Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 1

Prodrug - a pharmacologically inactive compound that is converted to an active drug by a metabolic or chemical biotransformation

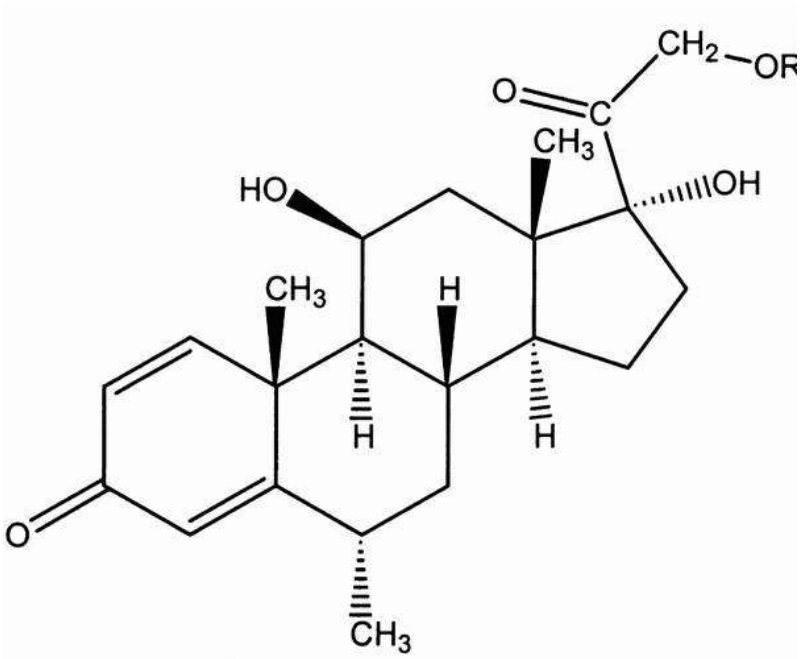
Ideally, conversion occurs as soon as the desired goal for designing the prodrug is achieved.

Prodrugs and drugs are opposite:

- a prodrug is inactive - requires metabolism to give active form
- a drug is active - uses metabolism to promote excretion

Utility of Prodrugs

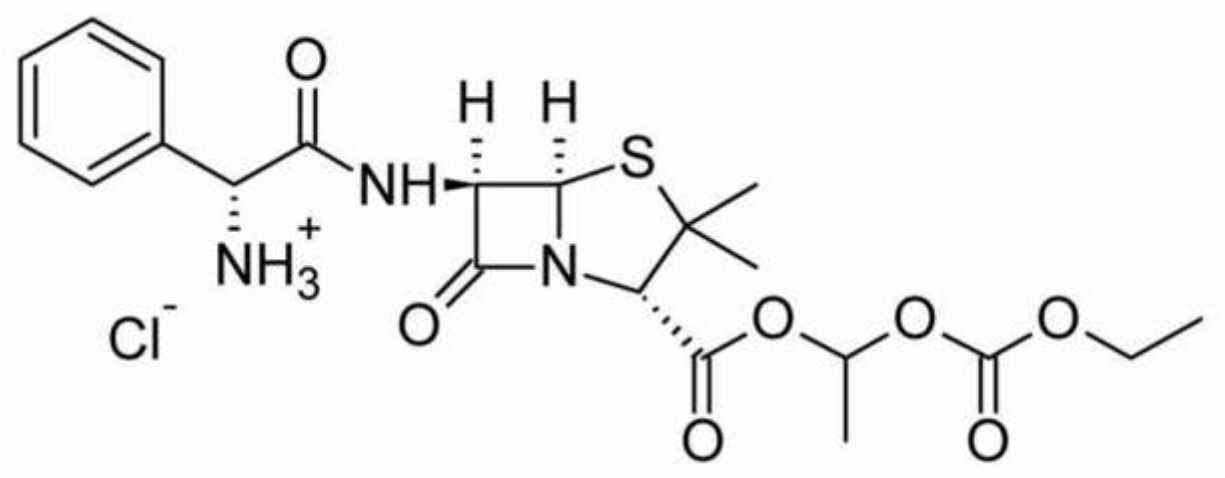
1. **Aqueous Solubility** - to increase water solubility so it can be injected in a small volume



