Lec 3 5th stage

Organic Pharmaceutical Chemistry IV

2018-2019

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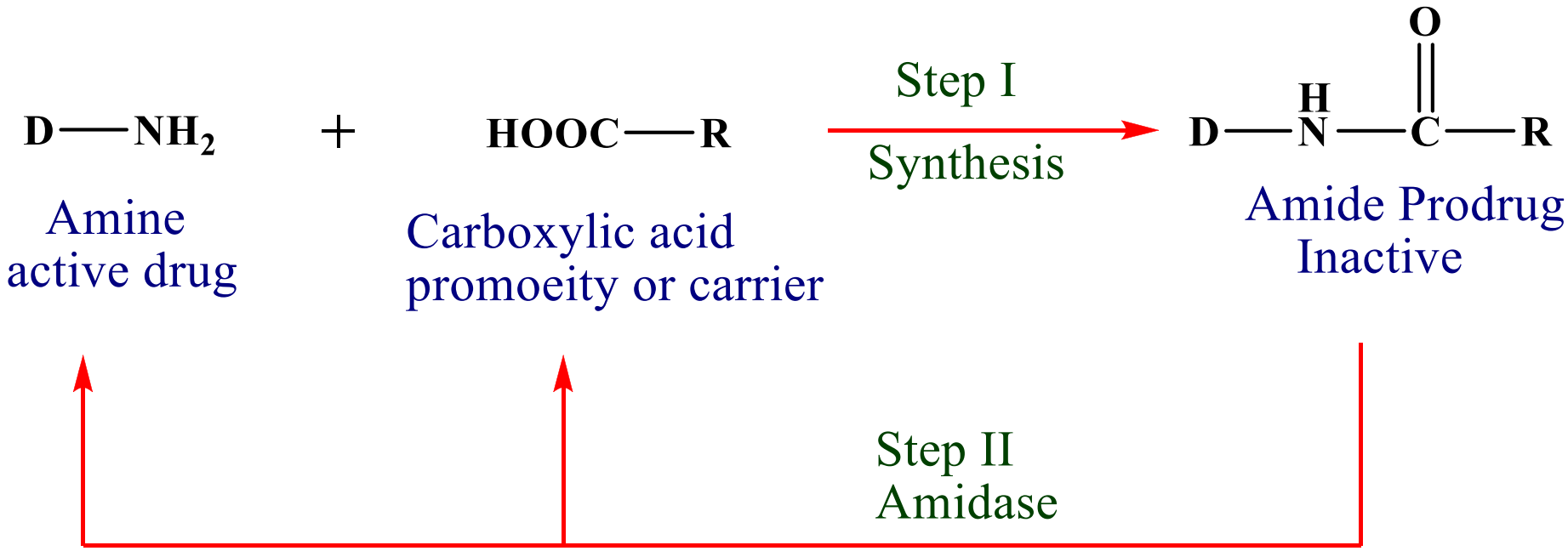
2- *Amines*



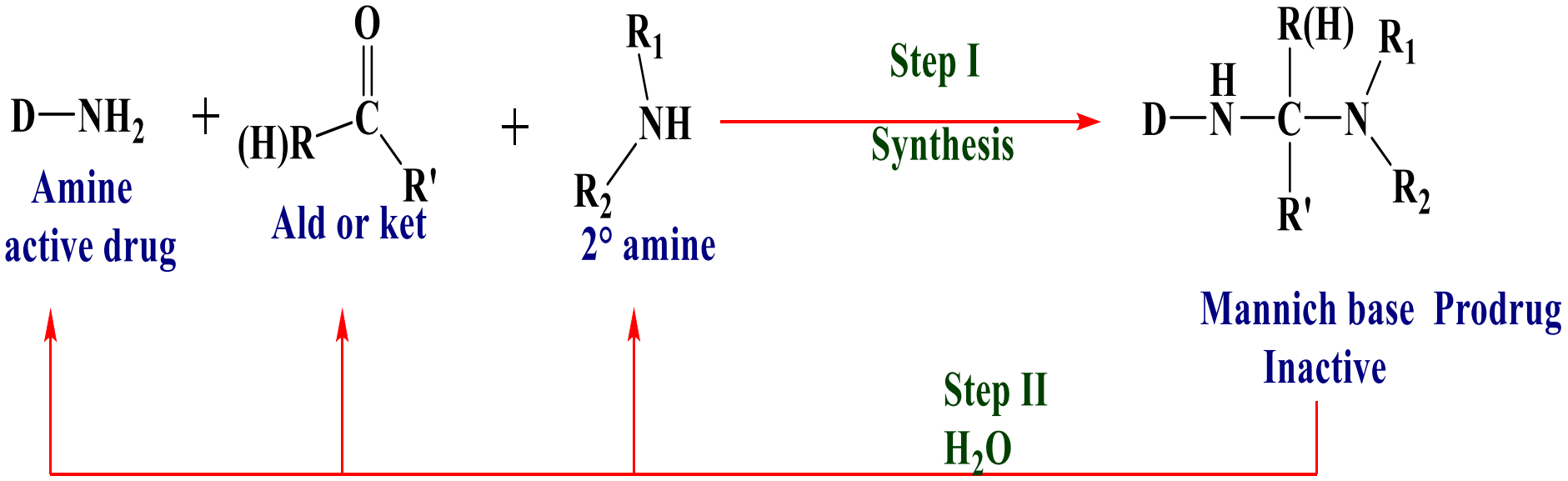
Amides have not been widely used us a prodrug strategy because of:-

