PRODRUGS OF AMİNES

- Amines are highly ionized functional groups under physiological conditions (pH= 1-8).
- However, this functional group is found in many drug molecules.
- Drug molecules that contain basic amine functional groups may actually permeate skin better than expected, and basic amine groups incorporated into a prodrug may enhance its skin permeation.
- Derivatizations of amines can result in reduction in basicity.
- That could be favorable for improving the rate of diffusion across biological membranes.
- Physicochemical and structural properties of the promoiety which is incorporated into a drug molecule are important.
- Hydrophilic promoieties are designed to improve water solubility and lipophilic ones are designed to improve membrane permeability

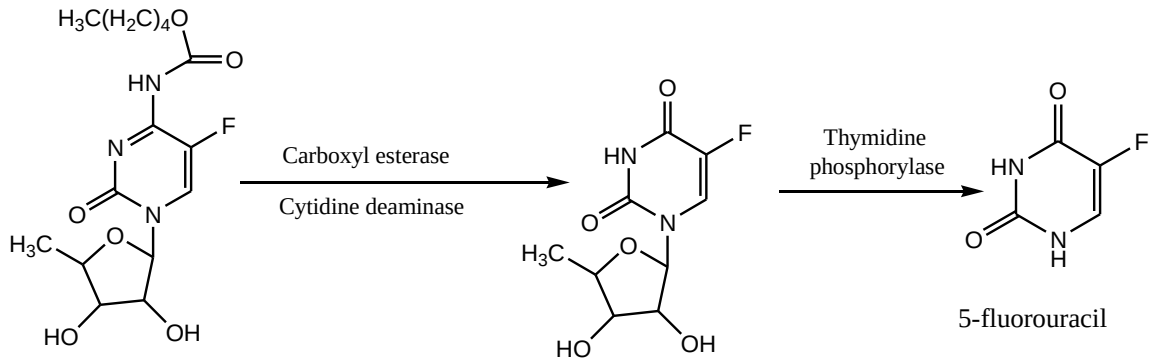
5-Fluorouracil (5-FU) is an antimetabolite with a broad spectrum of activity against solid tumors.

However, its administration is accompanied by severe toxic side effects and delivery problems. In order to solve these problems, low- and macromolecular prodrugs of 5-FU have been developed.

Capecitabine is a commercially available prodrug of 5-FU and it was first approved in the US in 1998 for the treatment of metastatic breast cancer.

This prodrug was designed to improve oral bioavailability and selectivity of 5-FU to tumor cells.

Capecitabine passes intact through the intestinal mucosa and selectively delivers 5-FU to tumor tissue by enzymatic conversion[141].



Capecitabine

5`-deoxy-5-fluorouridine

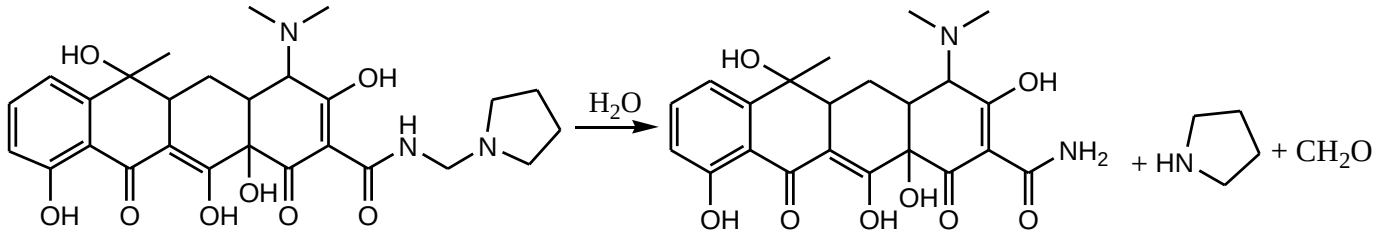
5-fluorouracil

- Mannich reactions have been extensively studied as prodrug systems for amine, amide and imide drugs.

