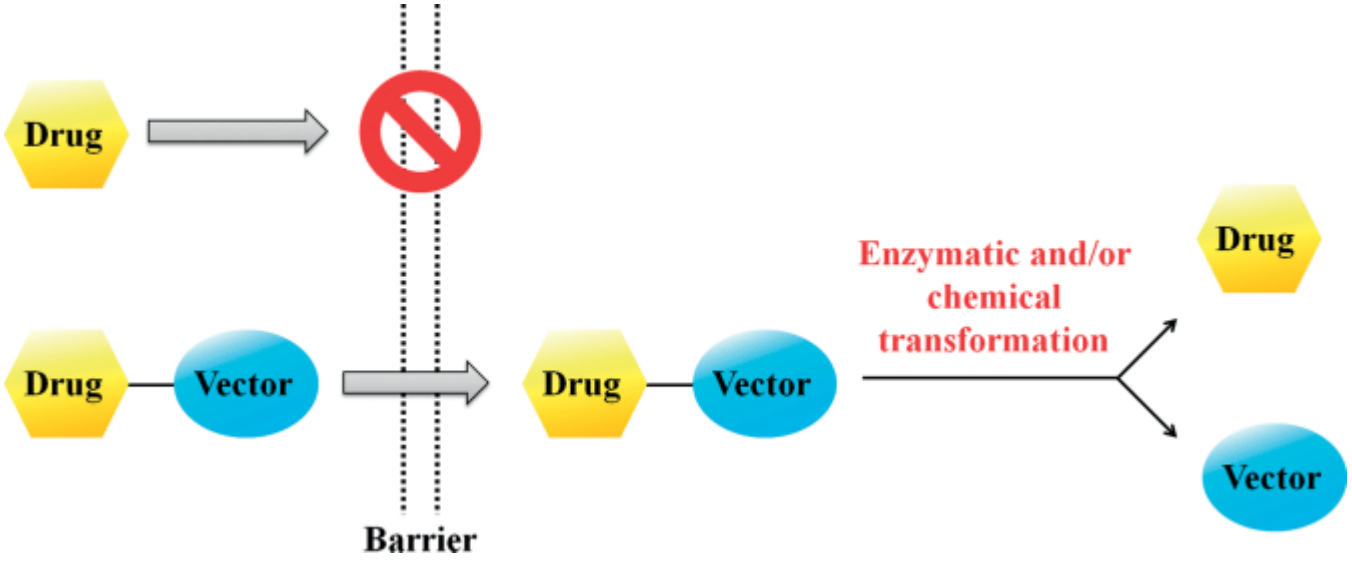
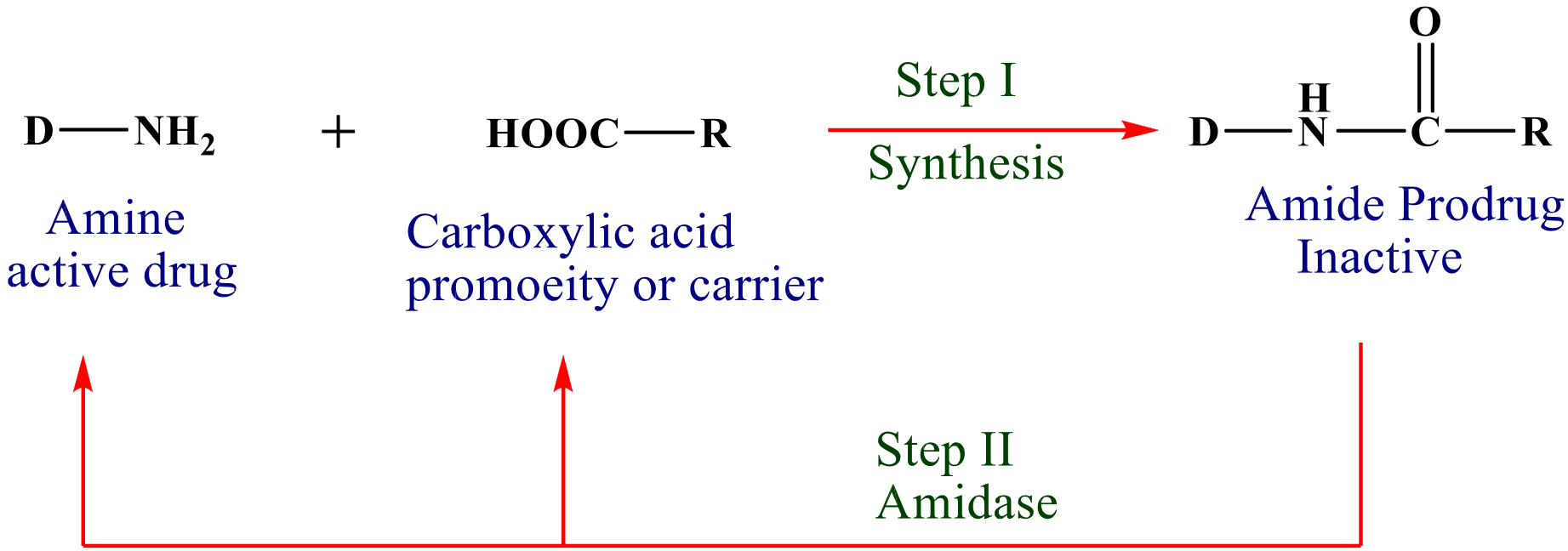


2- Amines



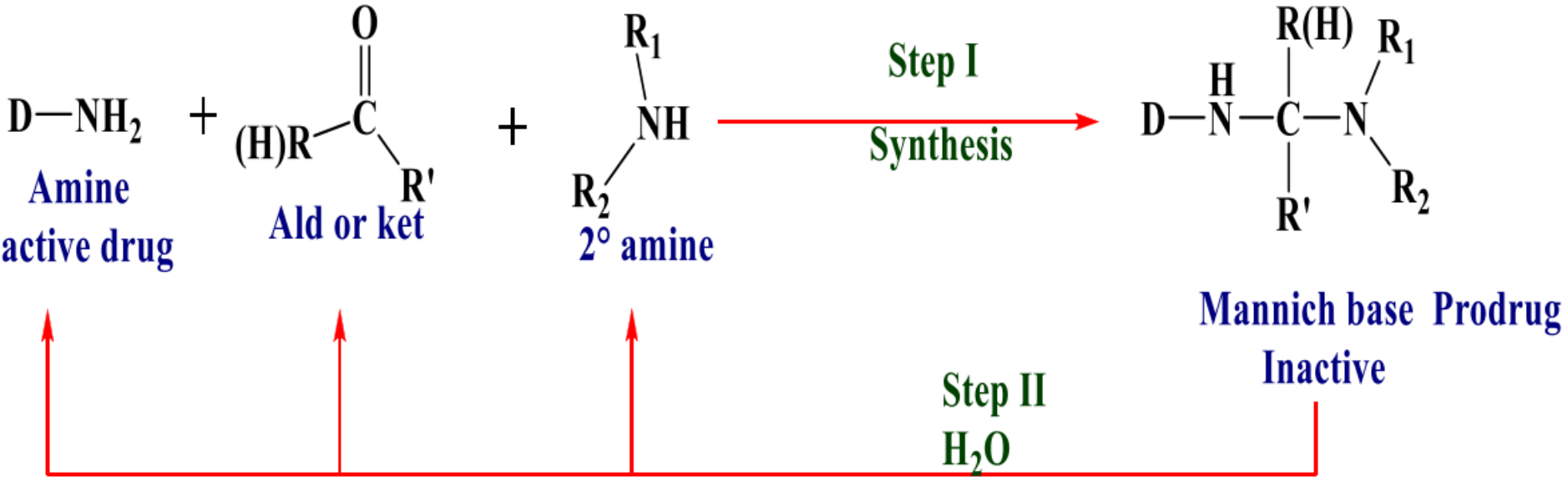
Amides have not been widely used us a prodrug strategy because of:-

a. The high chemical stability of the amide linkage.

