Prodrugs concept & Applications

Lec. 4

By:
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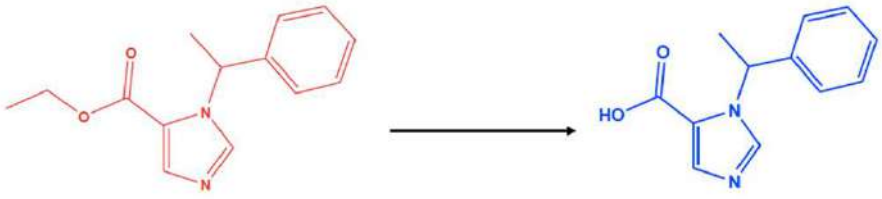
Non-Prodrugs

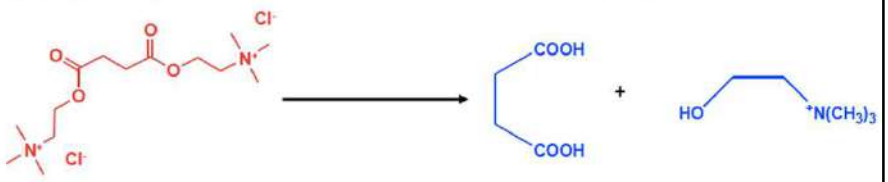
- "Hard Drugs" - compounds that contain structural characteristics required for activity but are not susceptible to metabolism
  - Increased efficiency by avoiding metabolism
  - No toxic metabolites are formed
  - HOWEVER, less readily eliminated due to lack of metabolism
- "Soft Drugs" - These are the ***opposite*** of prodrugs. These compounds are designed and synthesized as ACTIVE compounds that readily undergo metabolic inactivation to nontoxic products

SOFT DRUGS

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



Etomidate (hypnotic) metabolite



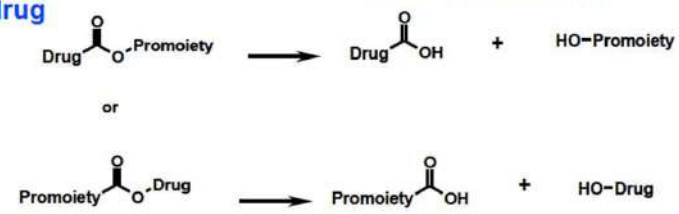
Succinylcholine (neuromuscular blocking agent)

Conversion of Prodrugs

- Metabolism (enzyme dependant)
- Chemical Methods (**non-dependant**)
  - Hydrolysis
  - Decarboxylation
  - NOT patient dependant!
  - Stability/Storage issues

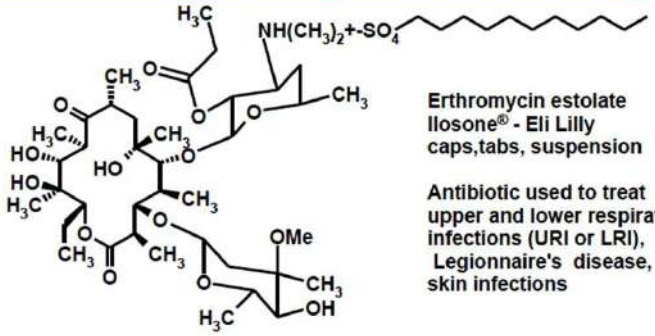
Functional Groups in Prodrugs

1 **Carboxylic acids and Alcohols:** **Most common type of prodrug**



- Types of esterase enzymes mediating the hydrolysis process
  - Ester hydrolase, Lipases, Cholesterol esterases, Acetylcholinesterase, Carboxypeptidase, Cholinesterase
  - Bacterial microflora enzymes
- Wide number of choices of promoiety alcohols available
  - Steric, electronic and hydrophobicity properties allow rate and extent of hydrolysis to be controlled

Functional Groups in Prodrugs



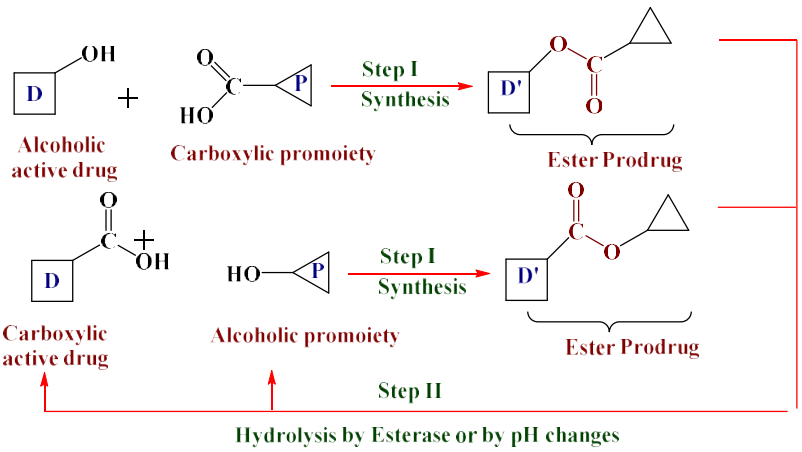
Erthromycin estolate
Ilosone® - Eli Lilly
caps,tabs, suspension

Antibiotic used to treat upper and lower respiratory infections (URI or LRI), Legionnaire's disease, skin infections

- **Erythromycin is a very bitter substance easily destroyed at acidic pH**
- **Propionate ester is to increase lipid solubility for improved absorption**
- **Ester must be hydrolyzed for antibacterial activity**
- **Lauryl sulfate salt – absorption not affected by food, less bitter after taste and is acid stable**

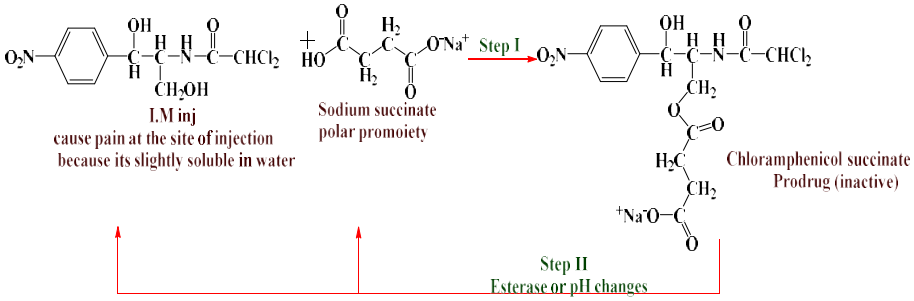
Ester pro drug.•

If the molecule contains either an alcohol or carboxylic acid functionality an ester prodrug may be easily synthesized.

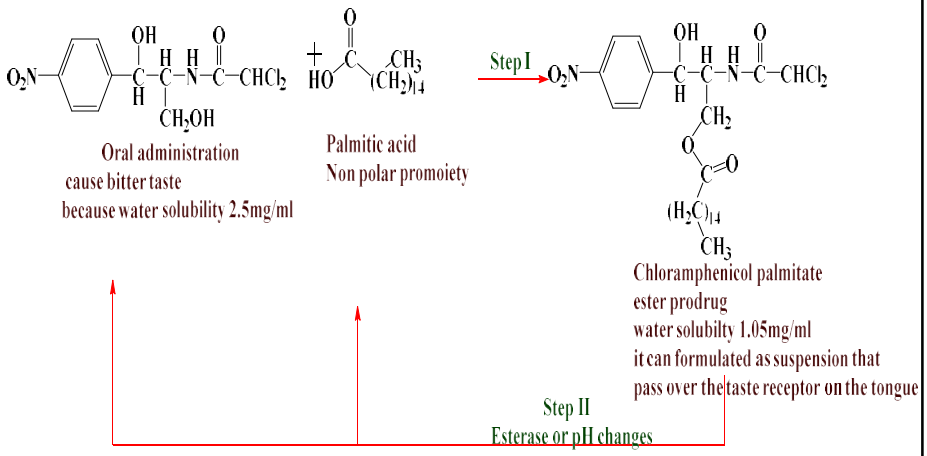


Examples:-

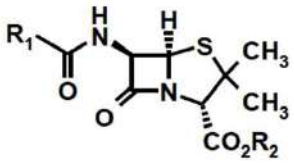
Chloramphenicol(antibiotic)



- Chloramphenicol when given parentrally by IM inj. it is painful ,since it ppt. at site of injection because of its low water solubility, so when polar functional group like succinate was added lead to increase water solubility and reduce pain.

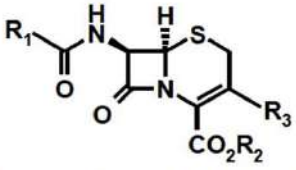


Esters Failure as Prodrugs



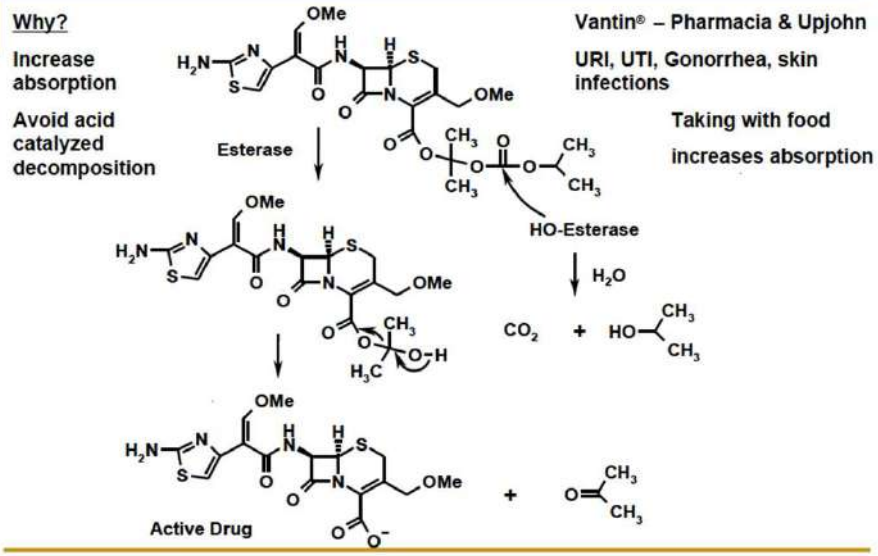
R_2 = ethyl, propyl, butyl, phenyl
Penicillin esters

Esterases → NO REACTION!