Methylprednisolone: R = H

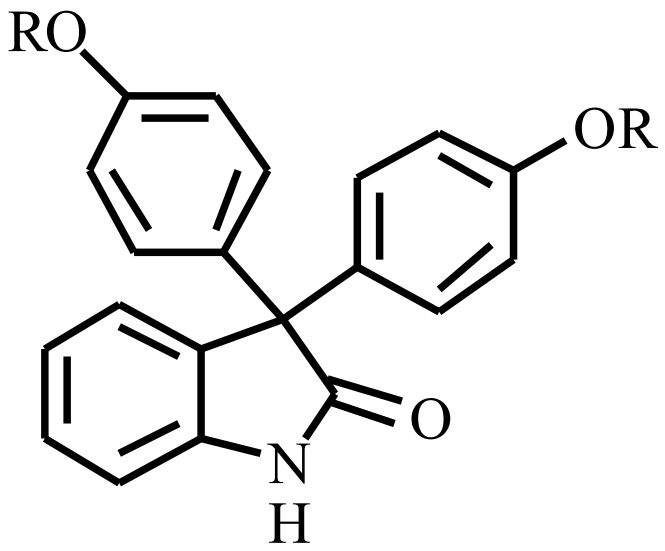
Methylprednisolone Sodium Succinate: R = $C(=O)CH_2CH_2COO^-$ Na^+

2. **Absorption and Distribution** - to increase lipid solubility to penetrate membranes for better absorption



Ampicillin double ester

3. **Site Specificity** - to target a particular organ or tissue if a high concentration of certain enzymes is at a particular site or append something that directs the drug to a particular site---



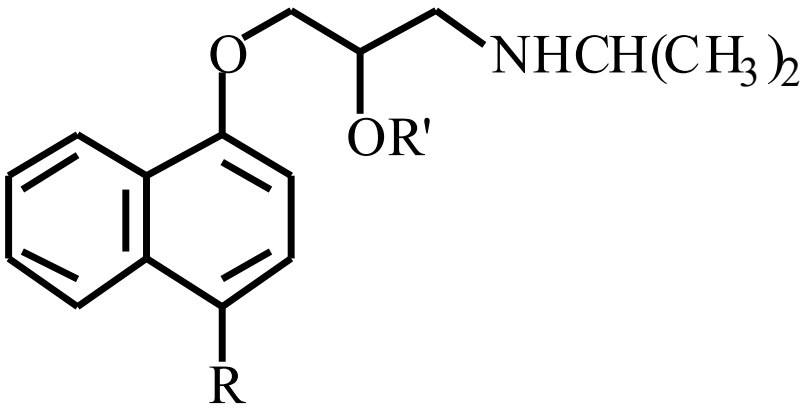
oxyphenisatin (R = H) (administer rectally)

8.16

prodrug R = Acetyl (administer orally)

hydrolyzed in intestines

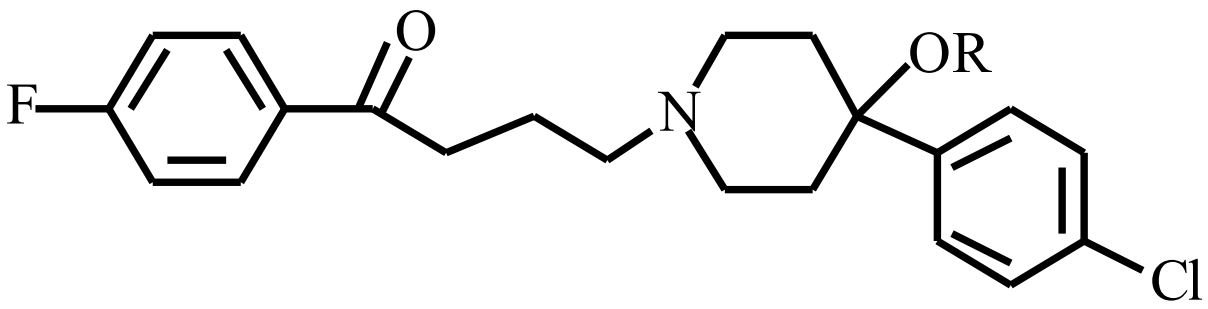
4. **Instability** - to prevent rapid metabolism; avoid first-pass effect