- The Mannich reaction is nucleophilic addition reaction of a non-enolizable aldehyde and any primary or secondary amine to produce resonance stabilized imine.

- Relative to their parent compounds, Mannich bases may have enhanced oral bioavailability, increased water solubility or increased skin permeation.

- One clinically used Mannich base is rolitetracycline, a water-soluble prodrug of tetracycline, developed for parenteral use.

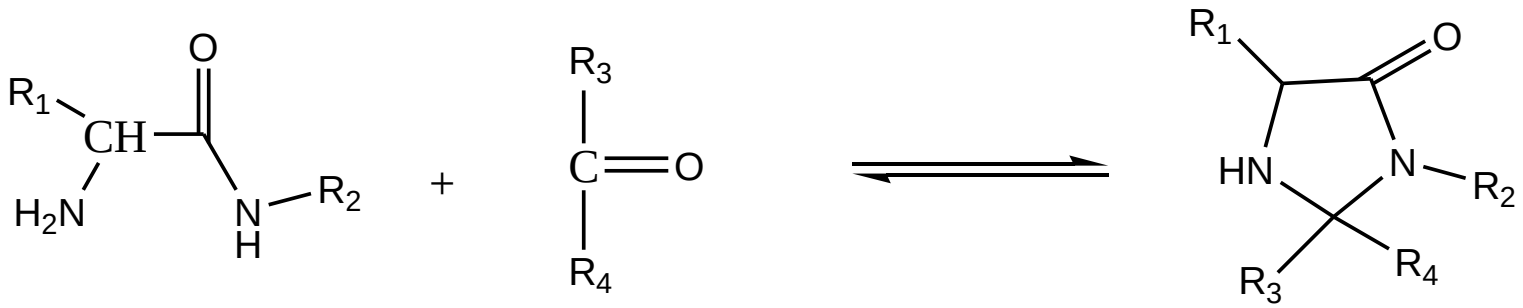


Rolitetracycline Tetracycline pyrrolidine

- Compounds containing an α-aminoamide moiety react with aldehydes and ketones to yield imidazolidinones.

- The 1,4-imidazolidinone structure can serve as a cylic N-mannich base prodrug of an acyclic α-aminoamide moiety.

- In aqueous solutions, 1,4-imidazolidinone revert back to the parent α-aminoamide (peptide) and aldehyde or ketone at a rate that is dependent on pH, the structure of the α-aminoamide substituents, and the structure of the carbonyl component.

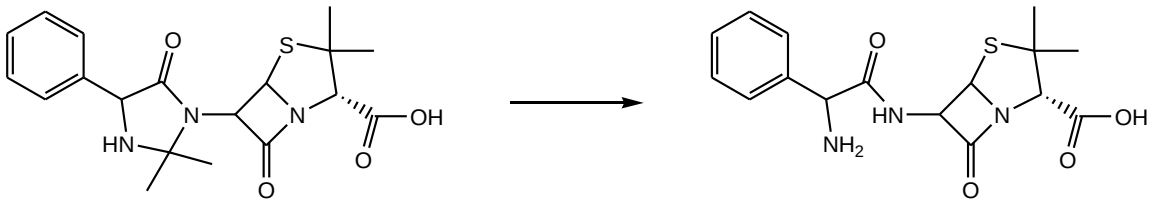


- The hydrolysis of imidazolidinone is not subject to enzyme catalysis and therefore has been suggested as potentially useful promoiety to protect the N-terminal amino acid residues of peptides against aminopeptidase-catalyzed hydrolysis.

- Hetacillin, a clinically used compound, is regarded as a cyclic Mannich base of ampicillin.

- This prodrug strategy has been extended to improve the bioavailability of ampicillin, a β-lactam antibiotic that also contains an α-aminoamide backbone.

- The corresponding imidazolidinone, hetacillin, is rapidly hydrolyzed to ampicillin in aqueous solutions and *in vivo*.



Hetacillin

Ampicillin