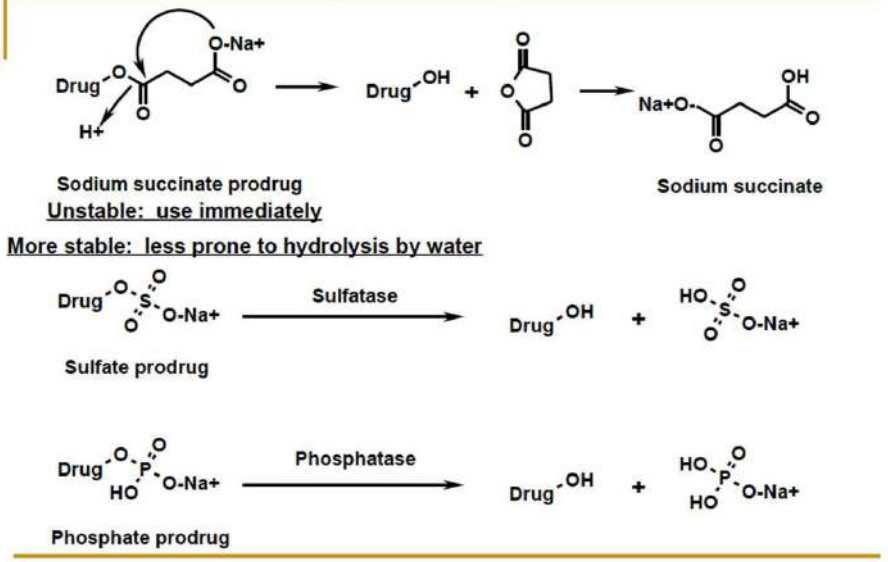


R_2 = ethyl, propyl, butyl, phenyl
Cephalosporin esters

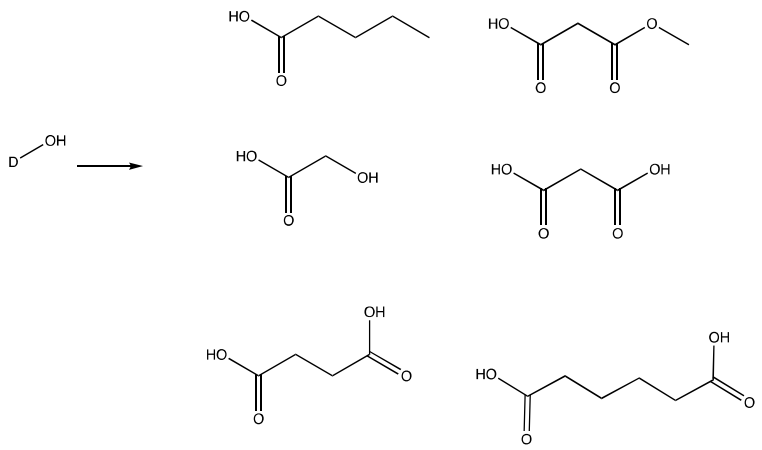
β-Lactam prodrug – Double esters



Other ester prodrugs - soluble



Drug D is intended to be given as an IV inj. With fast release. Which moiety(ies) is/are the optimum choice?



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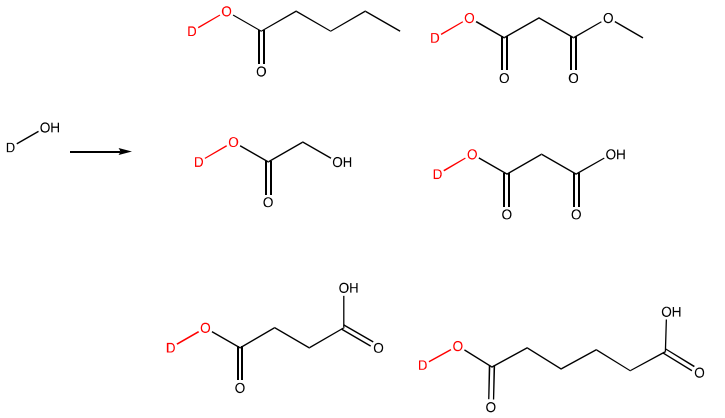

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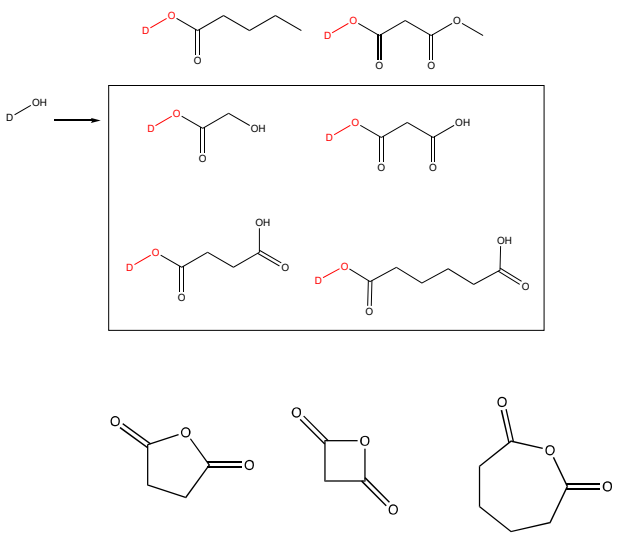
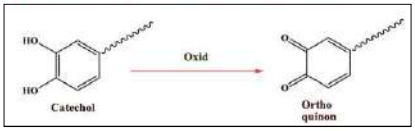
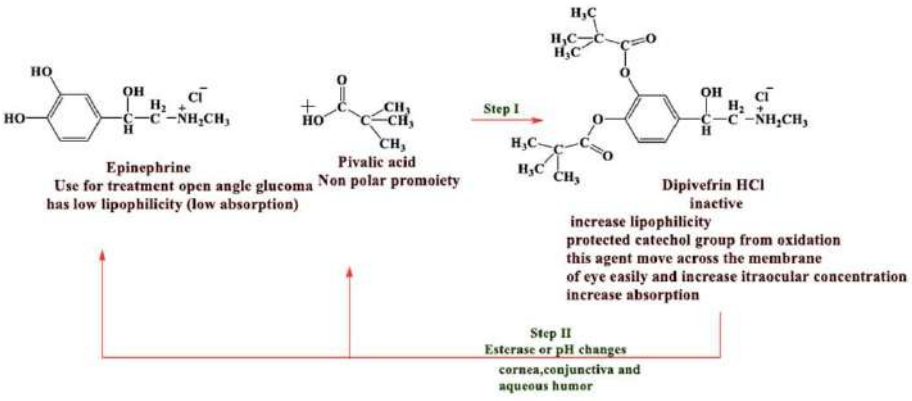


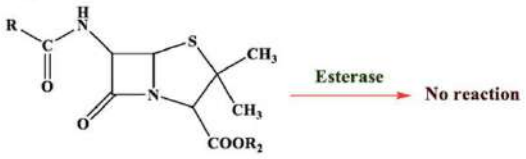
Example of increasing absorption by addition of a nonpolar carboxylic acid

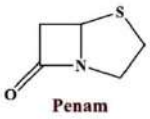




Example(β-lactams antibiotic)

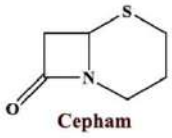
•penicillin ester





R_2= Ethyl, propyl, butyl, phenyl.

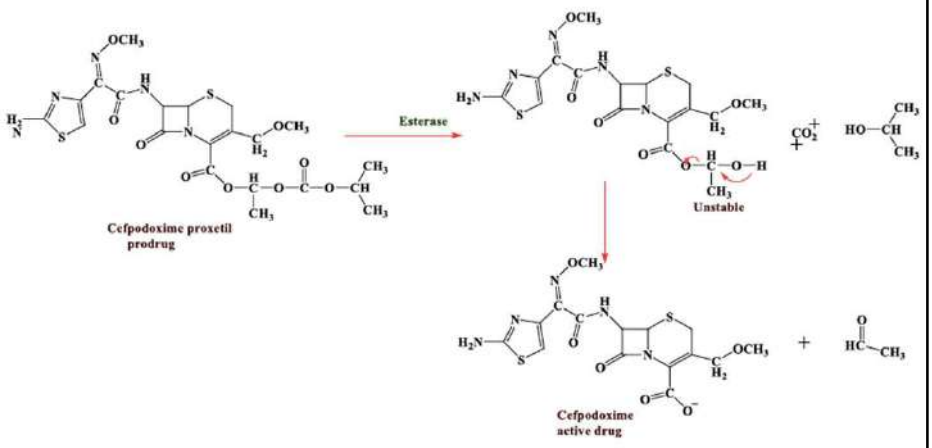
Cephalosporin ester•



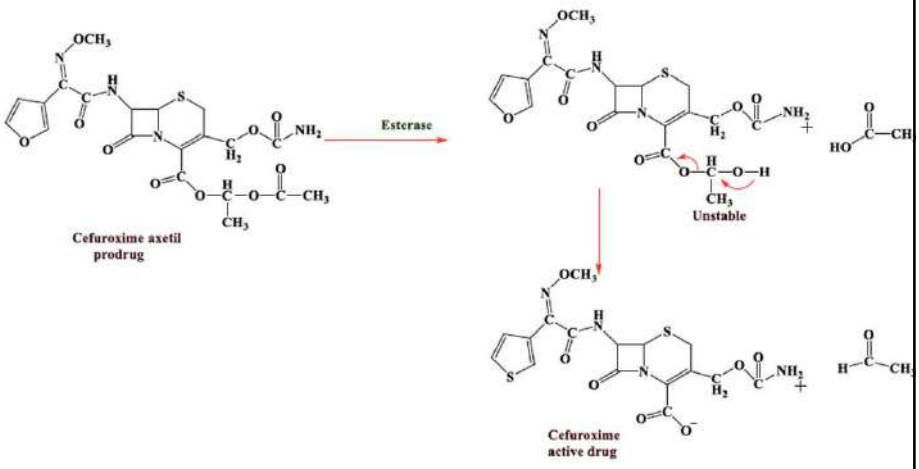
R_2= Ethyl, propyl, butyl, phenyl.