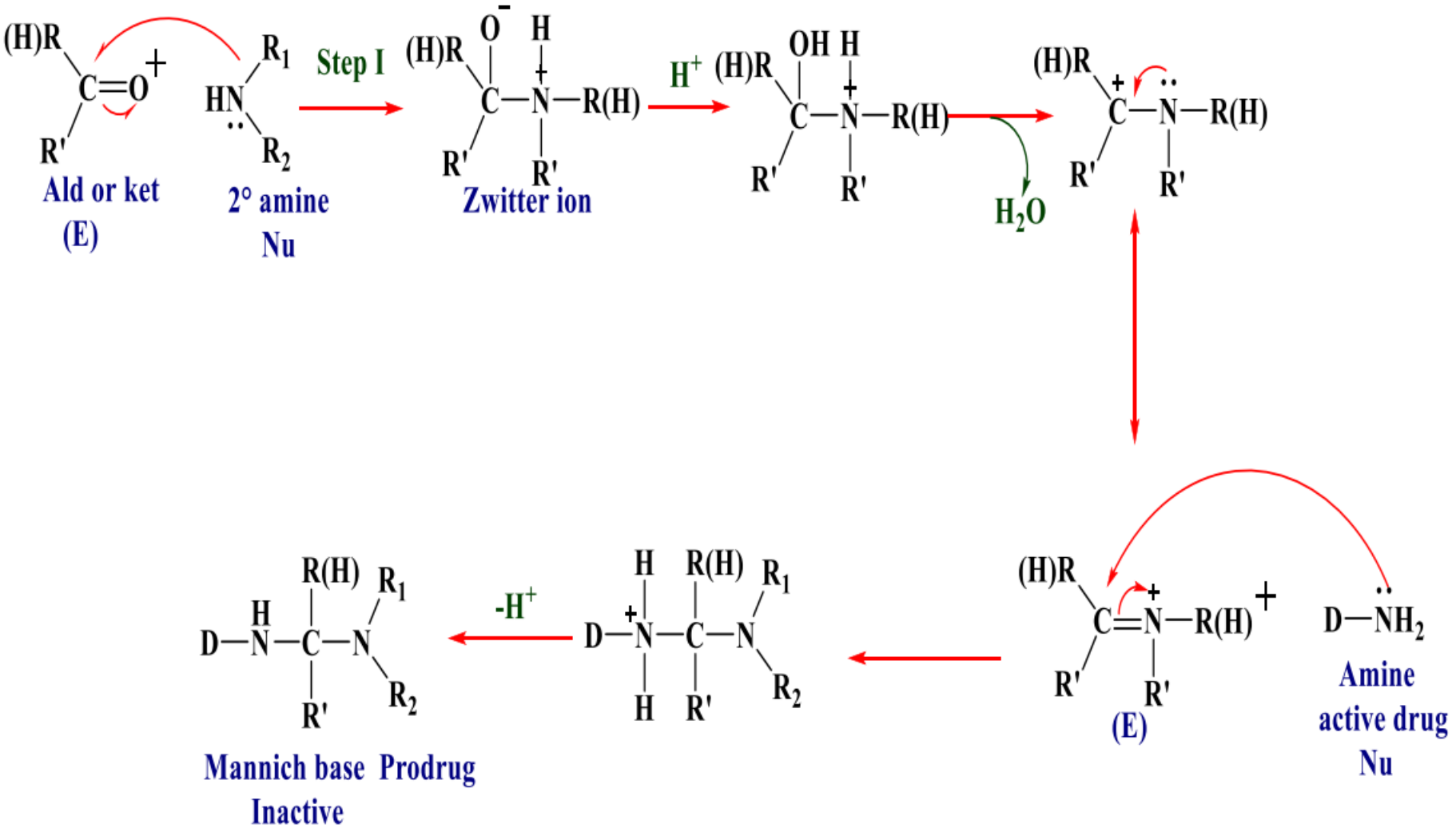
b. The lack of amidase enzymes necessary for hydrolysis.

A more common approach has been to use Mannich bases as a prodrug form of the amines.

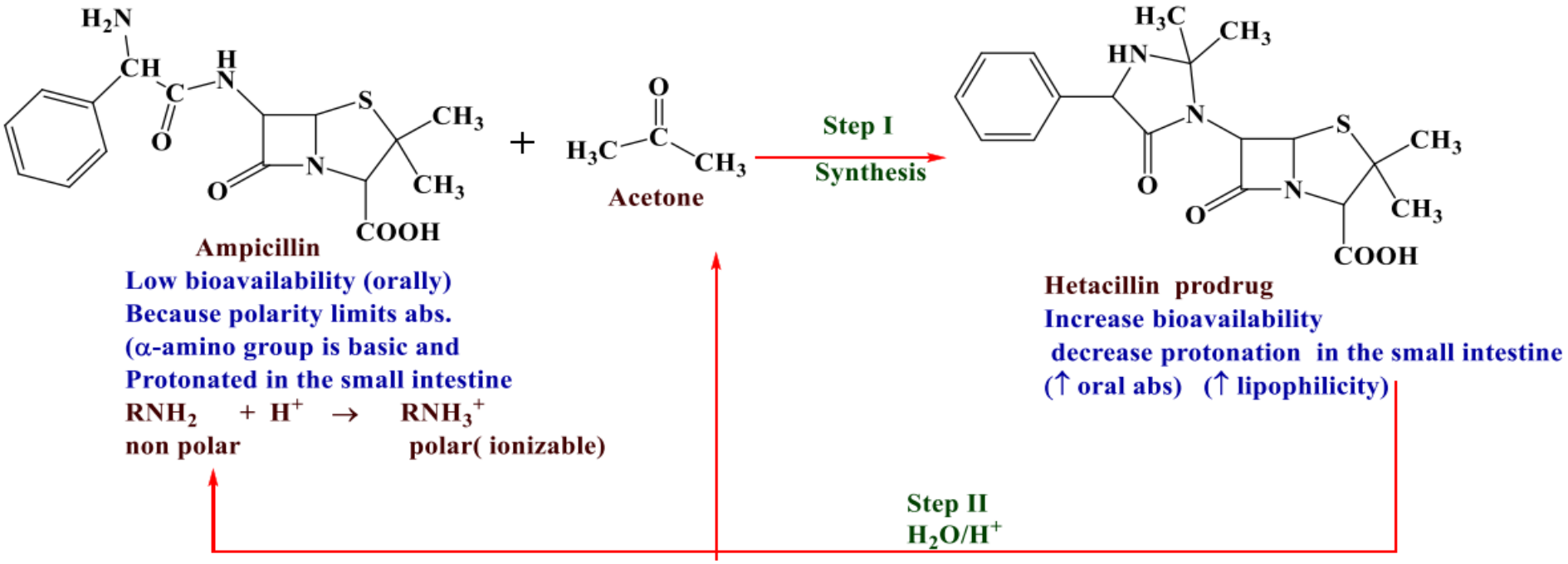
- **Mannich bases result from the reaction of two amines with an aldehyde or ketone.**



Mechanism of reaction



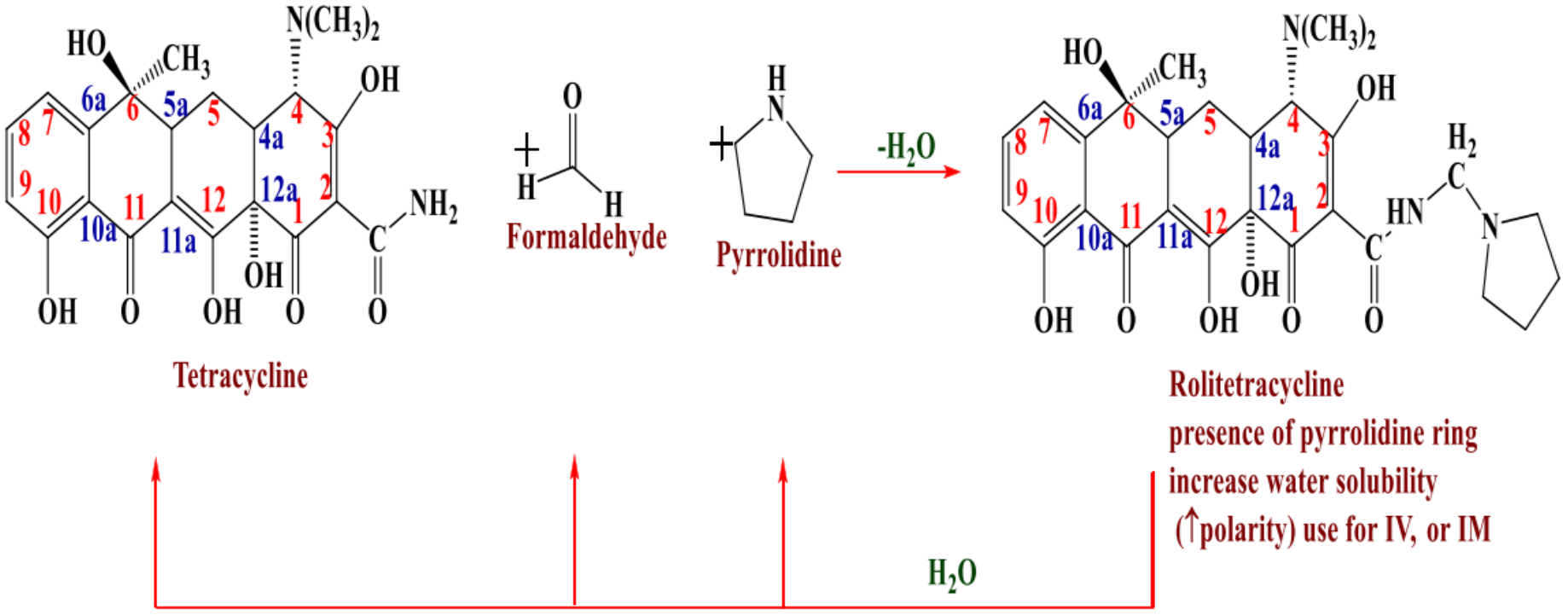
Ampicillin (antibacterial)