a. The high chemical stability of the amide linkage.

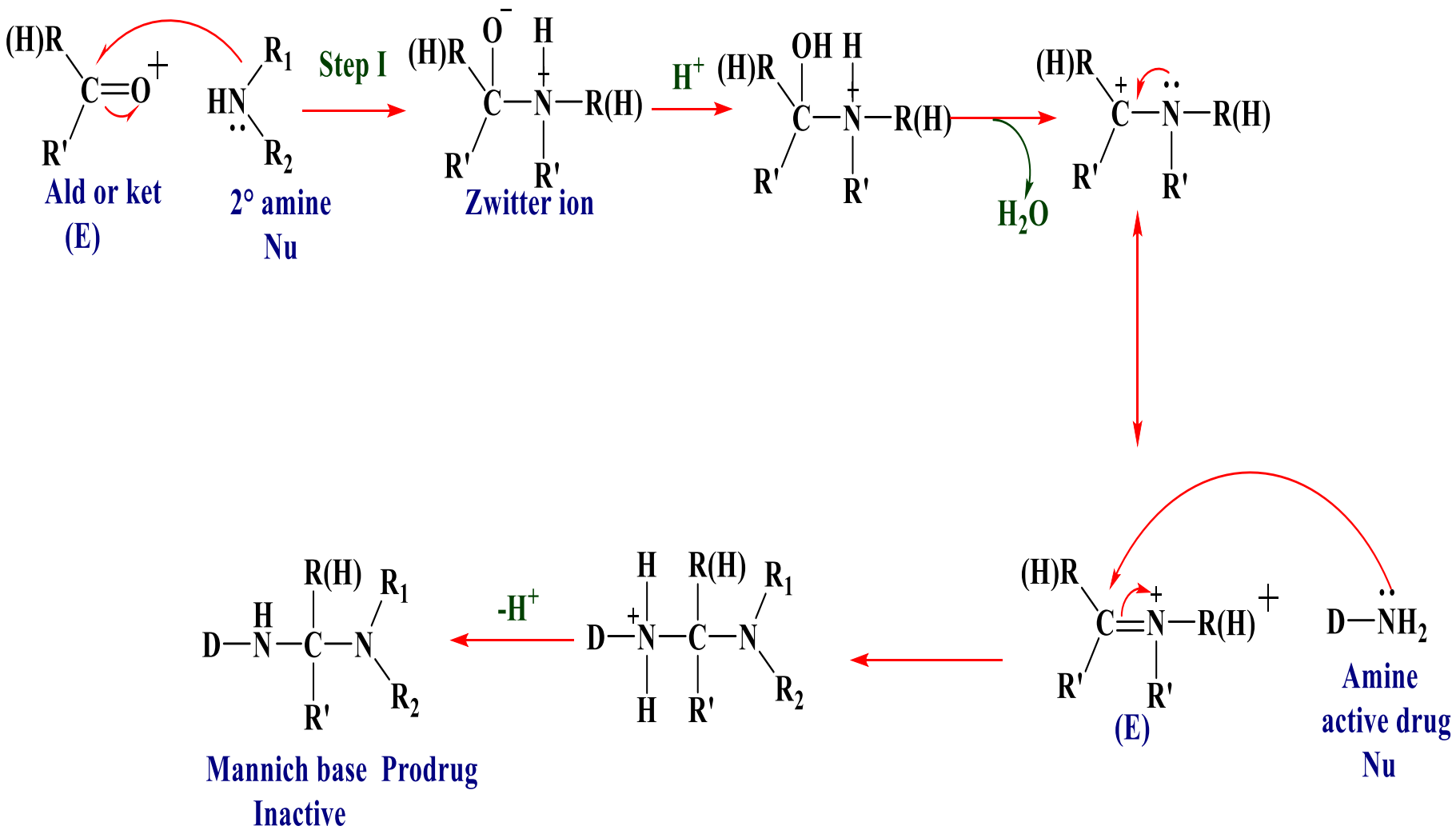
b. The lack of amidase enzymes necessary for hydrolysis.