Example (double ester prodrug)

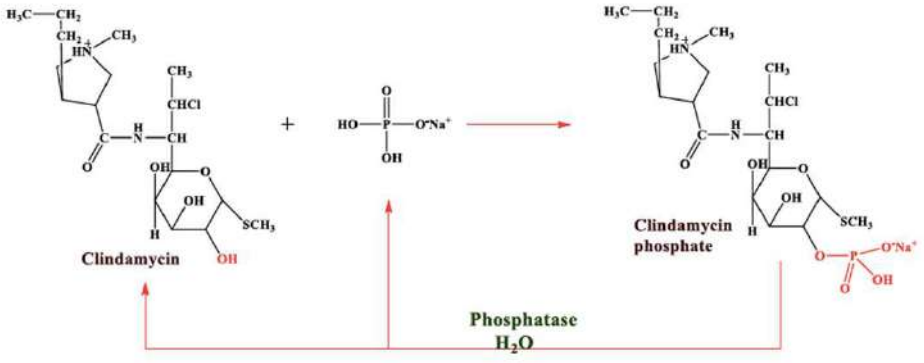
1)Cefpodoxime proxetile (prodrug)



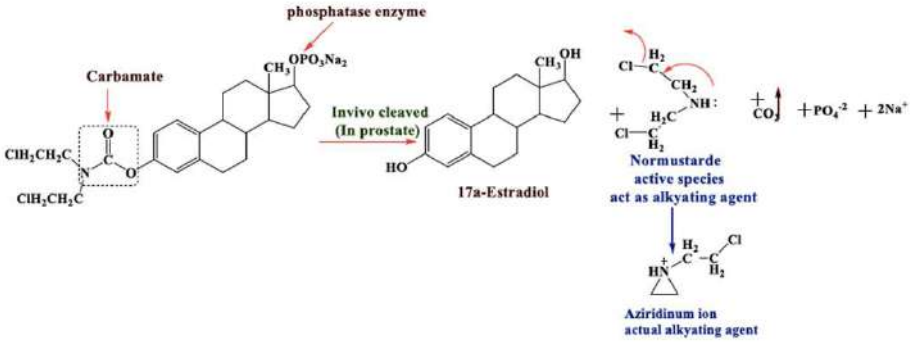
2)cefuroxime axetil (prodrug)



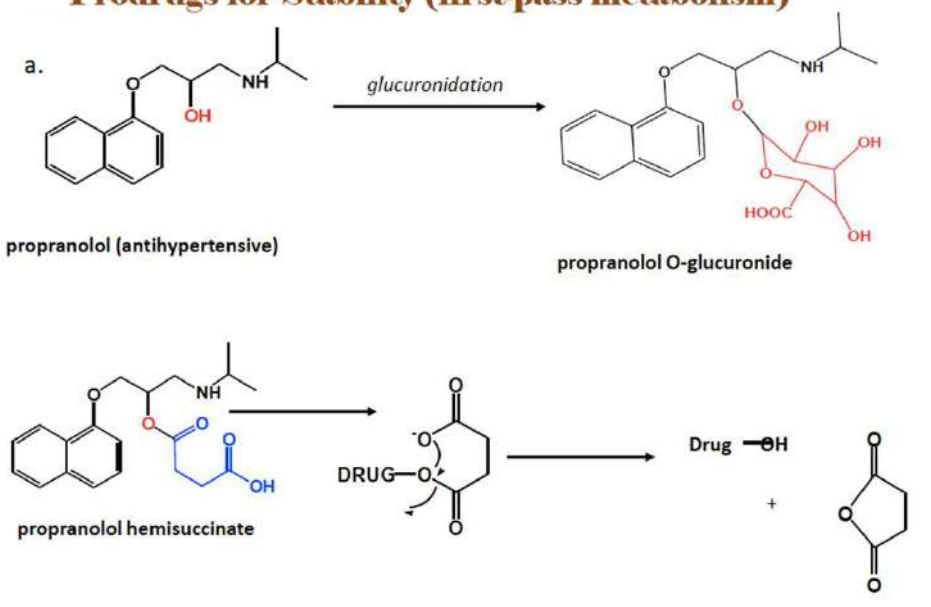
Clindamycin



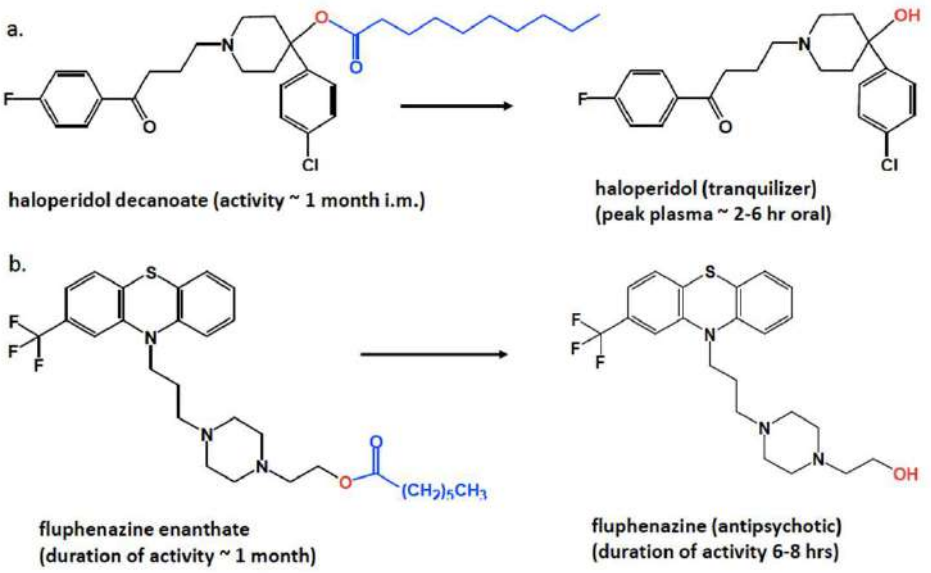
Example
Estramustine (mutual prodrug)



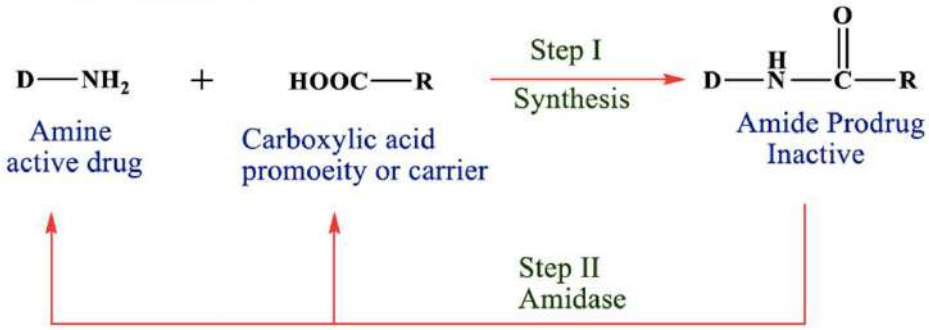
Prodrugs for Stability (first-pass metabolism)



Prodrugs for Slow and Prolonged Release



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.

- Activated amides, generally of low-basicity amines, or amides of amino acids are more susceptible to enzymatic cleavage (Table 9.3).

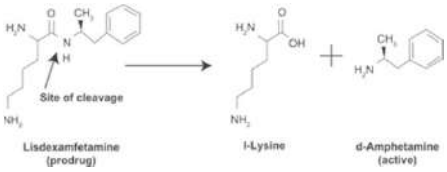
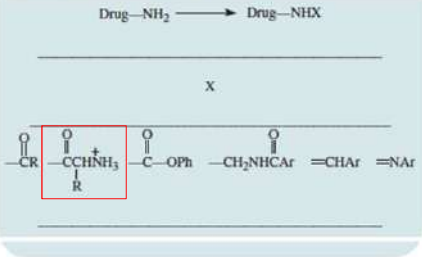
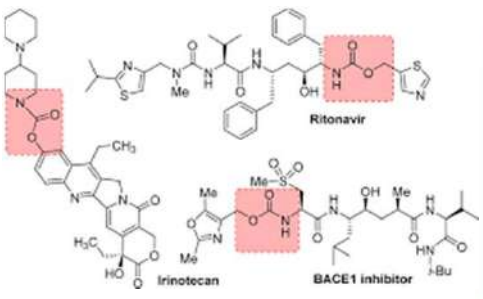


TABLE 9.3 Prodrug Analogs of Amines



- Activated amides, generally of low-basicity amines, or amides of amino acids are more susceptible to enzymatic cleavage (Table 9.3).
- Although carbamates in general are too stable, phenyl carbamates ($RNHCO_2Ph$) are rapidly cleaved by plasma enzymes, and, therefore, they can be used as prodrugs.