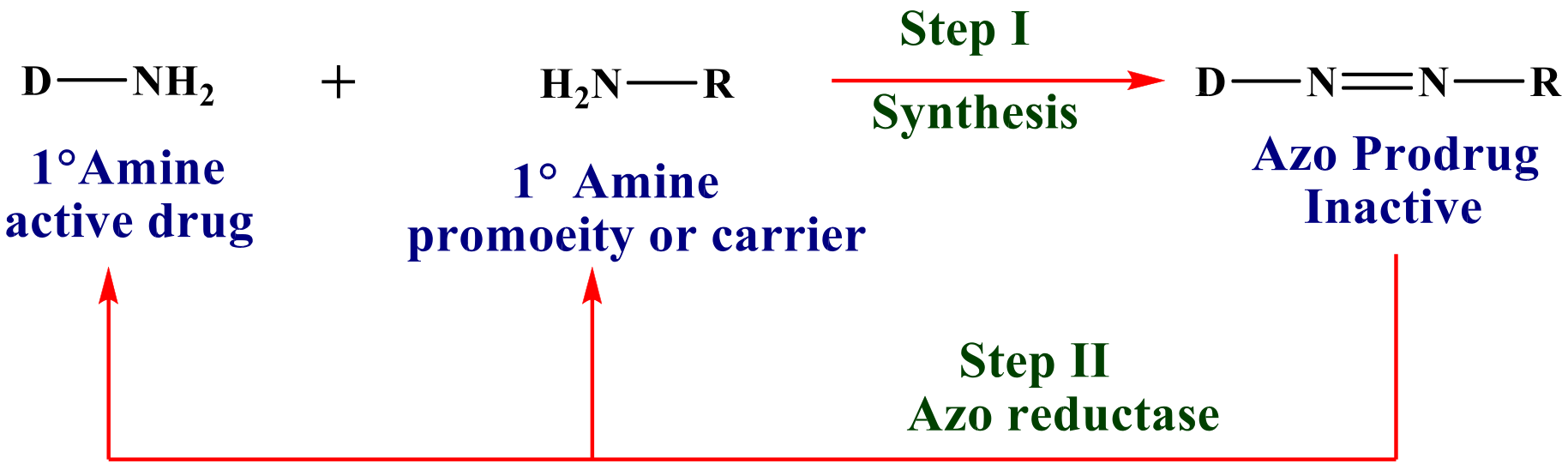
Hetacillin is a prodrug form of ampicillin in which the amide nitrogen and α-amino functionalities have been allowed to react with acetone to give an imidazolidinone ring system. This decreases the basicity of the α-amino group and reduces protonation in the small intestine so that the agent is more lipophilic. In this manner, the absorption of the drug from the small intestine is increased after oral dosing, and chemical hydrolysis after absorption regenerates ampicillin.

Rolitetracycline

This approach was also used with the antibiotic **tetracycline**—the amide nitrogen was allowed to react with formaldehyde and pyrrolidine to give the Mannich base **rolitetracycline**. In this case, addition of the basic pyrrolidine nitrogen introduces an additional ionizable functionality and increases the water solubility of the parent drug. The Mannich base hydrolyzes completely and rapidly in aqueous media to give the active tetracycline.



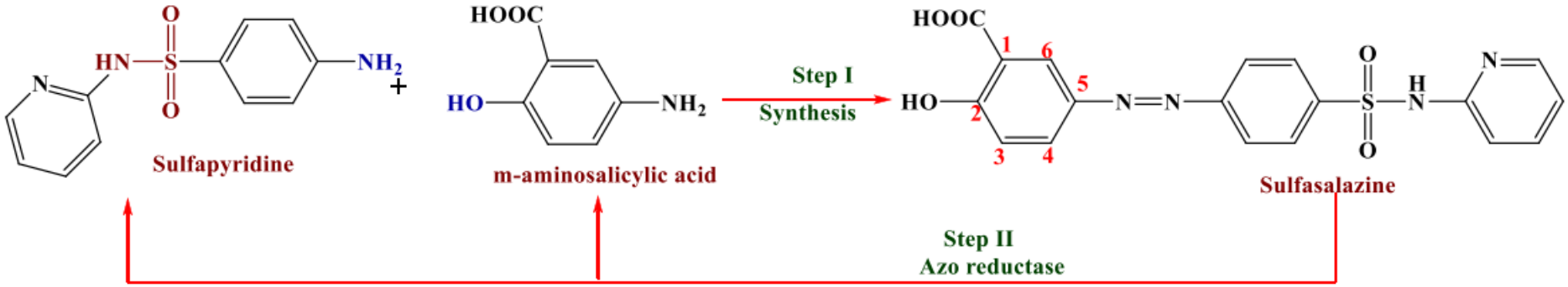
Azo prodrug•



This azo linkage is very useful to transport certain drug for colon, since azo linkage hydrolyse by azo reductase which is bacterial enzyme from the microflora located in large intestine (colon).

Example

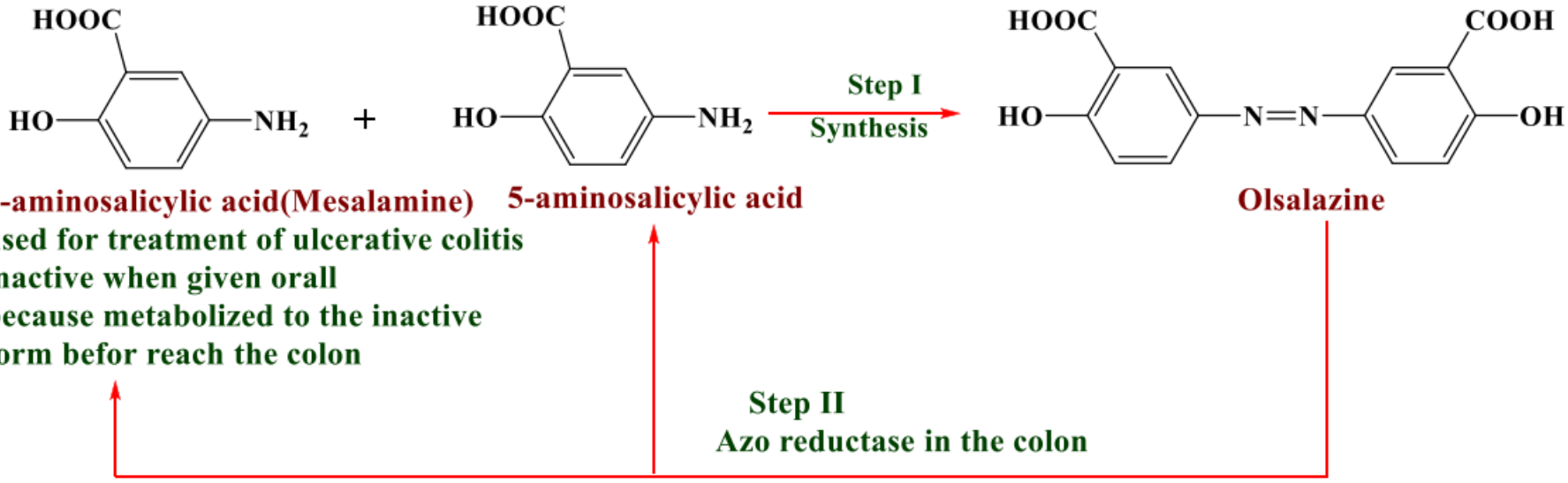
•Sulfasalazine



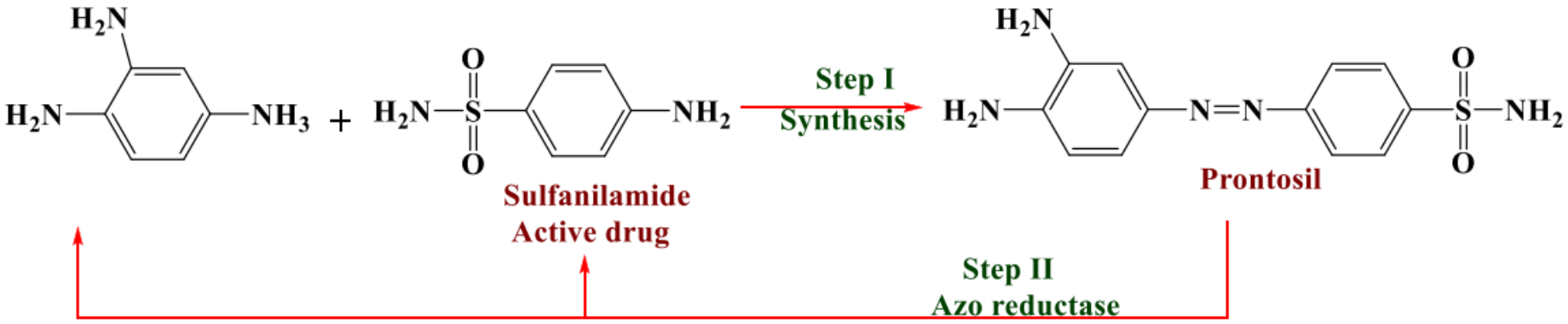
Advantage of sulfasalazine prodrug

- **Taken orally (no systemic absorption).**
- **Targeting (help to concentrate the active agent at site of action).**
- **Synergistic effect.**