propanolol (R = R' = H)
8.22

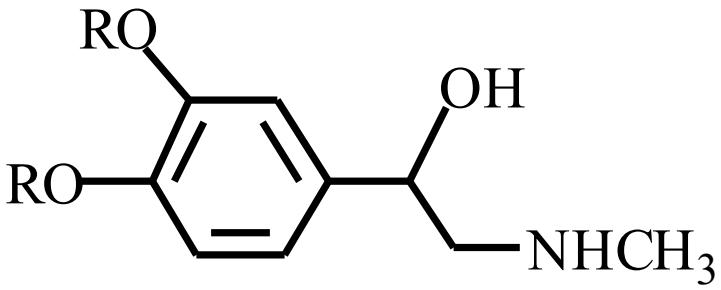
prodrug R' = 

5. **Prolonged Release** - to attain a slow, steady release of the drug



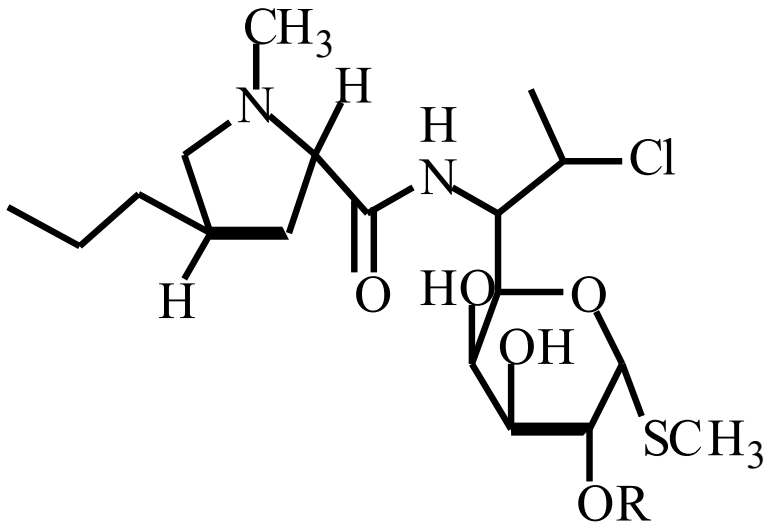
haloperidol (R = H)
haloperidol decanoate (R = $CO(CH_2)_8CH_3$)
8.24

6. **Toxicity** - to make less toxic until it reaches the site of action



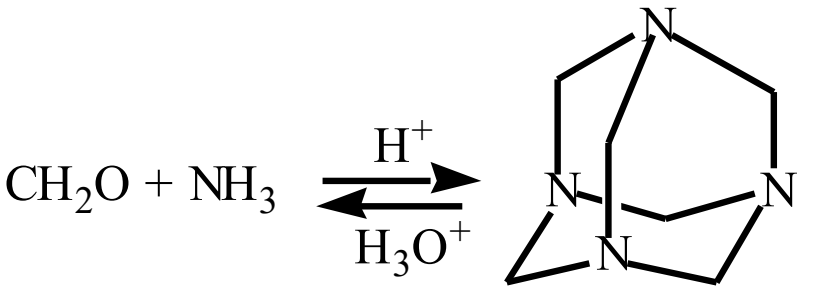
dipivefrin (R = Me_3CCO)
epinephrine (R = H)
8.15