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

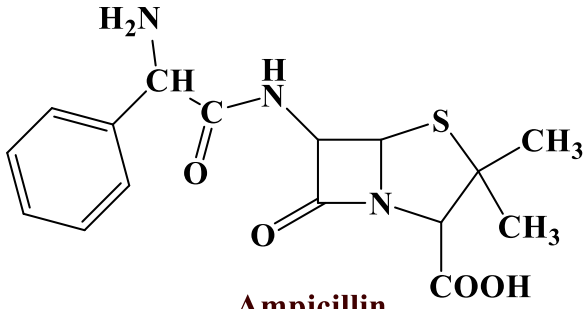
- **Mannich bases result from the reaction of two amines with an aldehyde or ketone.**



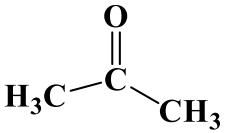
Mechanism of reaction



Ampicillin (antibacterial)



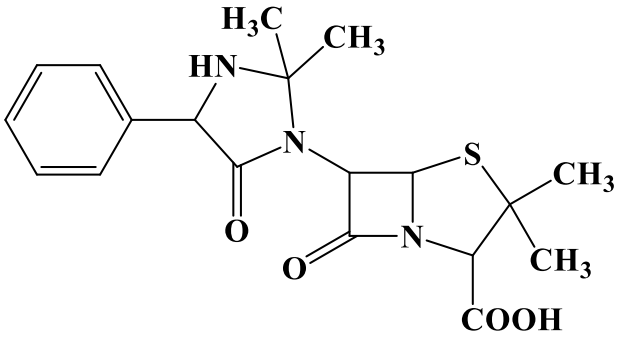
Ampicillin



Acetone

Step I

Synthesis



Hetacillin prodrug

Increase bioavailability

decrease protonation in the small intestine

(↑ oral abs) (↑ lipophilicity)

Low bioavailability (orally)

Because polarity limits abs.

(α-amino group is basic and

Protonated in the small intestine

$RNH_2 + H^+ \rightarrow RNH_3^+$

non polar polar(ionizable)

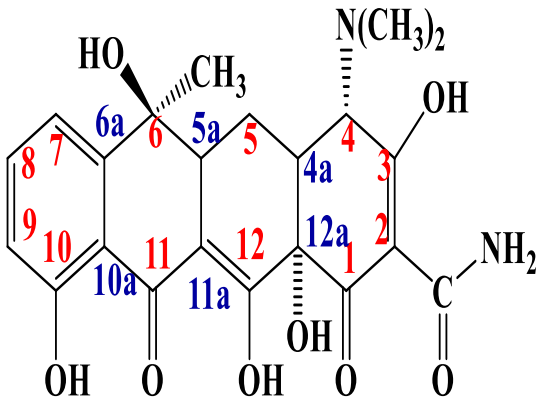
Step II

H_2O/H^+

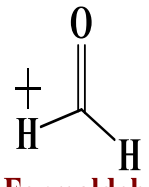
Hetacillin is a prodrug form of ampicillin in which the amide nitrogen and α-amino functionalities have been allowed to react with acetone to give an imidazolidinone ring system. This decreases the basicity of the α-amino group and reduces protonation in the small intestine so that the agent is more 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

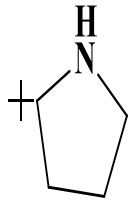
This approach was also used with the antibiotic **tetracycline**—the amide nitrogen was allowed to react with formaldehyde and pyrrolidine to give the Mannich base **rolitetracycline**. In this case, addition of the basic pyrrolidine nitrogen introduces an additional ionizable functionality and increases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