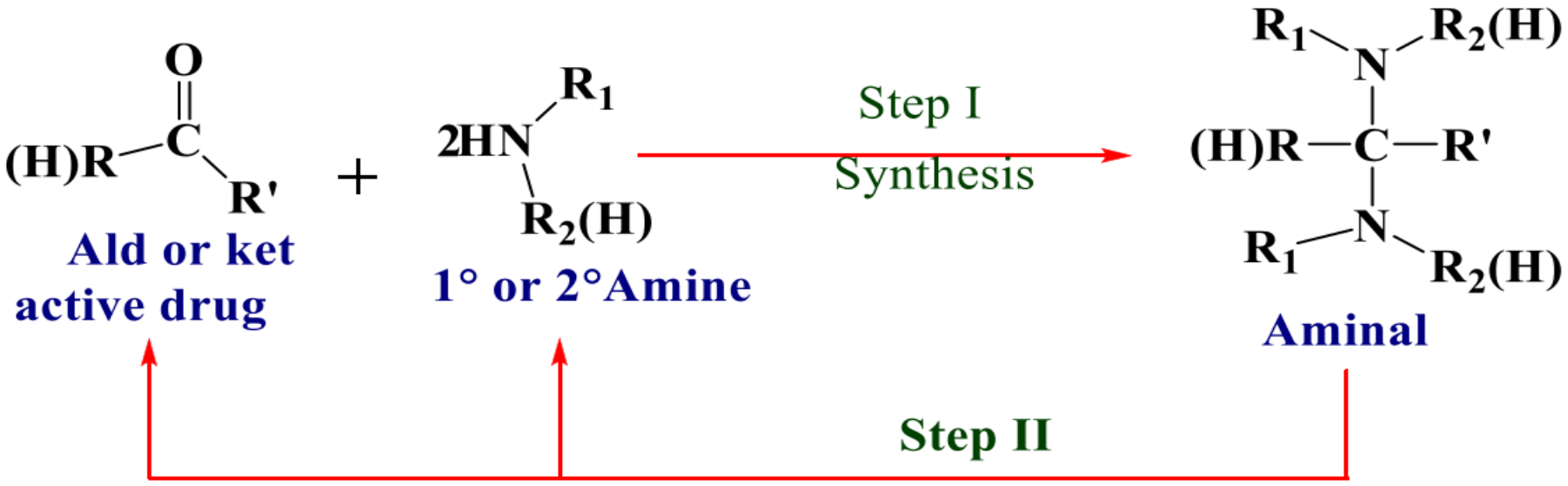
Olsalazine prodrug•



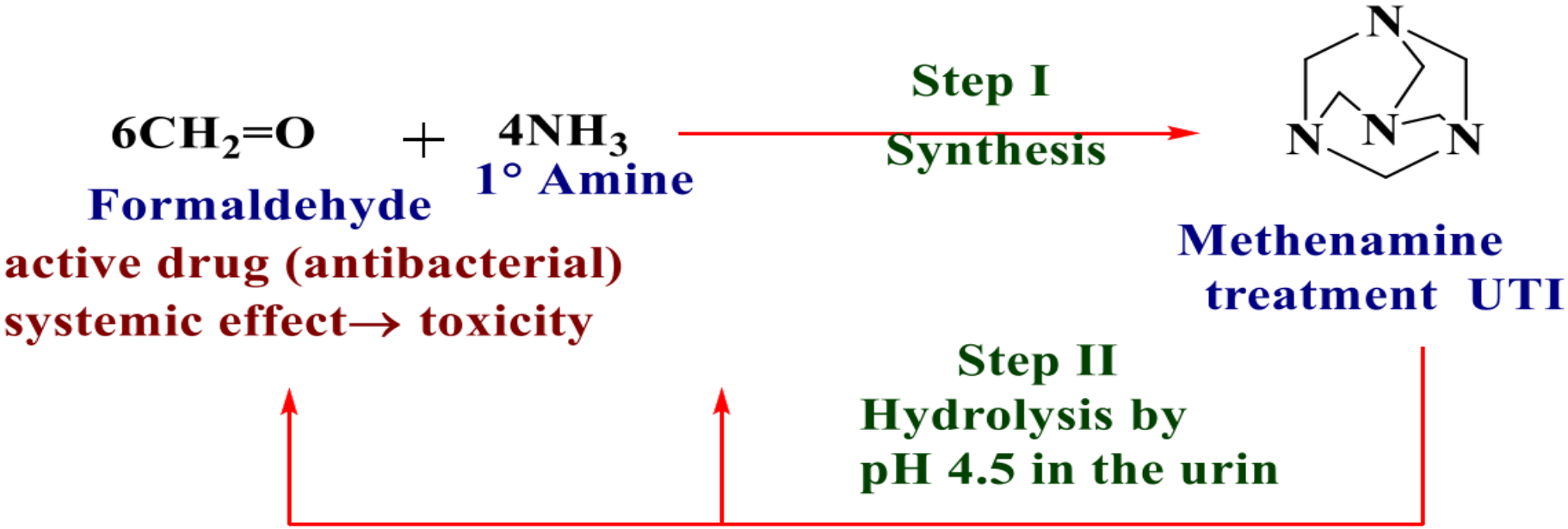
Prontosil (treatment of systemic infection)•



4- Carbonyl compounds•



Methenamine



Methenamine is only hydrolyse in acidic media which is found in acidic urine leading to liberation of formaldehyde and $4NH_{3,}$ where the formaldehyde act as antibacterial agent by reacting with nucleophiles present in bacteria. The agent is administered in enteric-coated capsules to protect it from premature hydrolysis in the acidic environment of the stomach. After dissolution of the enteric-coated capsules in the intestine, the agent is absorbed and moves into the bloodstream, eventually ending up in the urine, where the acidic pH catalyzes the chemical hydrolysis to give formaldehyde. Use of this prodrug approach prevents the systemic release of formaldehyde and reduces toxicity.

Rational For the Use of Prodrugs

- ❑ Fact: A drug can only exert a desired pharmacological effect if it reaches its site of action.
- ✓ The three major phases involved in the drug receptor interaction or biological bioavailability of drug includes:

1. *The pharmaceutical phase,*
2. *The pharmacokinetic phase, and*
3. *Pharmacodynamic phase.*

1. Use of Prodrugs to Overcome Pharmaceutical Barriers:

- The utility of prodrugs to overcome the various aesthetic and drug formulation problems are discussed in the following sections:

A. *Masking taste or odour.*
B. *Minimizing pain at site of injection.*
C. *Alteration of drug solubility.*
D. *Enhancement of chemical stability.*

Masking Taste or Odour:

- The undesirable taste arises due to adequate solubility and interaction of drug with taste receptors, which can be solved by lowering the solubility of drug or prodrug in saliva.
- Chloramphenicol, an extremely bitter drug has been derivatized to chloramphenicol-palmitate, a sparingly soluble ester.

Masking Taste or Odour:

- Chloramphenicol-palmitate possesses low aqueous solubility which makes it tasteless and later undergoes *in vivo* hydrolysis to active chloramphenicol by the action of pancreatic lipase.

Masking Taste or Odour:

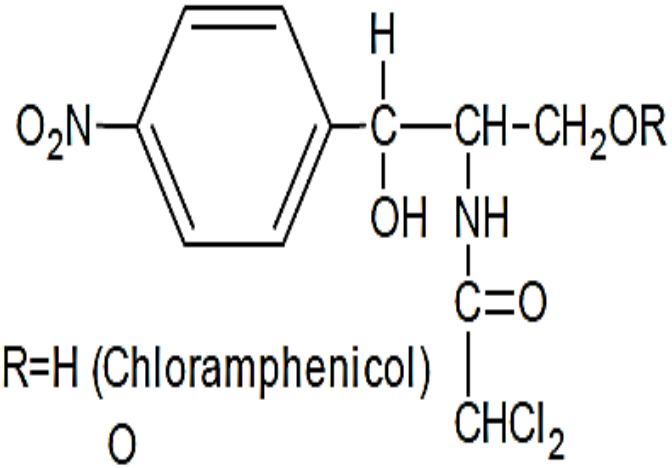
- Odour is another aesthetic concern for some drugs, that are often volatile liquid or solids with significant vapour pressure that makes them difficult to formulate.
- A classic example is the volatile mercaptans used as tuberculostatic agents for the treatment of leprosy.

Masking Taste or Odour:

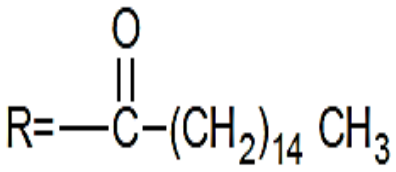
- The ethyl mercaptan has a boiling point of 25^{O}C and a strong disagreeable odour.
- On the other hand, diethyl dithio isophthalate, a prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless.

Masking Taste or Odour

(a) Chloramphenicol prodrug



R=H (Chloramphenicol)

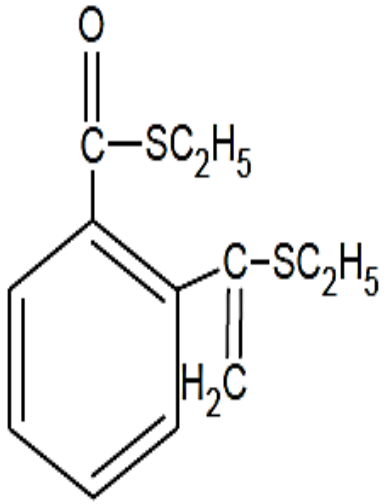


(Chloramphenicol palmitate)

(b) Mercaptane prodrug

CH_3CH_2SH

Volatile with thiol odour



Relatively non toxic with decreased thiol odour

Minimizing Pain at Site of Injection

- Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs.
- For example, intramuscular injection, of antibiotic like clindamycin and anticonvulsant drug like phenytoin, was found painful due to poor aqueous solubility.
- ***How to solve such problems?***