7. **Poor Patient Acceptability** - to remove an unpleasant taste or odor; gastric irritation



clindomycin (R = H)
clindomycin phosphate (R = PO_3H_2)
clindomycin palmitate (R = $O(CH_2)_{14}CH_3$)
8.28

8. **Formulation Problems** - to convert a drug that is a gas or volatile liquid into a solid



methenamine
8.30

Types of Prodrugs

Drug Latentiation - rational prodrug design

I. Carrier-linked prodrug

A compound that contains an active drug linked to a carrier group that is removed enzymatically or chemically

A. **bipartate** - comprised of one carrier attached to drug directly

B. **tripartate** - carrier connected to a linker that is connected to drug

C. **mutual** - two, usually synergistic, drugs attached to each other(directly or through linker)

II. Bioprecursor prodrug

A compound metabolized by molecular modification into a new compound, which is a drug or is metabolized further to a drug - not just simple cleavage of a group from the prodrug—e.g., amine getting oxidized to CO2H, to afford the active.

A. $RCO_2H \xrightarrow[\substack{HCl\\ \Delta}]{EtOH} RCO_2Et \xrightarrow[\text{on R}]{\text{reaction}} R'CO_2Et \xrightarrow[\Delta]{H_3O^+} R'CO_2H$

analogous to carrier-linked

B. $RCH{=}CH_2 \xrightarrow[\text{on R}]{\text{reaction}} R'CH{=}CH_2 \xrightarrow[2.\ H_2O_2]{1.\ O_3} R'CO_2H$

analogous to bioprecursor

Prodrugs and Drug Delivery Systems

Assist.Prof.Dr. Mohammed Hassan

Lecture 2

Steps in Prodrug Design

1-Identification of drug delivery problem

2-Identification of desired physicochemical properties

3-Selection of transport moiety (carrier moiety) which will give prodrug desired transport properties be readily cleaved in the desired biological compartment