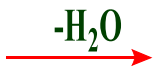
Tetracycline

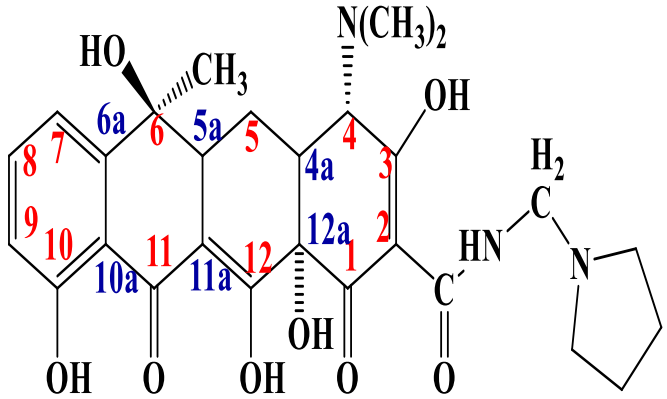


Formaldehyde



Pyrrolidine



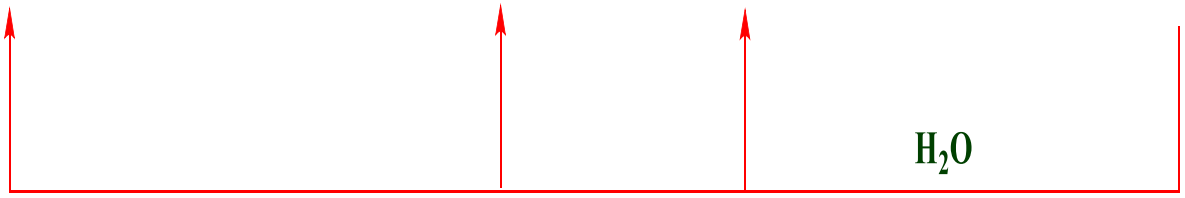


Rolitetracycline

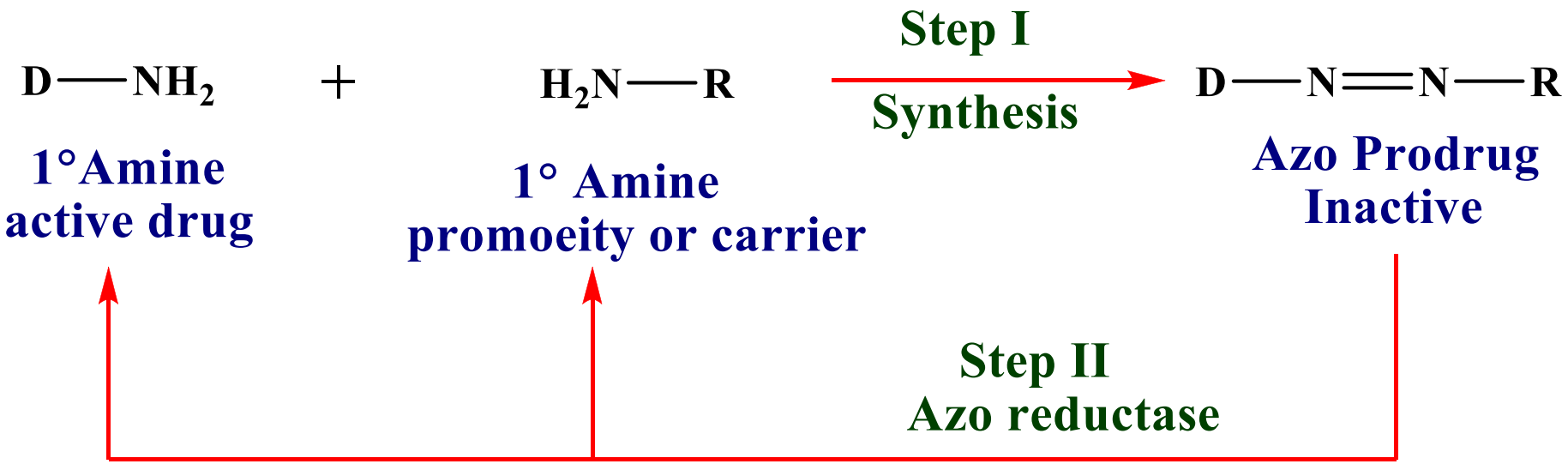
presence of pyrrolidine ring

increase water solubility

(↑polarity) use for IV, or IM



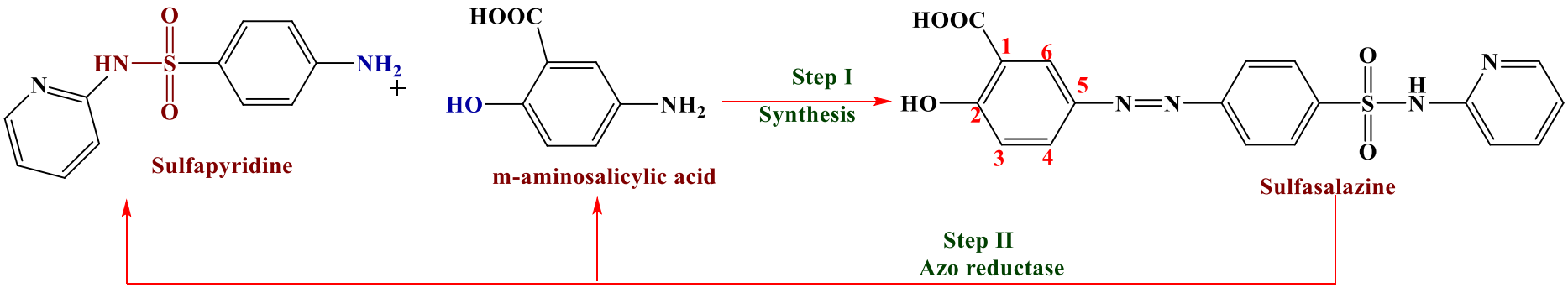