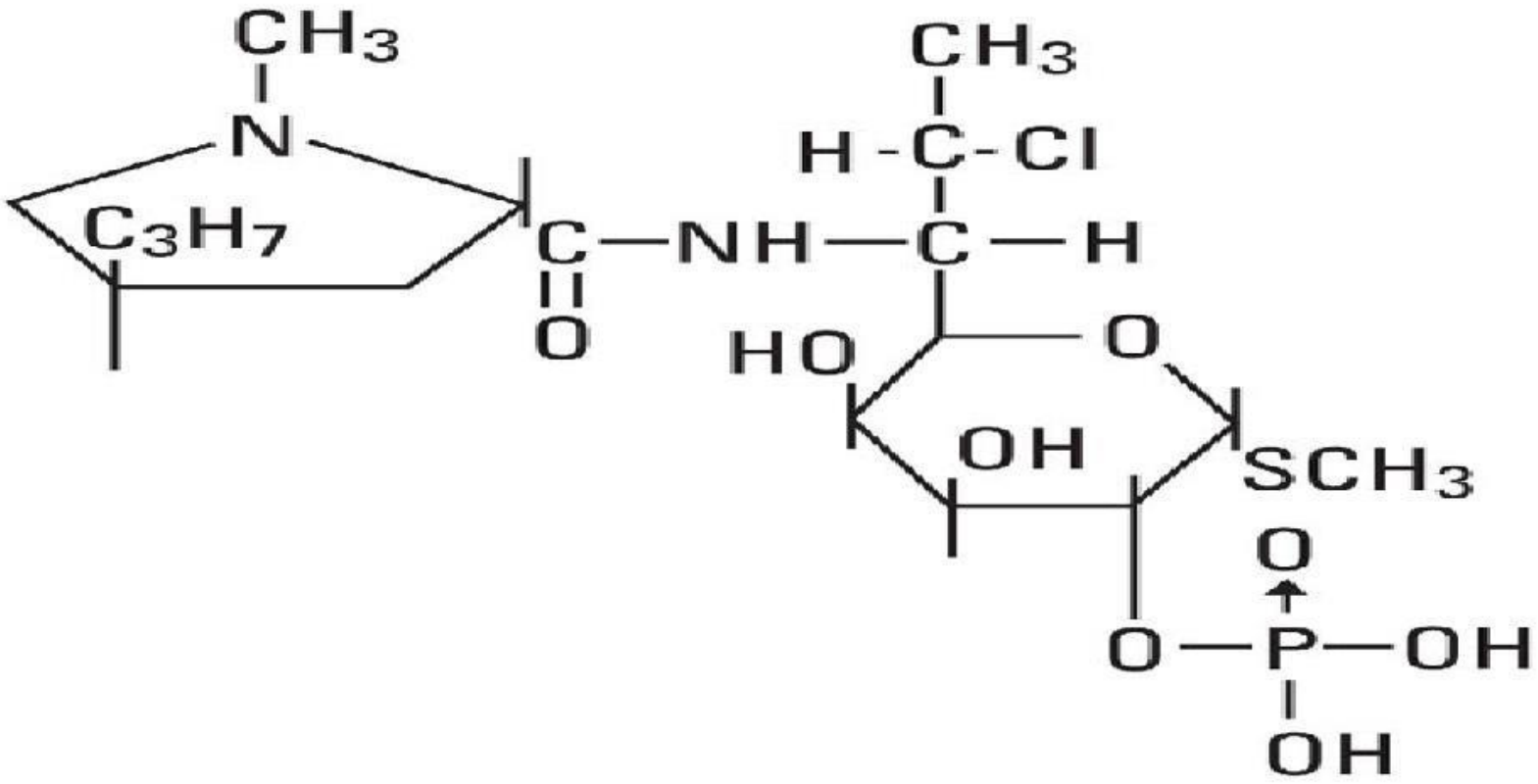
Minimizing Pain at Site of Injection

- **Solution:**

- To overcome this issue for both drugs, preparing phosphate ester prodrugs and maintaining the formulations at pH 12 were performed.

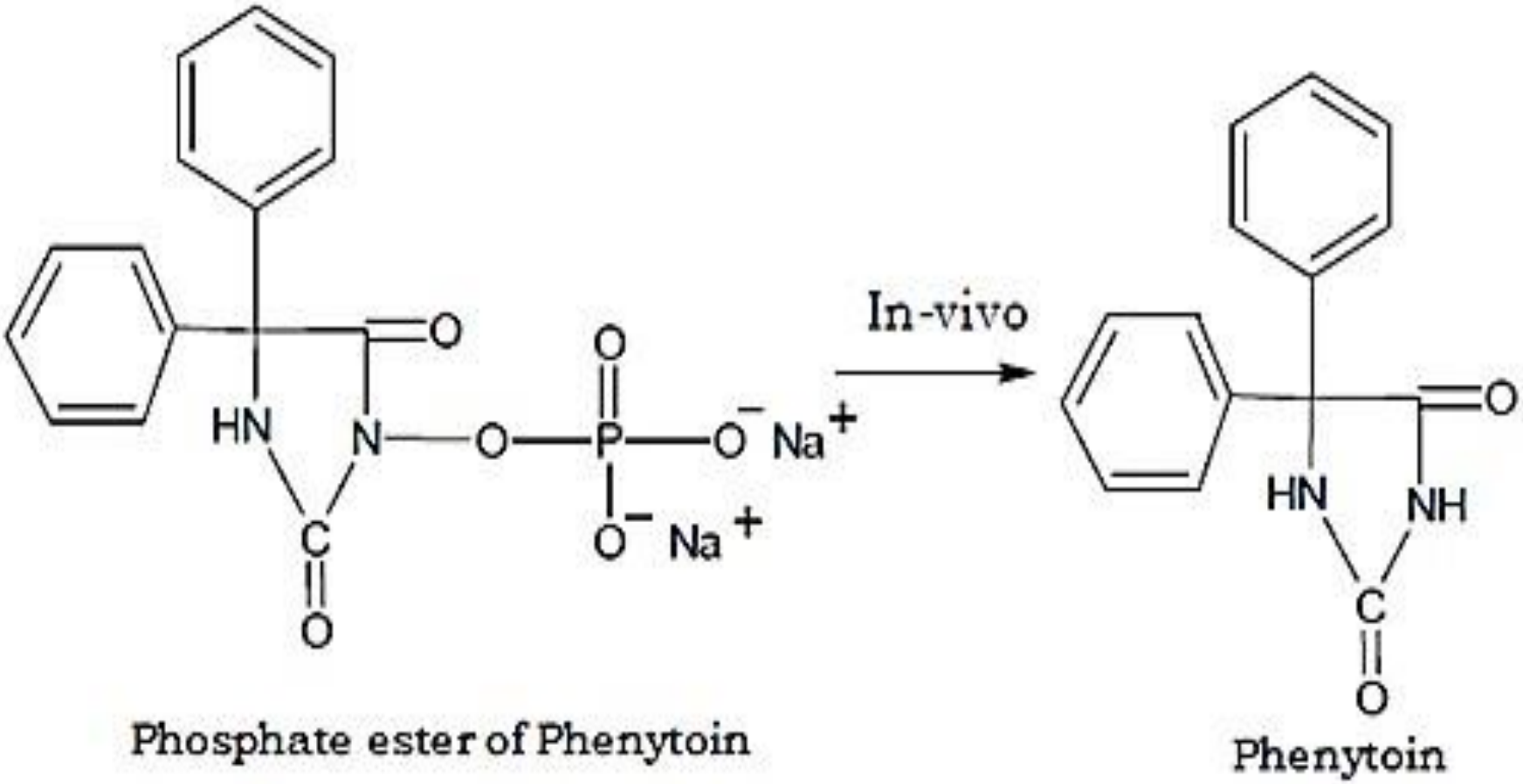
Minimizing Pain at Site of Injection

(a) Clindamycin–2 dihydrogen phosphate- prodrug of clindamycin



Minimizing Pain at Site of Injection

(b) Phenytoin and its prodrug

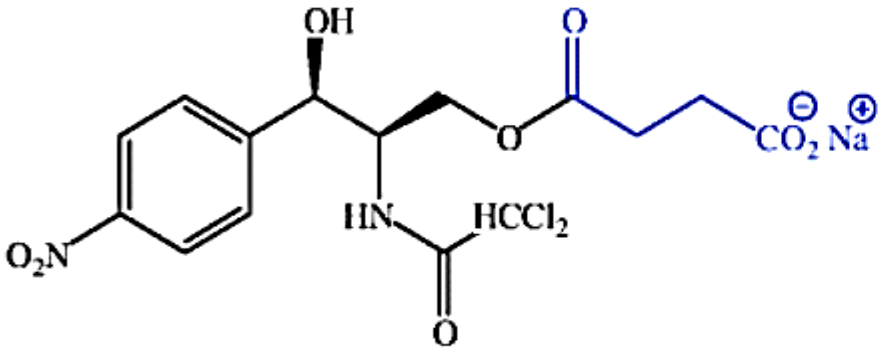


Alteration of Drug Solubility

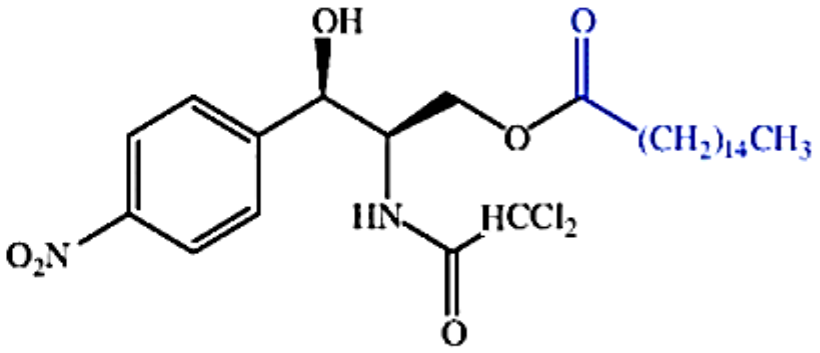
- The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use.
- For example, chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively.

Alteration of Drug Solubility

- On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration.