Prodrug Derivative Types

-Small molecule

Prodrug has MW in 200-500 g/mole range

Called a low molecular weight prodrug

-Macromolecule

conjugate drug reversibly to biomolecule

antibody

hormone

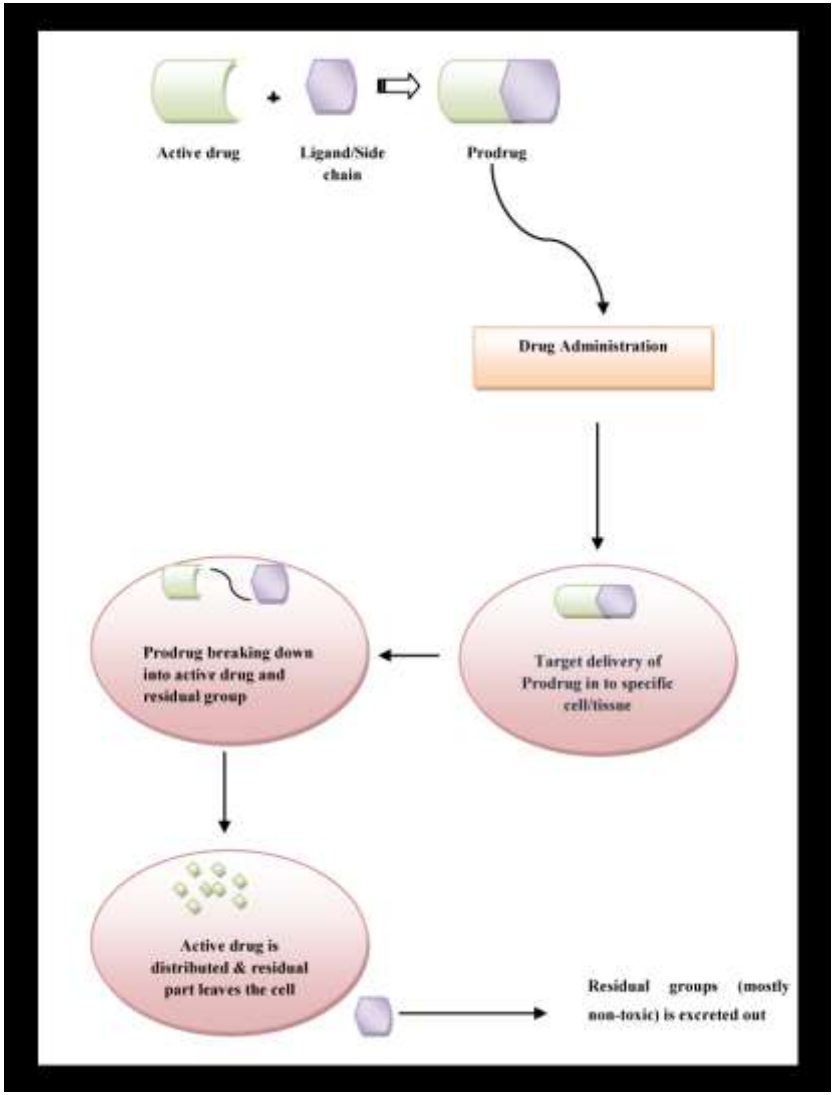
polymer

Ideal Drug Carriers

1. Protect the drug until it reaches the site of action
2. Localize the drug at the site of action
3. Allow for release of drug
4. Minimize host toxicity
5. Are biodegradable, inert, and nonimmunogenic
6. Are easily prepared and inexpensive
7. Are stable in the dosage form

General Mechanism of a Prodrug

1. The prodrug, containing its parent molecule and promoiety, is administered to the body.
2. It remains in that form while in the extracellular fluids and while crossing barriers to reach its target.
3. Once at the site of action, conversion of the prodrug will take place either by chemical or enzymatic reactions.
4. The prodrug is disassembled into its parent molecule (active drug) and the promoiety.
5. The parent molecule releases the active drug particles and the promoiety leaves the cell or tissue and is excreted.



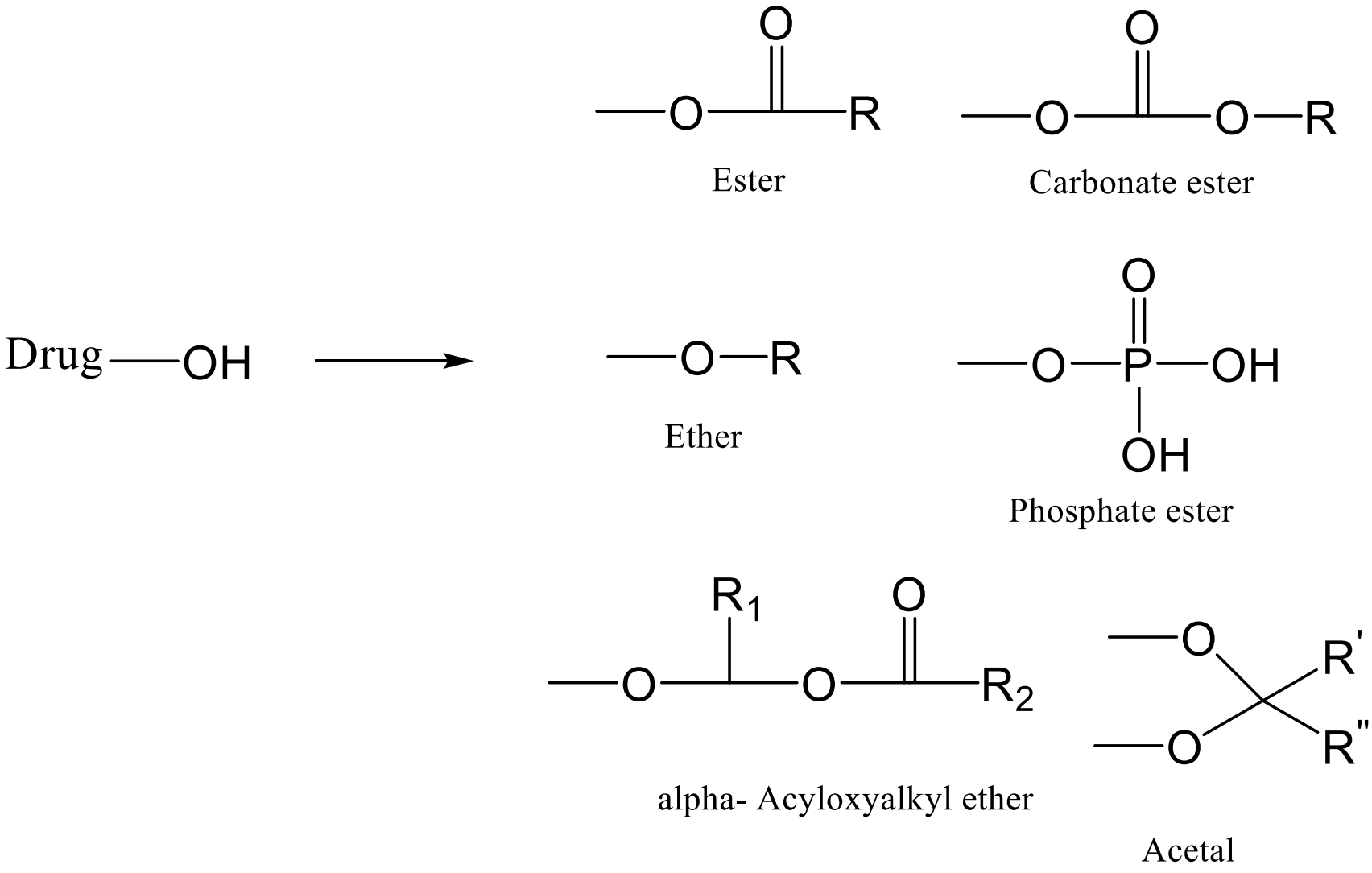
Carrier Linkages for Various Functional Groups