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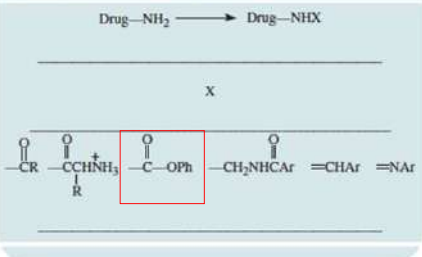


- Activated amides, generally of low-basicity amines, or amides of amino acids are more susceptible to enzymatic cleavage (Table 9.3).
- Although carbamates in general are too stable, phenyl carbamates ($RNHCO_2Ph$) are rapidly cleaved by plasma enzymes, and, therefore, they can be used as prodrugs.
- N-Mannich bases as a prodrug: The pKa of amines can be lowered by approximately three units by conversion to their N-Mannich bases.

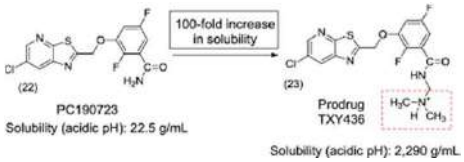
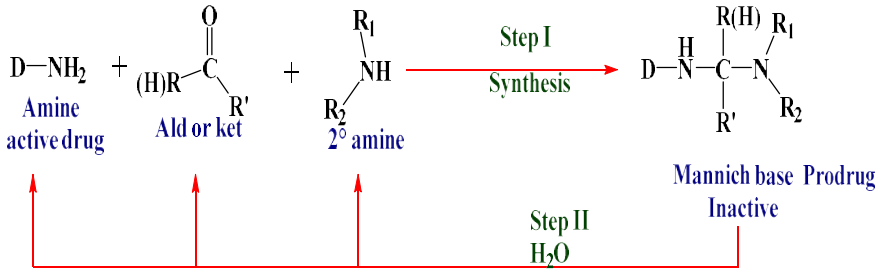


TABLE 9.3 Prodrug Analogs of Amines

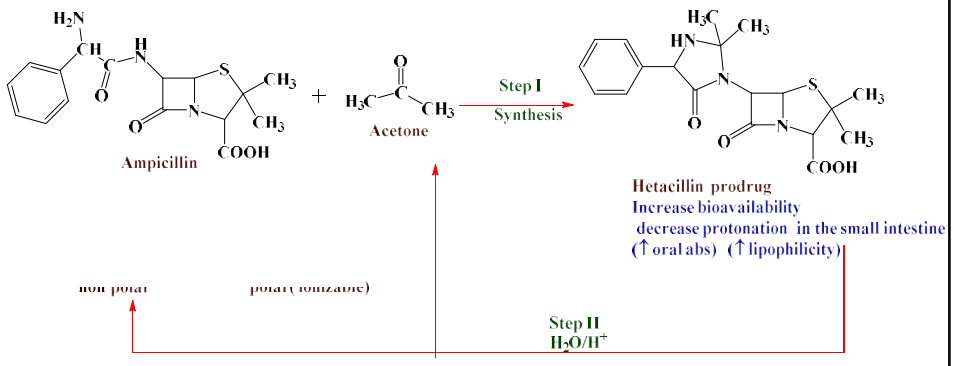
$Drug—NH_2 \longrightarrow Drug—NHX$

X
—CR
—CCHNH$_3$ (R)
—C—OPh
—CH$_2$NHCAr
=CHAr
=NAr

- 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.



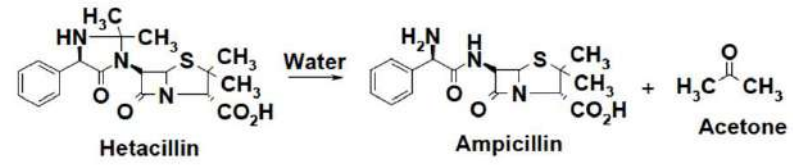
Mannich bases as a prodrug: Ampicillin (antibacterial)

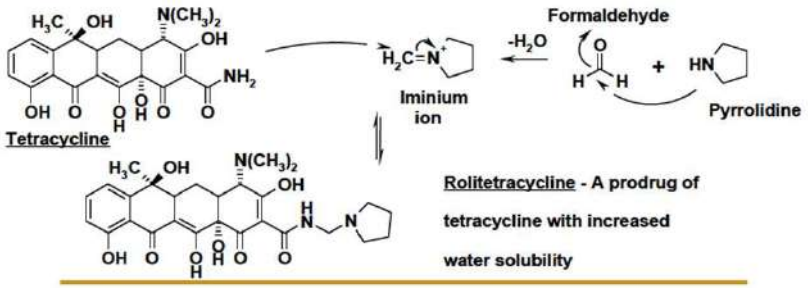


- Hetacillin is a prodrug form of ampicillin in which the amide nitrogen and α-amino functionalities have been allowed to react with acetone to give an imidazolidinone ring system.

Amine derivatives as prodrugs

- Amides not used due to high stability
- **Most common amine derivative used** is a Mannich Base prodrug



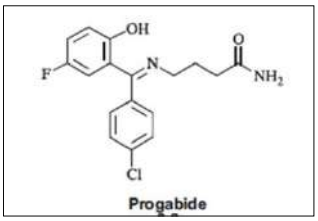


Rolitetracycline - A prodrug of tetracycline with increased water solubility

Mannich bases as a prodrug: 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
- 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. Expected to be give IV or IM

- Making the amine more lipophilic, is to convert them to imines (Schiff bases) ; however, imines often are too labile in aqueous solution.
- The anticonvulsant agent progabide is a prodrug form of γ -aminobutyric acid (GABA), an important inhibitory neurotransmitter.



Progabide

- The lipophilicity of progabide allows the compound to cross the blood–brain barrier; once inside the brain it is hydrolyzed to GABA.

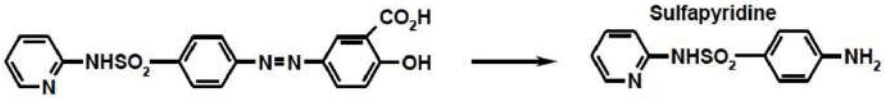
TABLE 9.3 Prodrug Analogs of Amines

Drug—NH_2 ⟶ Drug—NHX

X
—CR
—CCHNH$_3^+$ (R)
—C—OPh
—CH_2NHCAr
=CHAr
=NAr

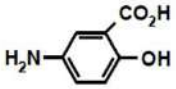
Azo Prodrugs

- Bacterial reductases → reductive cleavage
  - Release of 2 amine compounds
  - Occurs in ***colon*** → discourages small intestine systemic absorption
  - Concentrates the drug at the desired site of action



Sulfasalazine - Azulfidine® - Pharmacia & Upjohn
Sulfonamide antibiotic and antiinflammatory
Used to treat Ulcerative colitis, rheumatoid arthritis

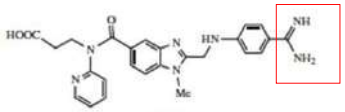
+



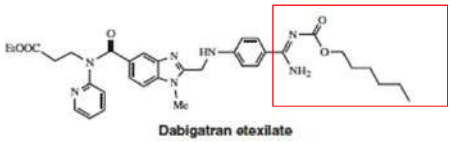
5-aminosalicylic acid

Amidines

- Amidines also can be acylated to give orally active prodrugs. For example, **dabigatran** etexilate an orally active antithrombotic and anticoagulant prodrug of the thrombin inhibitor **dabigatran** which must be administered intravenously.



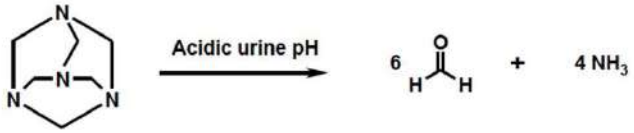
Dabigatran



Dabigatran etexilate

Carbonyl prodrugs

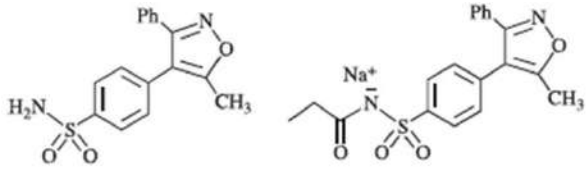
- Aldehyde and ketone derivatives
- Little clinical utility with one exception



- Methenamine hippurate
- Hiprex® - Hoechst Marion Roussel
- Urex ® - 3M Pharmaceuticals plus a number of combos
  - Used for prophylaxis or suppression/elimination of frequent UTI

Sulfonamides

- Just like amines, sulfonamides can be acylated, but this generates an acidic proton, which makes these compounds amenable to conversion to water-soluble sodium salts.
- Second-generation COX-2 inhibitor valdecoxib has been converted to parecoxib sodium, an injectable analgesic drug.