Chloramphenicol succinate

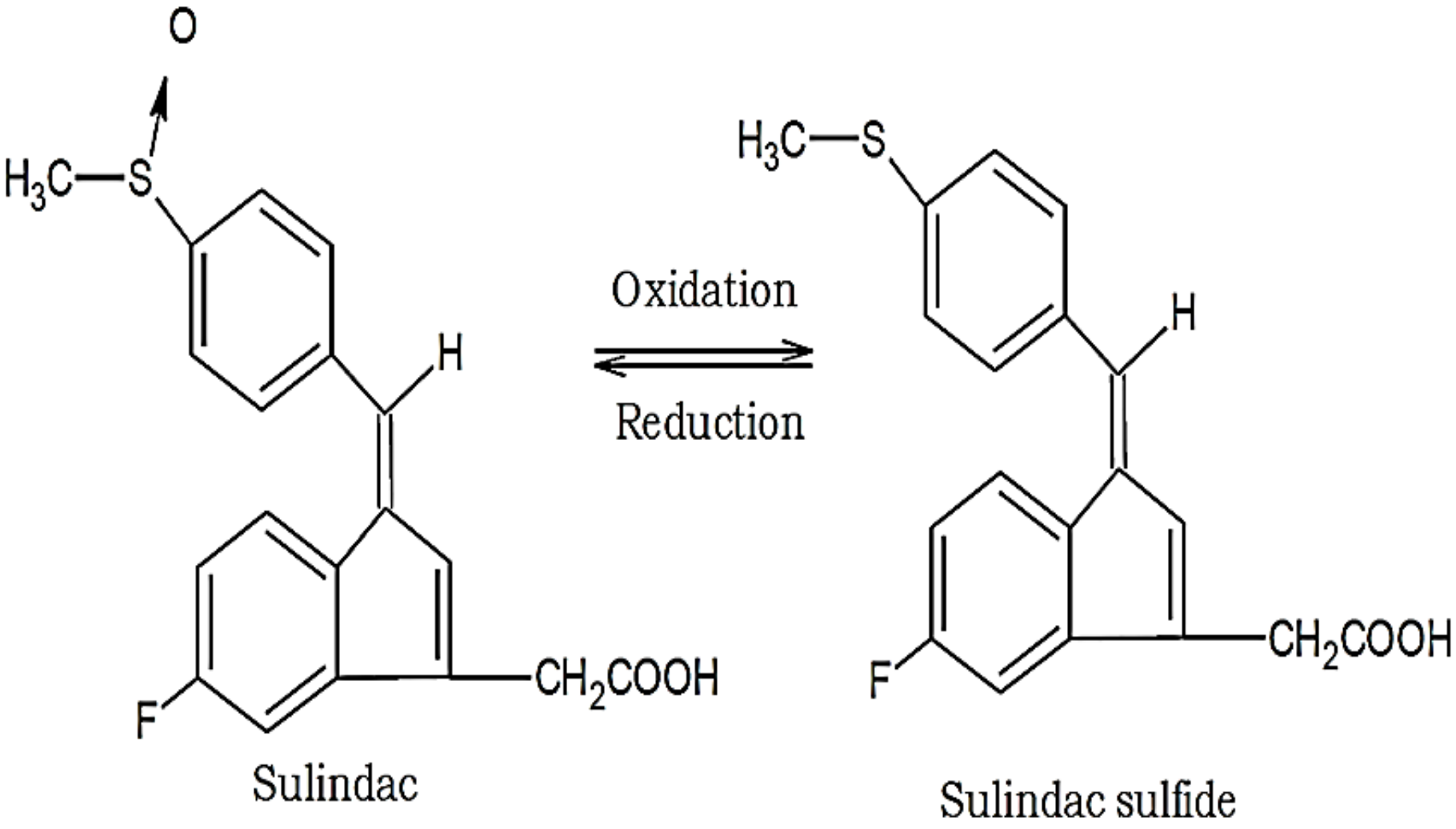


Chloramphenicol palmitate

Alteration of Drug Solubility

- The prodrug approach is also made useful for better gastrointestinal absorption.
- It was observed that sulindac, a prodrug of sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration.

Alteration of Drug Solubility



Sulindac

Sulindac sulfide

Enhancement of Chemical Stability

- Chemical stability is an utmost necessary parameter for every therapeutic agent to elicit its pharmacological activity for a longer duration.
- A shelf life of at least 2 years is desirable except for vaccines, cytotoxic agents and other lifesaving drugs.

Enhancement of Chemical Stability

- Although chemical instability can be solved to a greater extent by appropriate formulations, its failure necessitates the use of prodrug approach.
- ***Explain?***

Enhancement of Chemical Stability

- The prodrug approach is based on:

1. The modification of the functional group responsible for the instability.
2. The changing of the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable.

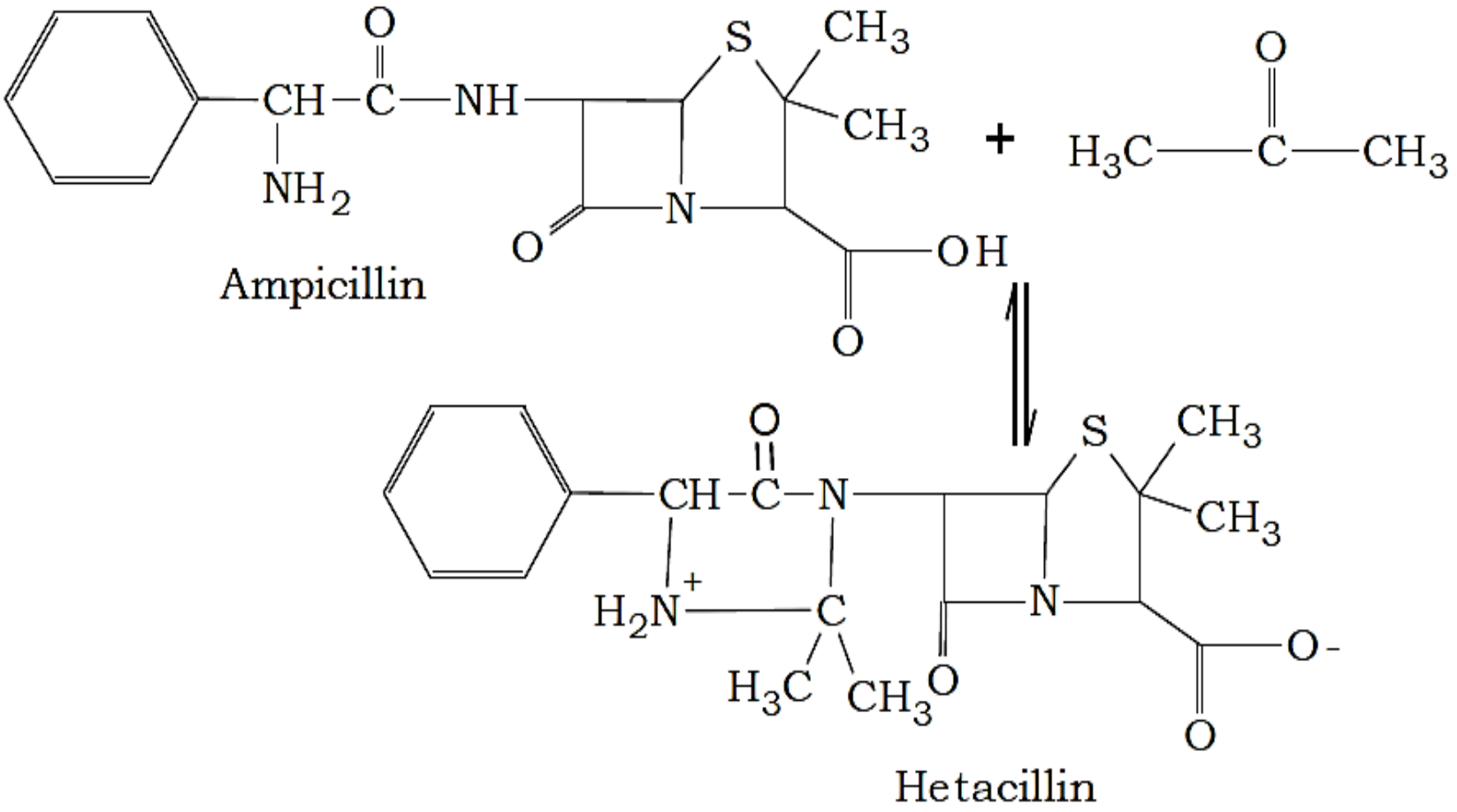
Enhancement of Chemical Stability

- This approach was successfully used to inhibit the auto aminolysis in ampicillin molecule in concentrated solution.
- This generates polymeric species of ampicillin.
- Auto aminolysis occurs due to capability of NH_2 group of side chain to attach β–lactam ring of other molecule.

Enhancement of Chemical Stability

- To synthesis of hetacillin is employed to solve such issue of auto aminolysis.
- Hetacillin is a prodrug of ampicillin formed by the reaction of acetone and ampicillin.
- Acetone ”ties up” the amine group and thus inhibits auto aminolysis.

Enhancement of Chemical Stability



2. Use of Prodrugs to Overcome Pharmacokinetic Barriers:

- The pharmacokinetic phase can be considered as the phase involving(ADME) of the drug:

1. *Absorption.*
2. *Distribution.*
3. *Metabolism.*
4. *Excretion.*

2. Use of Prodrugs to Overcome Pharmacokinetic Barriers:

- The principal barriers identified in the pharmacokinetic phase are:

  i. *Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood brain barrier.*

2. Use of Prodrugs to Overcome Pharmacokinetic Barriers:

ii. *Incomplete systemic delivery of an agent due to pre-systemic metabolism in the gastrointestinal lumen mucosal cells and liver.*

2. Use of Prodrugs to Overcome Pharmacokinetic Barriers:

iii. *Toxicity problems associated with local irritation or distribution into tissue other than the desired target organ.*

iv. *Poor site specificity of the drug (drug targeting).*

To Overcome Absorption Problems:

- Poor absorption of drug may be due to physicochemical properties of drug itself.

- Bioavailability after oral dosing of various *water insoluble agents* is often dissolution rate limited, whereas the absorption of *highly polar agents* is often limited by their transport across the gastrointestinal cell membrane.

To Overcome Absorption Problems:

- Since most drugs are absorbed by passive diffusion, a degree of lipophilicity is necessary for efficient absorption through the gastrointestinal barrier.
- For highly polar compounds, the administration of less polar and more lipophilic prodrug promotes gastrointestinal absorption.