Alcohols, Carboxylic Acids, and Related Groups

Most common prodrug form is an ester

- esterases are ubiquitous
- can prepare esters with any degree of hydrophilicity or lipophilicity
- ester stability can be controlled by appropriate electronic and steric manipulations

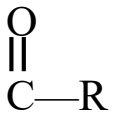
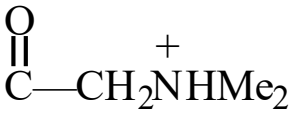
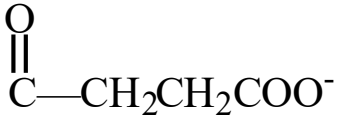
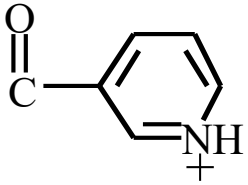
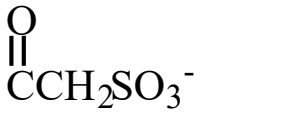
Prodrugs for Alcohol-Containing Drugs



Ester analogs as prodrugs can affect lipophilicity or hydrophilicity

Drug—OH ⟶ Drug—OX

alcohols

X	Effect on Water Solubility
	(R = aliphatic or aromatic) decreases (increases lipophilicity)
	increases (pK_a ~ 8)
	increases (pK_a ~ 5)
	increases (pK_a ~ 4)
$PO_3^=$ (phosphate ester)	increases (pK_a ~ 2 and ~ 6)
	increases (pK_a ~ 1)

Mechanisms of Prodrug Activation

Carrier-Linked Prodrugs

Most common activation reaction is hydrolysis.

Rate of hydrolysis can be modified by locating alkyl groups in area of the carbonyl group to Increase steric hindrance, and retard hydrolysis rate.