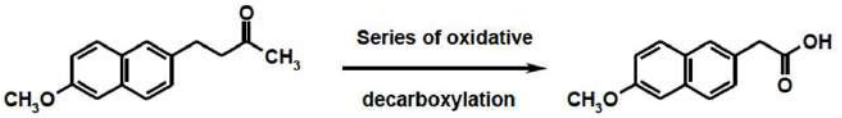


Valdecoxib

Parecoxib sodium

Bioprecursor Prodrugs

- Do NOT contain a carrier or promoiety
  - Contain latent functionality
  - Metabolically or chemically transformed into an active drug
  - Types of activation at are predictable
    - Oxidative (most common method)
    - Reductive
    - Phosphorylation (antiviral agents)
  - Oxidation Example – Nabumetone – Relafen® – Smith Kline Beecham



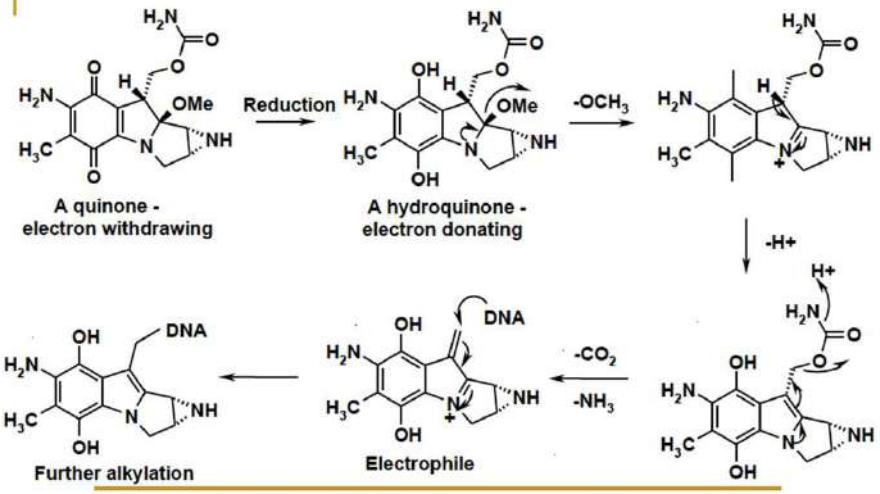
Non-steroidal antiinflammatory

Use: Arthritis

Active form of the drug that inhibits Prostaglandin biosynthesis by cyclooxygenase

Bioprecursor Prodrugs

Reduction example - Mitomycin C - Mutamycin® - Bristol Myers
Adenocarcinoma of the stomach and pancreas



A quinone - electron withdrawing

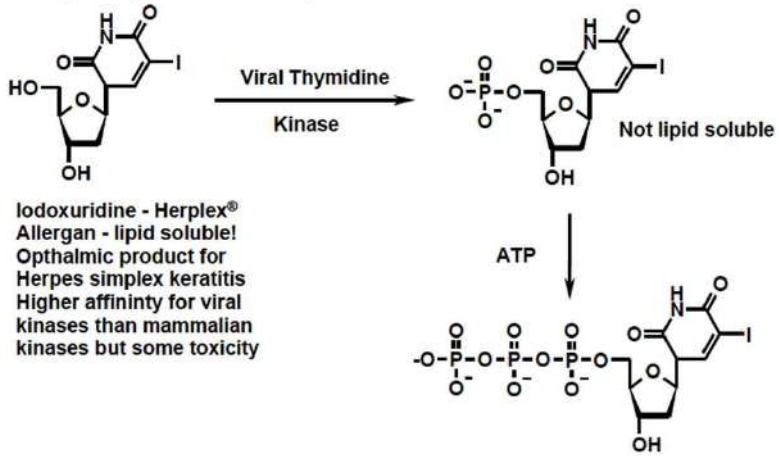
A hydroquinone - electron donating

Electrophile

Further alkylation

Bioprecursor Prodrugs

Phosphorylation example –



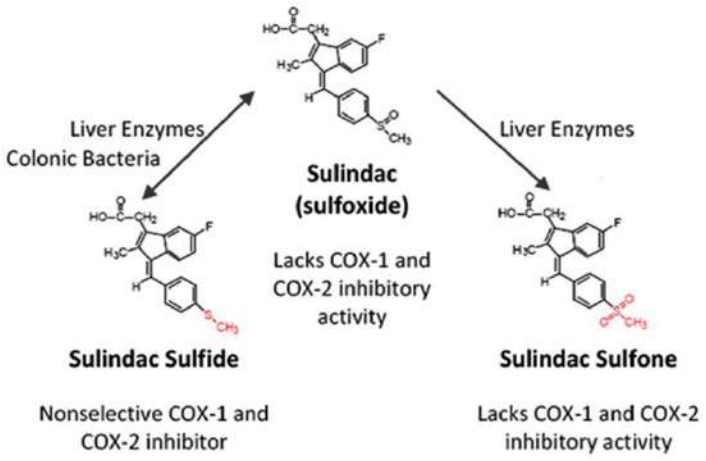
Iodoxuridine - Herplex®
Allergan - lipid soluble!
Opthalmic product for
Herpes simplex keratitis
Higher affininty for viral
kinases than mammalian
kinases but some toxicity

TWO mechanisms of action: 1. Inhibits DNA polymerase 2. Incorporated into DNA affording incorrect base pairing and template activity

The problems associated with bioprecursor prodrugs approach:

- Participation of alternate metabolic paths that may inactivate the compound. In this case, after absorption of sulindac, irreversible metabolic oxidation of the sulfoxide to the sulfone can also occur to give an inactive compound.
- Although seen less frequently, some prodrugs rely on chemical mechanisms for conversion of the prodrug to its active form.
- Metabolite generated after chemical hydrolysis some times toxic (it must be nontoxic and easily removed after it has performed its function).

Sulindac

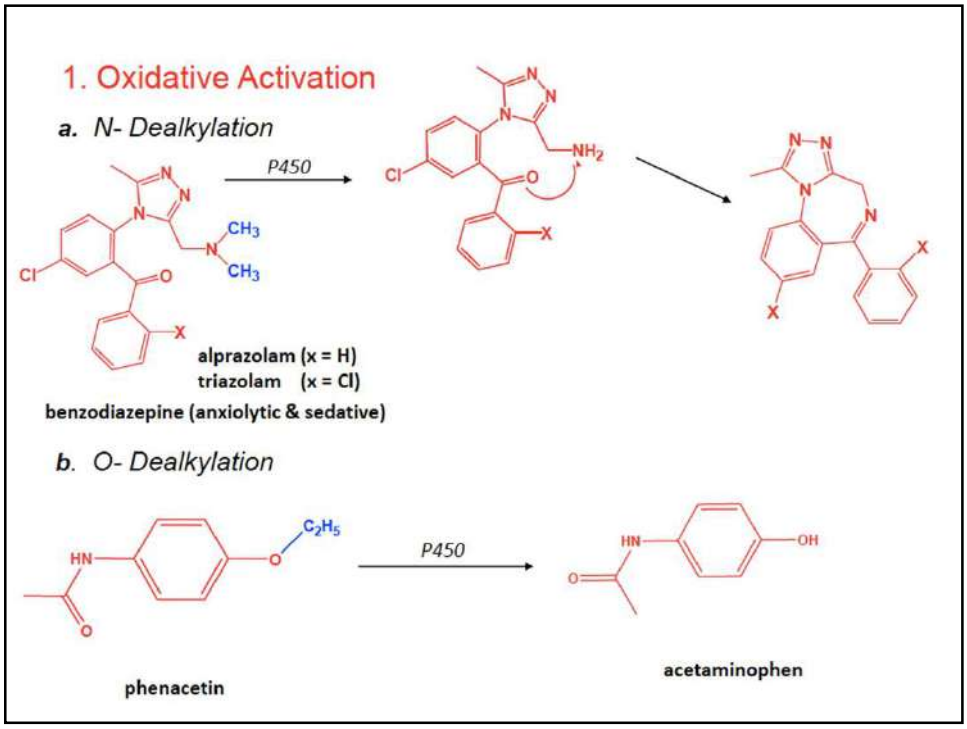


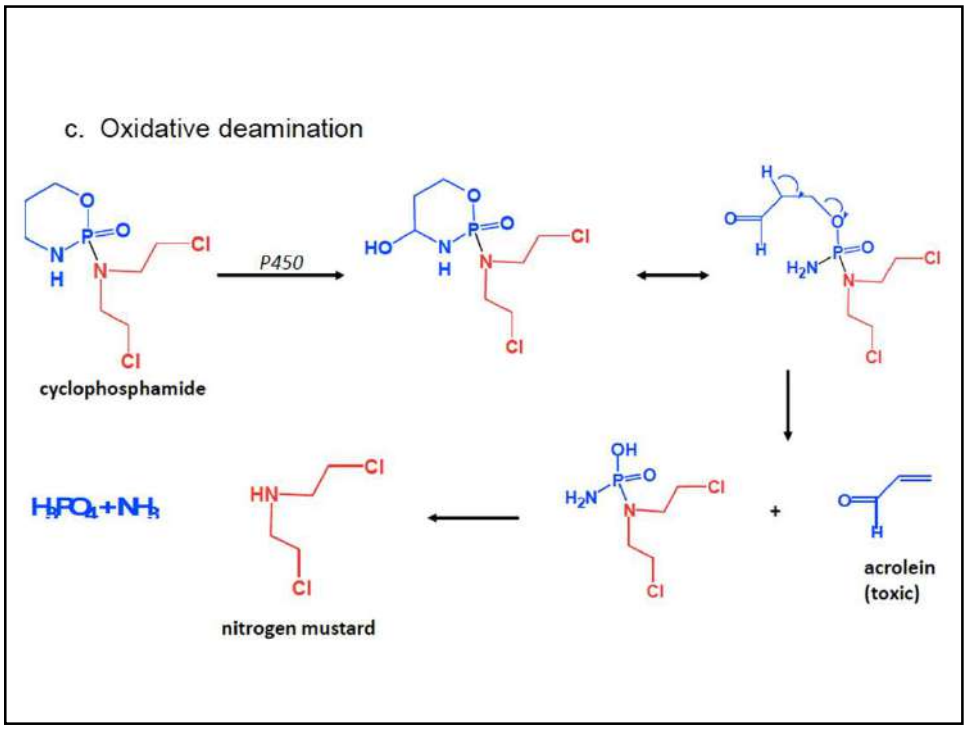
BIOPRECURSOR PRODRUGS

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

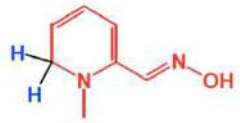
Metabolic Activation of Bioprecursor Prodrugs:

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
P450
alprazolam (x = H)
triazolam (x = Cl)
benzodiazepine (anxiolytic & sedative)
b. O- Dealkylation
P450
phenacetin
acetaminophen


c. Oxidative deamination
P450
cyclophosphamide
acrolein
(toxic)
nitrogen mustard

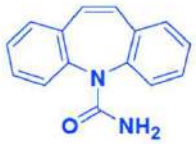
d. N-Oxidation



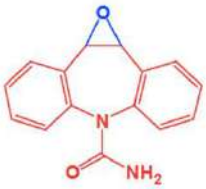
5, 6 dihydropyridine
bioprecursor

pralidoxime
(acetylcholine esterase activator)

e. Epoxidation



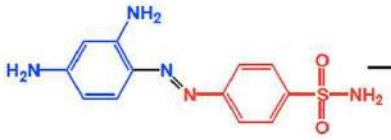
carbamazepine (anticonvulsant)



carbamazepine 10, 11-oxide

2. Reductive Activation

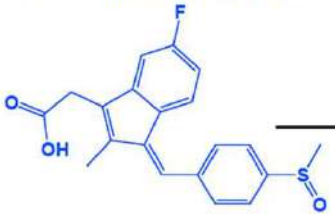
a. Azo reduction



prontosil

sulfanilamide

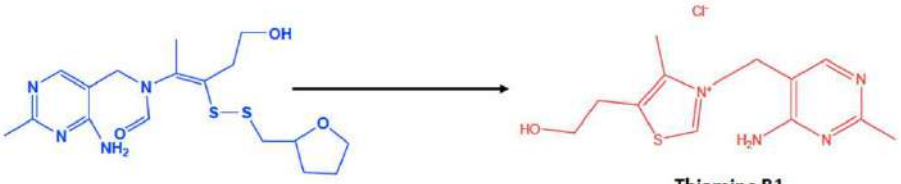
b. Sulfoxide reduction



Sulindac (NSAID)

sulfide derivative

c. Disulfide reduction

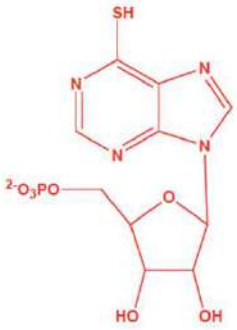


thiamine tetrahydrofurfuryl disulfide

Thiamine B1

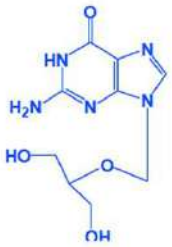
3. Nucleotide Activation

6-mercaptopurine

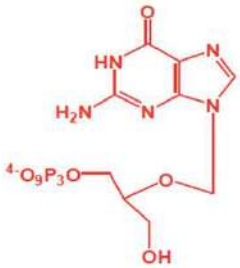


inhibits purine synthesis

4. Phosphorylation Activation

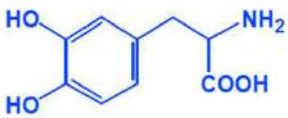


ganciclovir

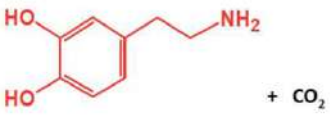


substrate for DNA polymerase

5. Decarboxylation Activation



levodopa



dopamine

Chemical Delivery Systems

- We have already seen 2 examples of this:
  - Sulfasalazine – an azo compound
  - Methenamine – An urinary antibacterial agent
- Requirements
  - Prodrug reach the site of action in high concentrations
  - Knowledge of high metabolism at site
  - Other factors
    - Extent of organ or site perfusion
    - Information on the rate of prodrug conversion to the active form at both target and non-target sites
    - Rate of input/output of prodrug from the target site
- Limit side effects and increase effectiveness

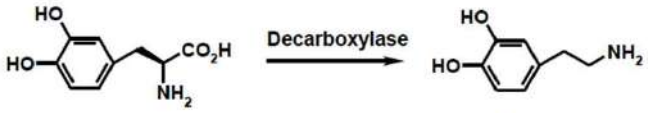
Chemical Delivery Systems

- The ideal situation:
  - Prodrug readily transported to the site of action
  - Prodrug is rapidly absorbed at the site
  - Selective and rapid conversion to the active drug
  - Kidney and Liver are easy targets due to high perfusion and high metabolic rates
    - Other tissue sites can be problematic for the same reasons
  - Drug migrate slowly (site of action to a site of excretion)
  - Ideal situation is VERY complex to achieve
- Example: Methenamine
  - the lower the pH, the faster the rate of formaldehyde formed
  - blood pH 7.4 therefore, little formaldehyde formed

Chemical Delivery Systems

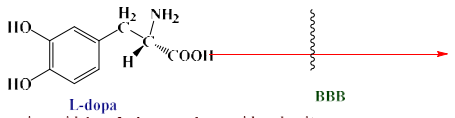
- Example: Cancer Chemotherapy
  - Tumor cells have a much higher growth fraction
  - This translates into higher enzymatic activity that can be exploited
  - Target a prodrug to these sites and exploit higher enzyme activity

- Example: L-Dopa or Levodopa – Anti-Parkinsonism agent
  - Larodopa® – Roche and Dopar® - Procter & Gamble



Dopamine

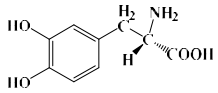
  - Brain has a specific transport system for L-amino acids
  - Dopamine does not cross the blood brain barrier efficiently, is rapidly metabolized by oxidative deamination, and can cause peripheral side effects



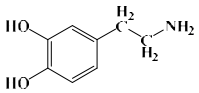
L-dopa

BBB

The amino acid drug L-dopa can be considered a site specific chemical delivery system that delivers the drug dopamine to the brain. The brain has an active transport system that operates to incorporate L amino acids into the central nervous system (CNS), and L-dopa is transported into the brain in this manner. Once across the Blood-brain barrier, L-dopa undergoes decarboxylation to yield the active metabolite, dopamine.



L-aromatic Amino acid Decarboxylase

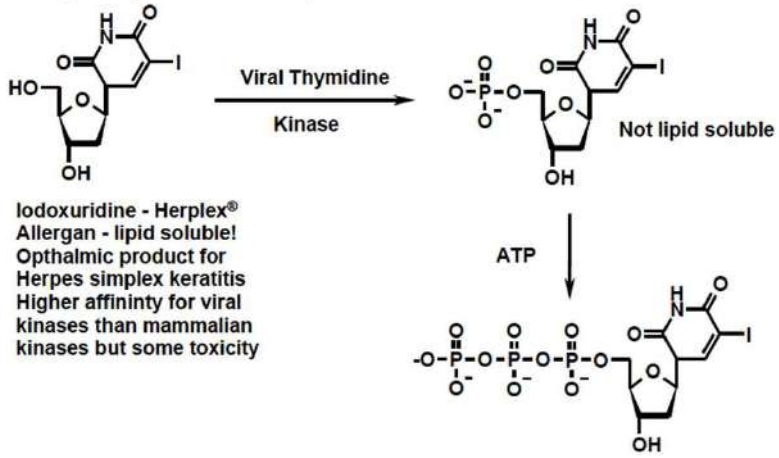


Dopamine

Direct systemic administration of Dopamine does not produce Significant levels of the drug in the brain because of its high polarity and poor membrane permeability as well as its facile metabolic degradation by oxidative deamination.

Chemical drug delivery systems

Phosphorylation example –



Iodoxuridine - Herplex®
Allergan - lipid soluble!
Opthalmic product for
Herpes simplex keratitis
Higher affininty for viral
kinases than mammalian
kinases but some toxicity

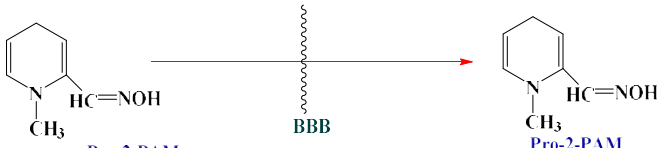
TWO mechanisms of action: 1. Inhibits DNA polymerase 2. Incorporated into DNA affording incorrect base pairing and template activity

Antiviral agent (Idoxuridine)

- These drugs serve as substrates for phosphorylating enzymes found in viruses, and the phosphorylated species is the active antiviral agent. The active phosphorylated species is incorporated into viral DNA, disrupting viral replication and, thus, producing the antiviral effect. These drugs do not undergo phosphorylation by mammalian cells, so the prodrug is specific for those sites where it serves as a substrate for phosphorylation enzymes.
- One of the requirements for site-specific chemical delivery was the proper input/output ratios for prodrug and active drug species at the target. The relative physicochemical properties of prodrug and its phosphorylated derivative suggest an appropriate input/output ratio for site specificity.
- The prodrug can readily penetrate the virus, and the increased polarity of the phosphorylated derivative would serve to retain that active species inside the virus. The combination of increased polarity and viral retention of the active phosphorylated species likely reduces any human toxicity that might be associated with this active species.

Chemical drug delivery systems

Pro 2-PAM is the prodrug form of 2-PAM, an important antidote for the phosphate and carbamate acetylcholinesterase inhibitors used in insecticides and nerve gases.