To Overcome Absorption Problems:

- Also, many drugs are poorly absorbed into the central nervous system, through the eye, or the skin due to their highly polar nature and prodrug approach helps in overcoming these barriers.

To Overcome Absorption Problems:

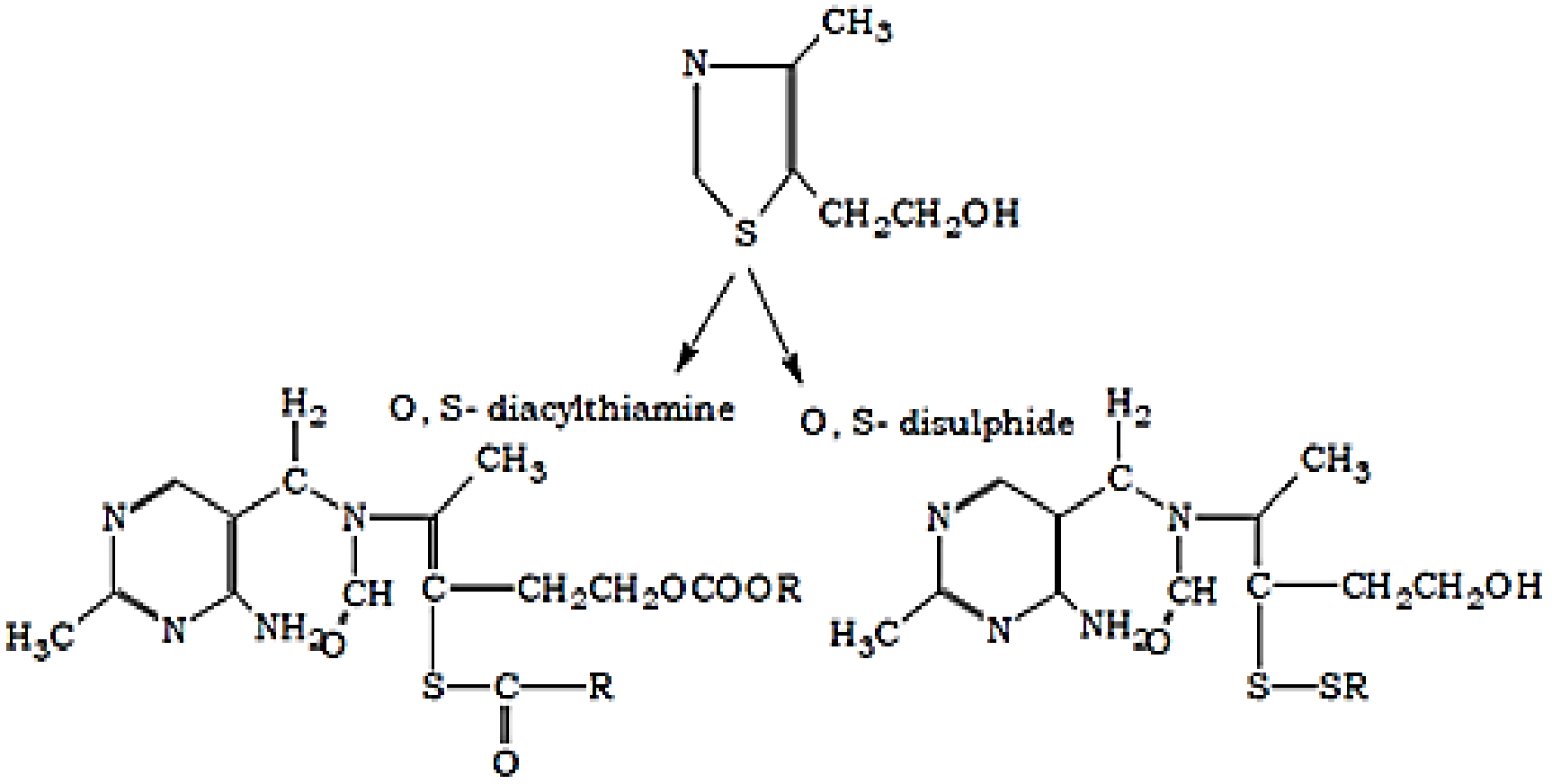
A. *Enhancement of Oral Absorption.*
B. *Enhancement of Ophthalmic Absorption.*
C. *Enhancement of Percutaneous Absorption.*

Enhancement of Oral Absorption

- Various therapeutic agents have poor gastrointestinal absorption such as:
  - ✓ *Water soluble vitamins.*
  - ✓ *Structural analogues of natural purine and pyrimidine nucleoside.*
  - ✓ *Dopamine.*
  - ✓ *Cardiac glycoside such as gitoxin.*

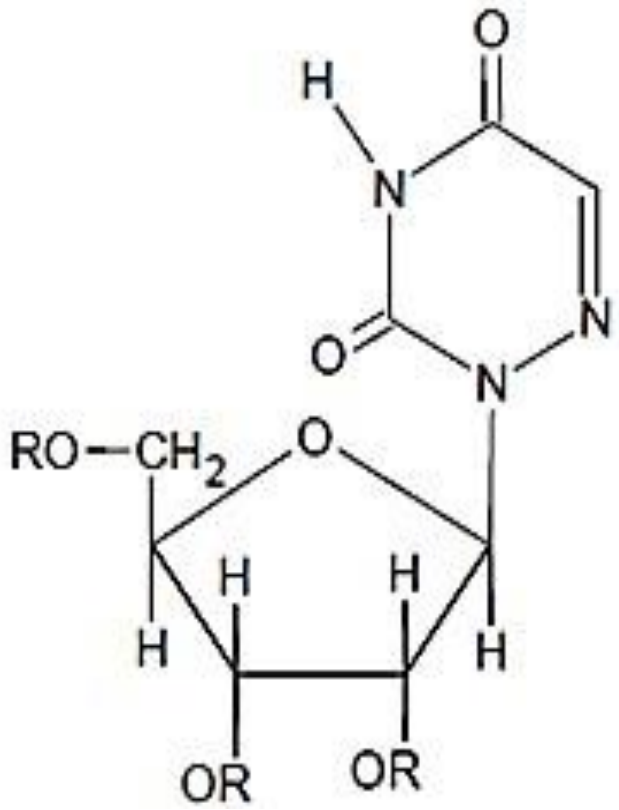
Enhancement of Oral Absorption

(a) Thiamine prodrugs



Enhancement of Oral Absorption

(b) Prodrugs of azauridine

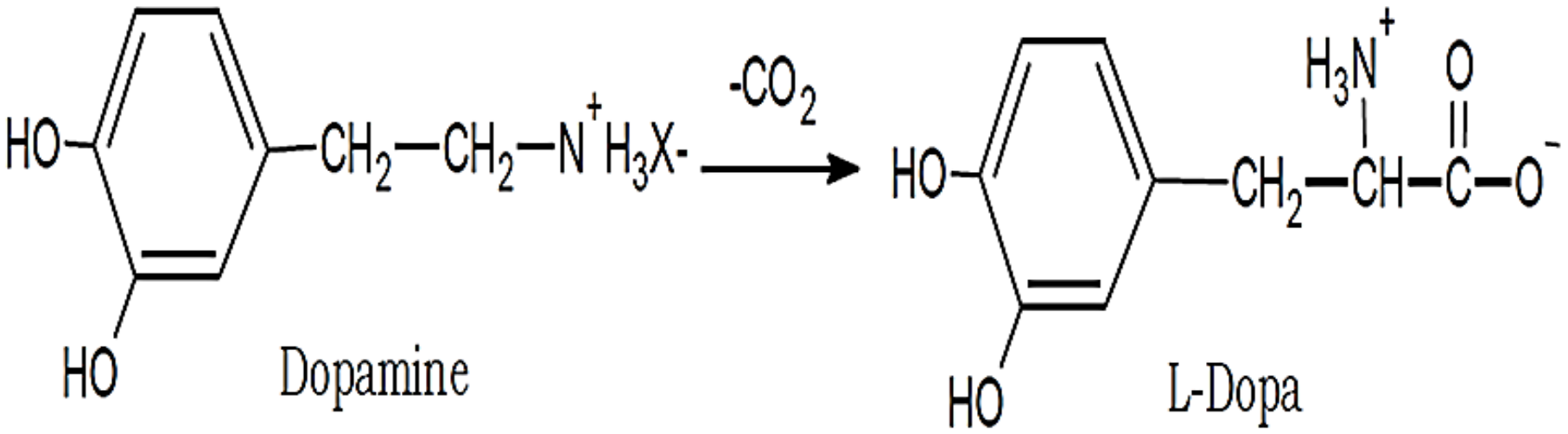


R= $COCH_3$-2', 3', 5' – triacetyl-6-azauridin

R= - (OCC_6H_5) 2', 3', 5' – tribenzoyl-6-azauridin

Enhancement of Oral Absorption

(c) Dopamine prodrug



Enhancement of Oral Absorption

- The causes of the poor absorption of these agents can be one or more of the followings:

  a. *The highly polar nature.*

  b. *Poor lipophilicity.*

  c. *Metabolism during the absorption process.*

Enhancement of Oral Absorption

- The absorption of water soluble vitamin was enhanced by derivatization of thiolate ion to form lipid soluble prodrugs.
- Dopamine was made useful by making its precursor L-Dopa.

Enhancement of Oral Absorption

- Though L-Dopa is highly polar, it is actively transported through specific L–amino acid active transport mechanism and regenerates dopamine by decarboxylation.