Azo prodrug•



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

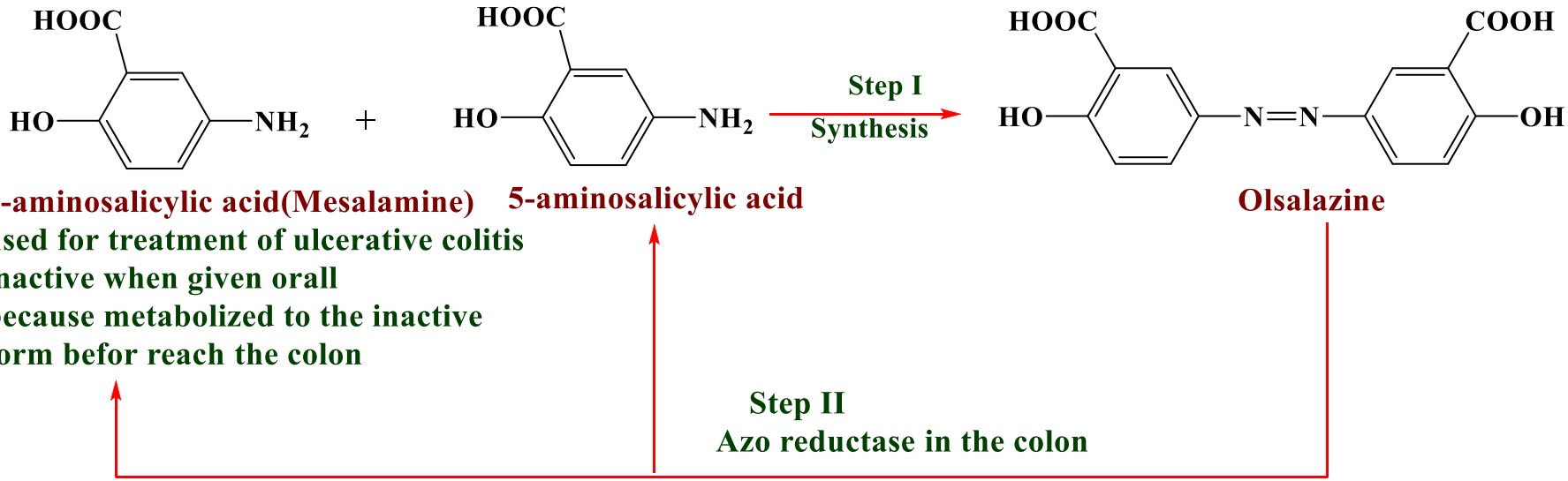
- Sulfasalazine



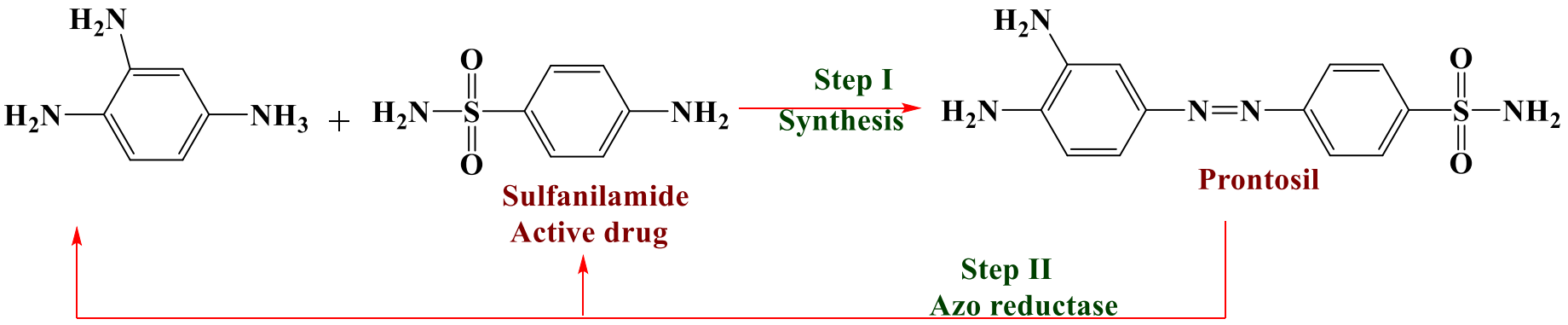
Advantage of sulfasalazine prodrug

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

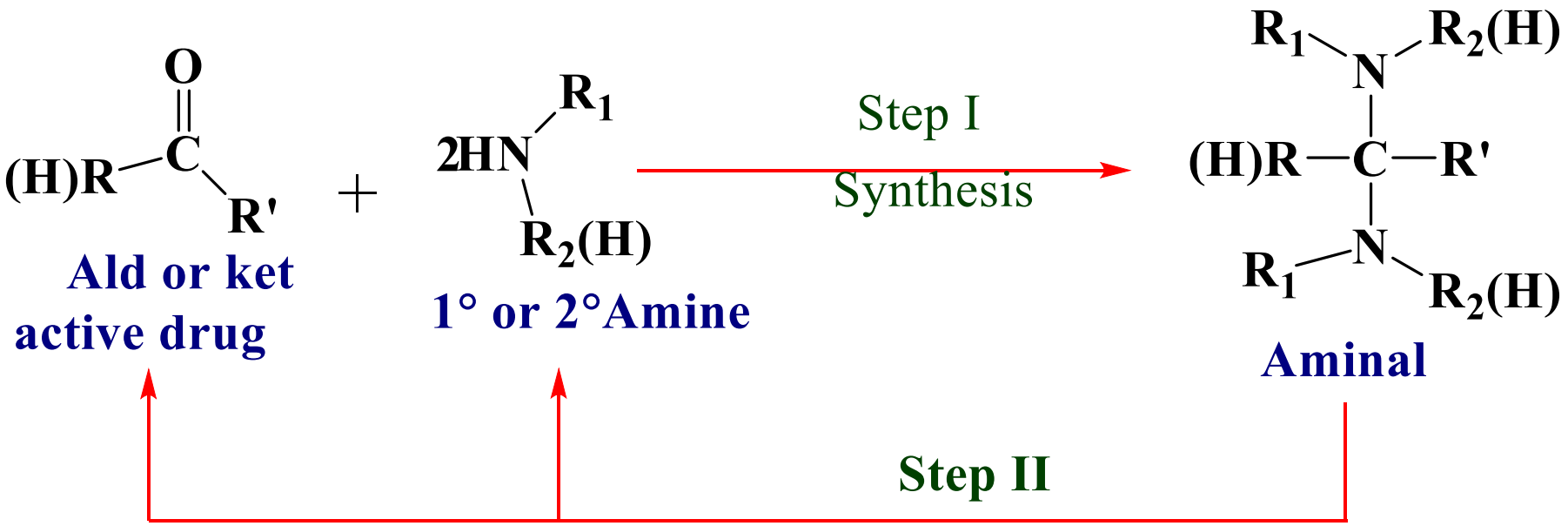
Olsalazine prodrug•



Prontosil (treatment of systemic infection)•



4- Carbonyl compounds•



Methenamine

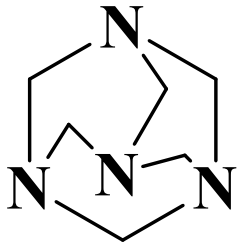
$6CH_2=O$ + $4NH_3$

Formaldehyde

1° Amine

Step I

Synthesis



Methenamine

treatment UTI

active drug (antibacterial)

systemic effect→ toxicity

Step II

Hydrolysis by

pH 4.5 in the urin

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.