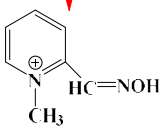


Pro-2-PAM

is a dihydropyridine derivative that undergoes metabolic and chemical oxidation to yield the active drug 2-PAM
The nonionic pro-2-PAM can easily cross the blood—brain barrier, and oxidation to 2-PAM within the brain essentially traps the active cationic drug species inside the brain.

Pro-2-PAM

Oxidation



2-PAM

the polar properties of 2-PAM because the presence of cationic species, prevent this drug from being absorbed following oral administration and restrict the drug from access to the brain, even after IV administration

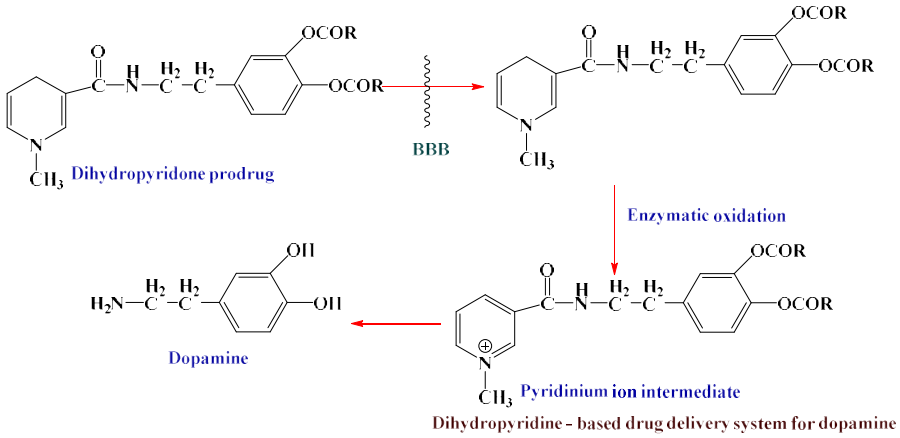
Dihdropyridine -prodrug of dopamine

The delivery of drugs across the blood—brain barrier has been a significant issue in the design of many therapeutic compounds. Only very lipophilic drugs can cross into the brain without the aid of some active uptake process, such as the one that operates to incorporate essential amino acids into the CNS. The facile oxidation of the **dihydropyridine** ring system has been extensively investigated as a general process for chemical delivery of a number of drugs to the CNS.

This process is a multistep procedure involving delivery of the drug—dihydropyridine derivative to the brain via facile diffusion across the blood—brain barrier, followed by oxidation to the quaternary pyridine cation, which is trapped in the brain. The drug is then released from
the pyridine cation by a second metabolic/chemical event.

Chemical drug delivery systems

Dihdropyridine -prodrug of dopamine



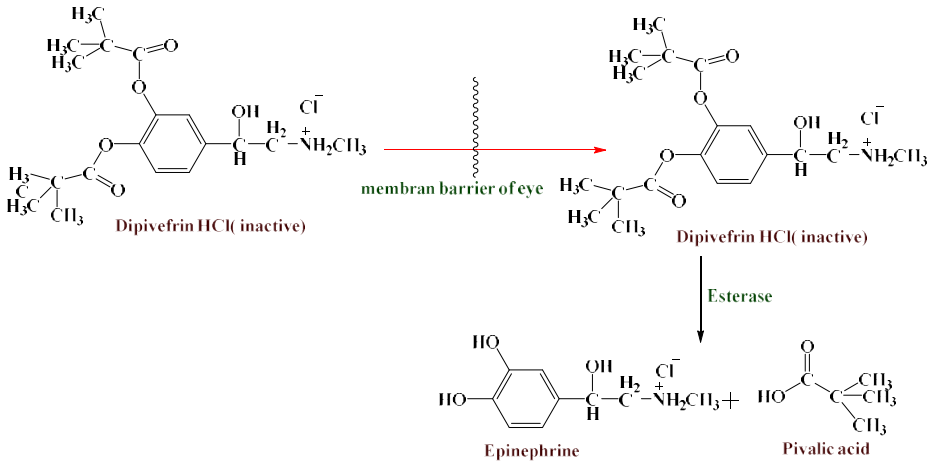
Dihydropyridine - based drug delivery system for dopamine

4. Human eye (Dipivefrin)

Lipophilic esters of epinephrine, such as the dipivaloyl ester of epinephrine show better corneal penetration following direct application to the eye than the more polar parent drug epinephrine.

The esterases necessary for the hydrolysis of the prodrug are readily available in the eye and skin. The more polar drug species, epinephrine is then localized within the lipophilic membrane barriers of the eye, and the drug remains available at the target site to produce its antiglaucoma effect.

Chemical drug delivery systems

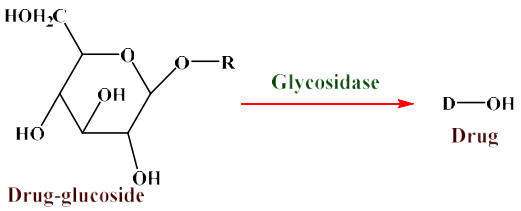


4. Colon and lower GI tract

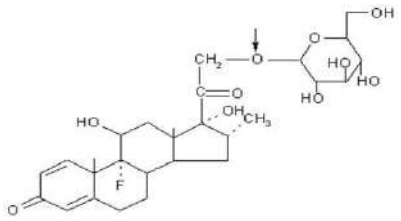
The delivery of drugs to the **colon** and **lower GI tract** has taken advantage of the unique enzymatic processes found in colon bacteria. The glycosidase activity of these bacteria allows hydrolysis of glycoside derivatives of drugs in the colon and provides higher concentrations of active drug.

A number of **steroid** drugs demonstrate increased effectiveness in the lower GI tract following administration as their glycoside derivatives. The polar glycoside derivatives of the steroids are not well absorbed into the bloodstream from the GI tract and remain available to serve as substrates for the bacteria that are found primarily in the human colon.

Chemical drug delivery systems



Activation of drug -glucoside by bacterial glycosidase



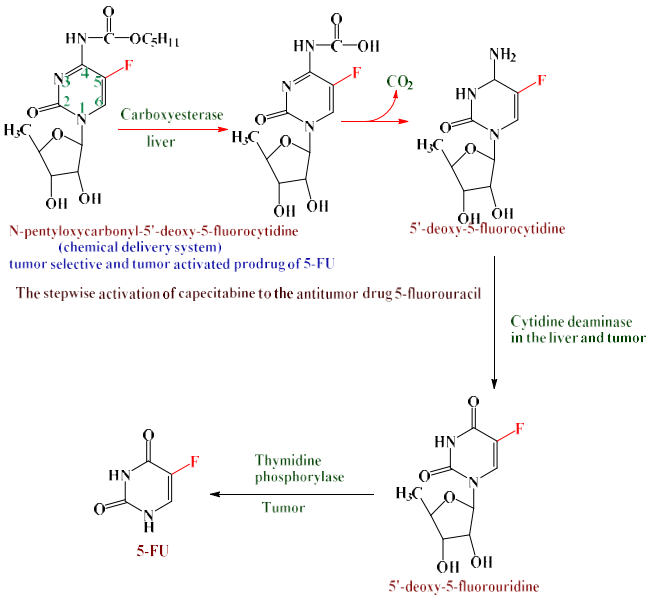
Dexamethasone-21-β-D-glucoside (Arrow shows site of action of glycosidase)

b. Antitumor agent (Capecitabine)

A number of prodrugs for cancer chemotherapy have been designed for selective delivery of active drug to tumor tissue, based on [1)] higher levels of activating enzyme in the tumor cell than in normal tissue.[2)] Many enzymatic systems show higher activity in tumor cells than in normal tissue because of the higher growth rates associated with tumor tissue. Peptidases and proteolytic enzymes are among those systems showing higher activity in and near tumor cells.

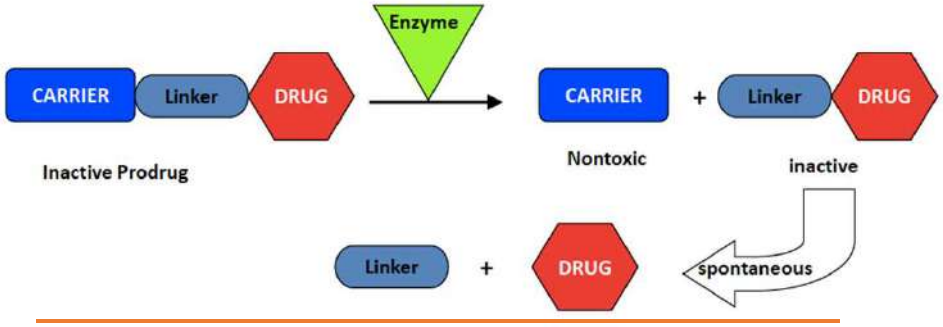
Capecitabine is well absorbed orally and undergoes three activation steps resulting in high tumor concentrations of the active drug. It is first hydrolyzed by liver carboxylesterase, the resulting metabolite being a carbamic acid which spontaneously decarboxylates to 5-deoxy-5-fluorocytidine. The enzyme cytidine deaminase, which is present in the liver and tumors, then transforms 5-deoxy-5-fluorocytidine into 5-deoxy-5-fluorouridine. Transformation into 5-FU is catalyzed by thymidine phosphorylase and occurs selectively in tumor cells.