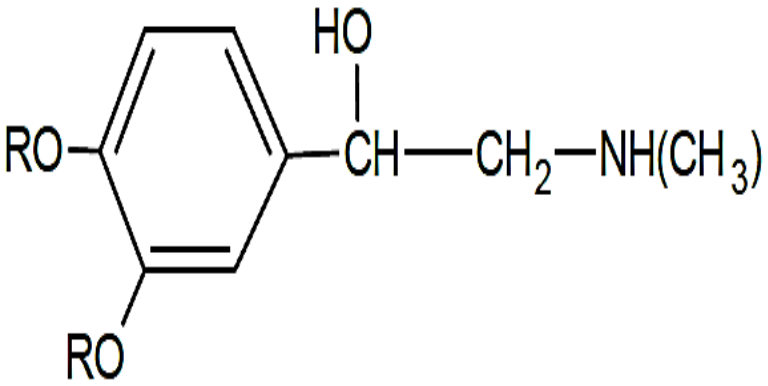
Enhancement of Ophthalmic Absorption

- The usefulness of epinephrine as adrenergic agent in the treatment of glaucoma is limited due to its highly polar nature.
- Dipivalyl derivative of epinephrine formed by the acylation of phenolic hydroxyl groups showed enhanced therapeutic effectiveness.

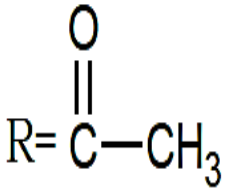
Enhancement of Ophthalmic Absorption

- Lipid solubility of dipivalyl derivatives is far superior to its parent compound, which facilitates its transport through a lipoidal barrier during corneal absorption

Enhancement of Ophthalmic Absorption



R=H Epinephrine



Dipivalyl derivative of epinephrine

Enhancement of Percutaneous Absorption

- Mafenide (sulfa antibiotics) and corticosteroid are used in the treatment of inflammatory, burn therapy, allergic and pruritic conditions, however the above agents have limited topical application due to poor percutaneous absorption.

Enhancement of Percutaneous Absorption

- It was observed that mafenide acetate salt showed better response than mafenide hydrochloride salt.
- Mafenide HCl< Mafenide acetate

Enhancement of Percutaneous Absorption

- The sulfa drug mafenide used in burn therapy was relatively ineffective when applied percutaneously as its hydrochloride salt, however, application of the acetate salt of mafenide was found to be very effective in burn treatment.
- ***Explain why?***

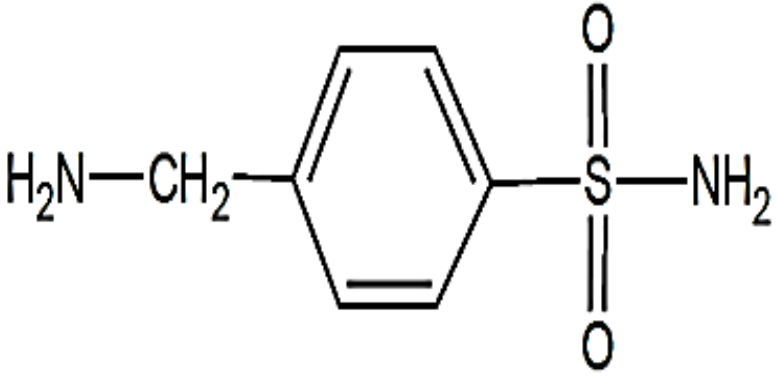
Enhancement of Percutaneous Absorption

- Hint: to solve the problem of mafenide use the following formula:

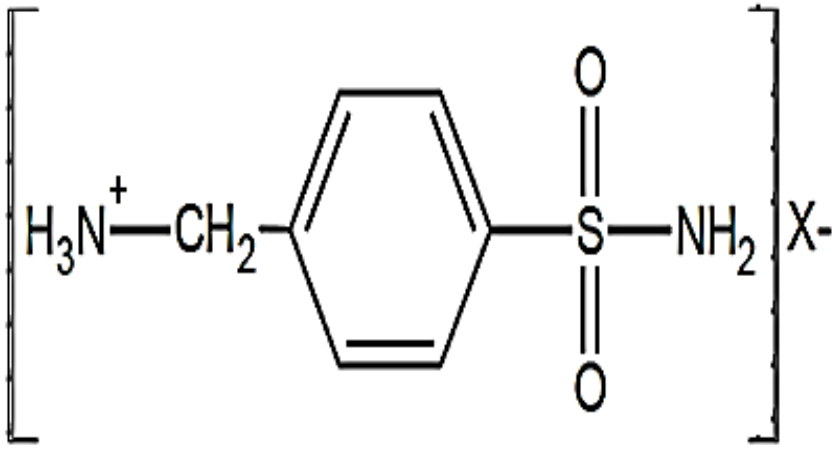
$$\%\ ionization = \frac{100}{1 + 10^{(pKa - pH)}}$$

- The problem of poor percutaneous absorption of corticosteroid was overcome by making various ester prodrugs.

Enhancement of Percutaneous Absorption



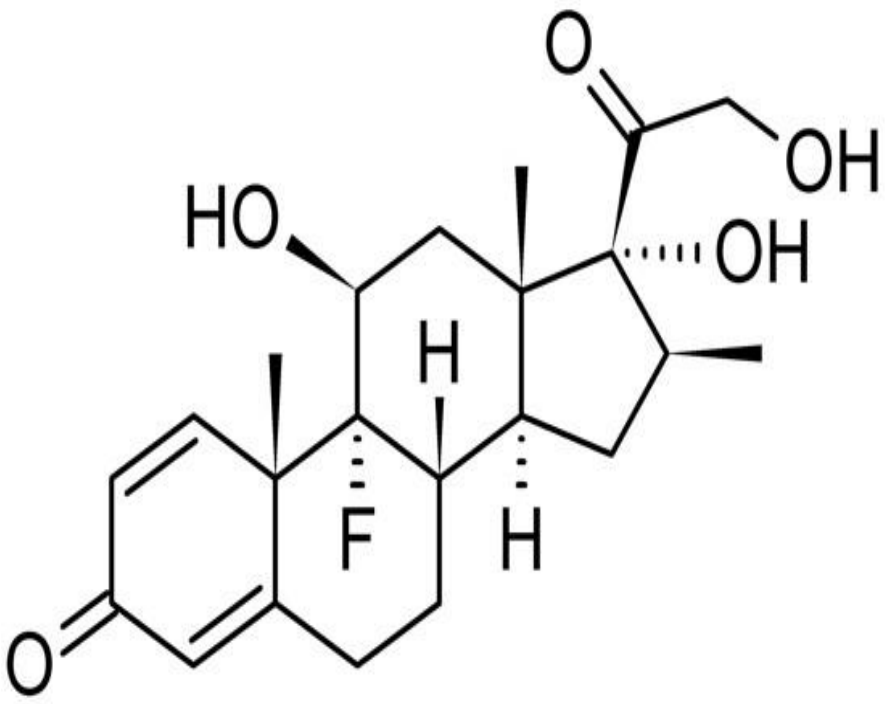
Mefenide



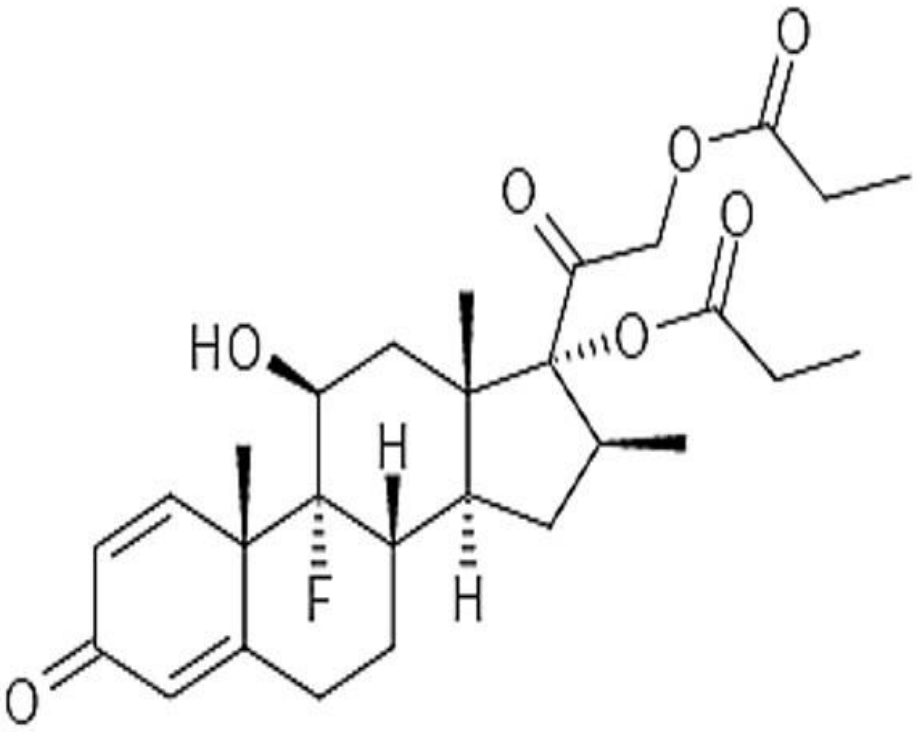
Mefenide acid salt

$X^- = Cl^-$ or $X^- = CH_3COO^-$

Enhancement of Percutaneous Absorption



Betamethasone



Betamethasone-17, 21-dipropionate

References:

- Wilson and Gisvold Textbook of Organic Medicinal and Pharmaceutical Chemistry; Delgado JN, Remers WA, (Eds.); 12th ed., 2011.

- http://shodhganga.inflibnet.ac.in/bitstream/10603/3457/10/10_chapter%201.pdf
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