Chemical drug delivery systems



TRIPARTATE PRODRUGS

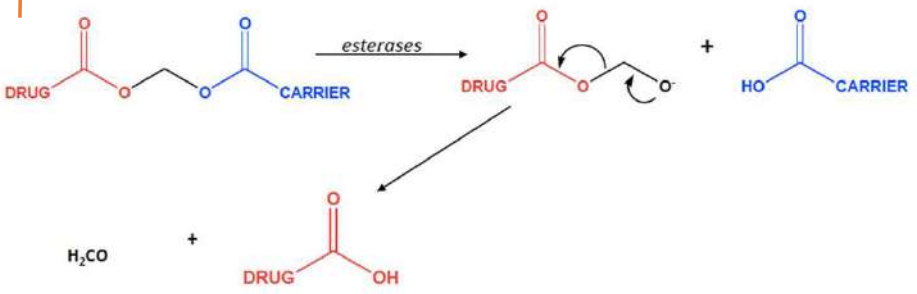
- The **carrier** is not linked directly to the **drug** but instead through a **linker**
- Allows for decreased steric hindrance during enzymatic cleavage that may occur with bipartate prodrugs
- **Carrier** is enzymatically cleaved from **Linker**
- **Linker** spontaneously cleaves from **Drug**



Tripartate Drugs (Self-immolative Prodrugs)

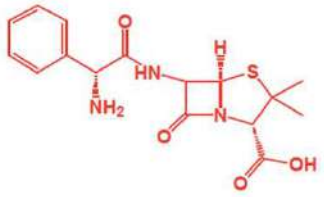
- A bipartate prodrug may be ineffective because the linkage is too labile or too stable.
- In a tripartate prodrug, the carrier is not attached to the drug; rather, to the linker.
- Therefore, more flexibility in the types of functional groups and linkages that can be used, and it moves the cleavage site away from the carrier.
- The linker-drug bond must cleave spontaneously (i.e., be self-immolative) after the carrier-linker bond is broken.

Tripartate Drugs (Self-immolative Prodrugs)

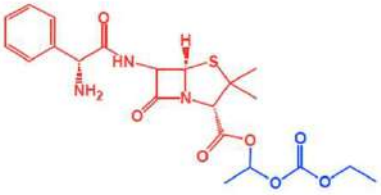


Examples of Carrier-linked Tripartate Prodrugs

a.



ampicillin (antibiotic)

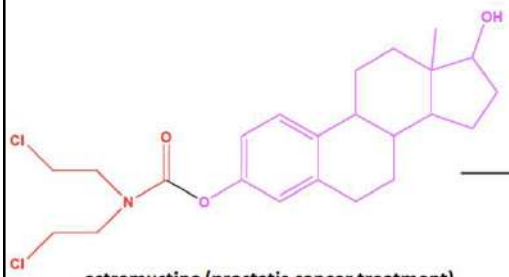


bacampicillin

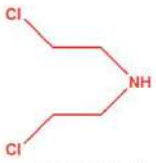
pivampicillin

MUTUAL PRODRUGS

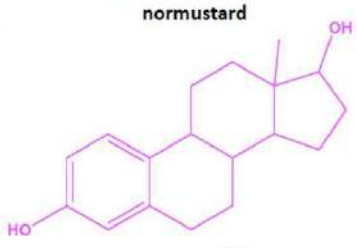
- Useful when 2 synergistic drugs need to be administered at the same site at the same time
- Mutual prodrug is bipartate or tripartate where a synergistic drug acts as the carrier



estramustine (prostatic cancer treatment)



normustard



estradiol

Macromolecular Drug Delivery

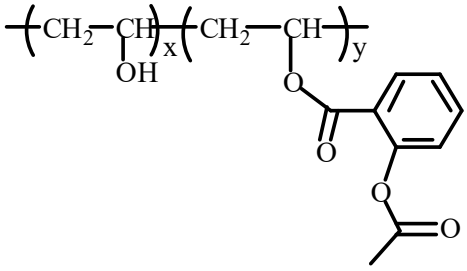
- To address these shortcomings, macromolecular drug delivery systems have been developed.
- A bipartate carrier-linked prodrug in which the drug is attached to a macromolecule, such as a synthetic polymer, protein, lectin, antibody, cell, etc.
- Absorption/distribution depends on the physicochemical properties of macromolecular carrier, not of the drug. Therefore, attain better targeting.
- Minimize interactions with other tissues or enzymes. Fewer metabolic problems; increased therapeutic index.

Disadvantages of Macromolecular Delivery Systems

- Macromolecules may not be well absorbed
- Alternative means of administration may be needed (injection)
- Immunogenicity problems

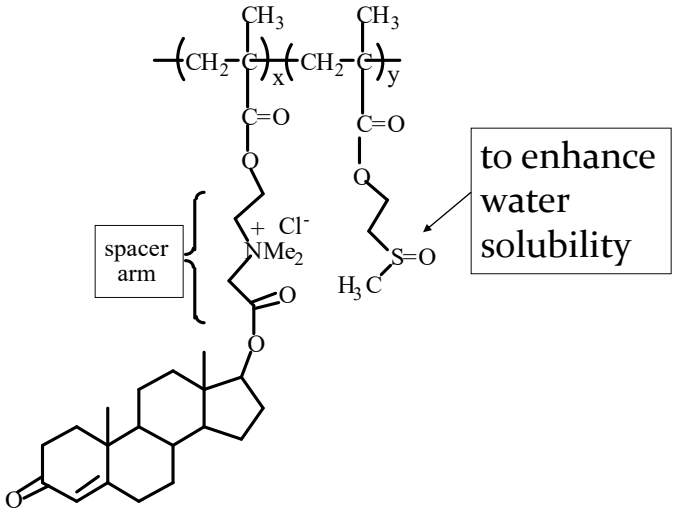
Macromolecular Drug Carriers

Synthetic polymers



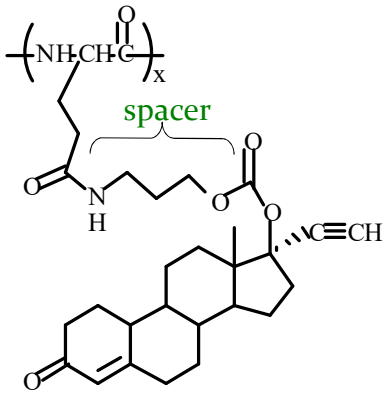
Aspirin linked to poly(vinyl alcohol) has about the same potency as aspirin, but less toxic.

A spacer arm was added, and it was as effective as testosterone.



Poly(α-Amino Acid) Carriers

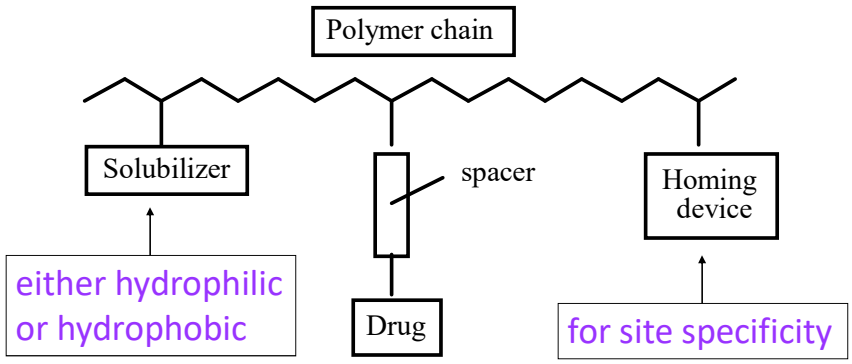
poly(*L*-glutamine)



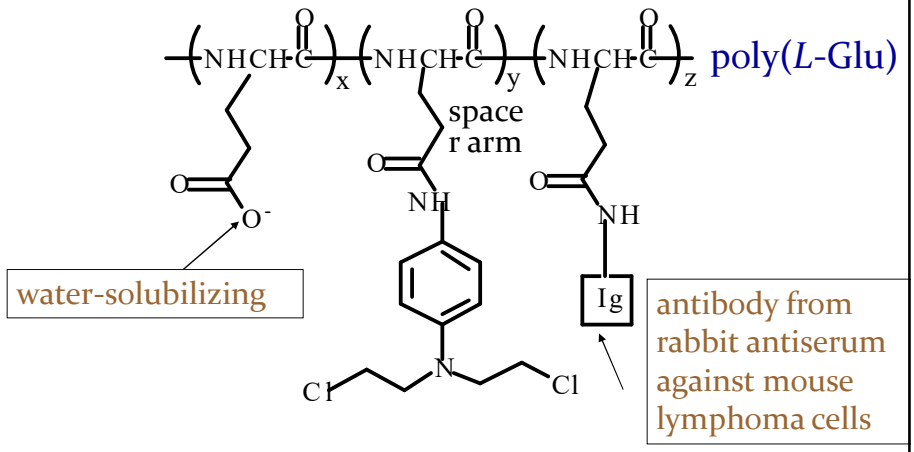
norethindrone - contraceptive

Slow release over nine months in rats

General Site-Specific Macromolecular Drug Delivery System



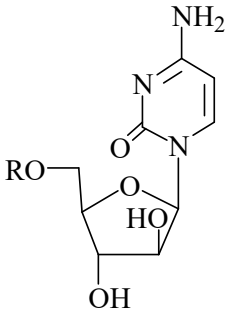
Site-Specific Delivery of a Nitrogen Mustard



- All 5 mice tested were alive and tumor free after 60 days (all controls died).
- Also, therapeutic index greatly enhanced (40 fold).

Tumor Cell Selectivity

- Drug attached to albumin (R = albumin)
- Tumor cells take up proteins rapidly. Proteins broken down inside cells, releasing the drug.
- Shown to inhibit growth of *Ectomelia* virus in mouse liver, whereas free inhibitor did not.



cytosine arabinoside (R = H)