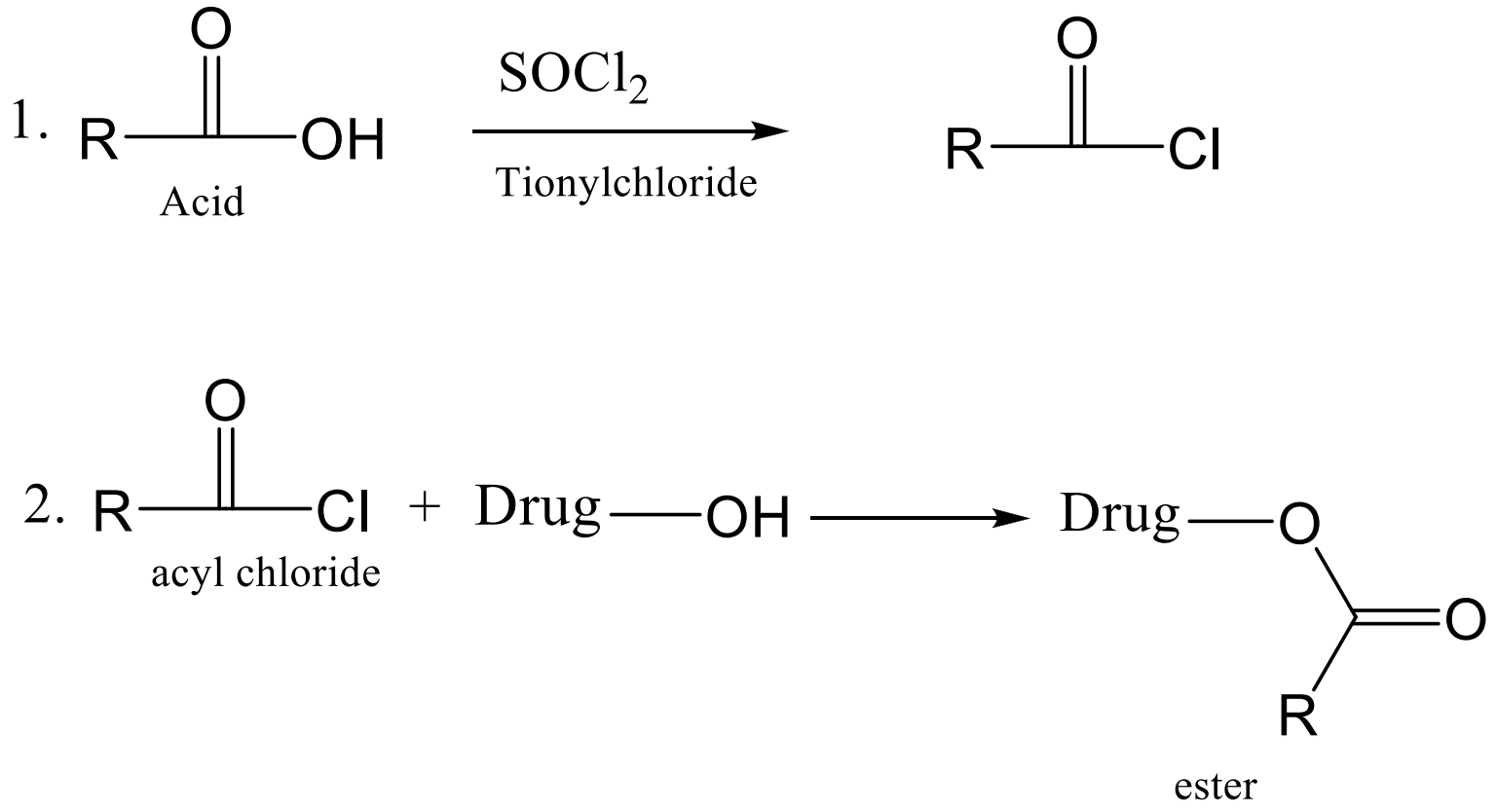
To accelerate hydrolysis rate:

- attach an electron-withdrawing group if a base hydrolysis mechanism is important
- attach an electron-donating group if an acid hydolysis mechanism is important

To slow down hydrolysis rate:

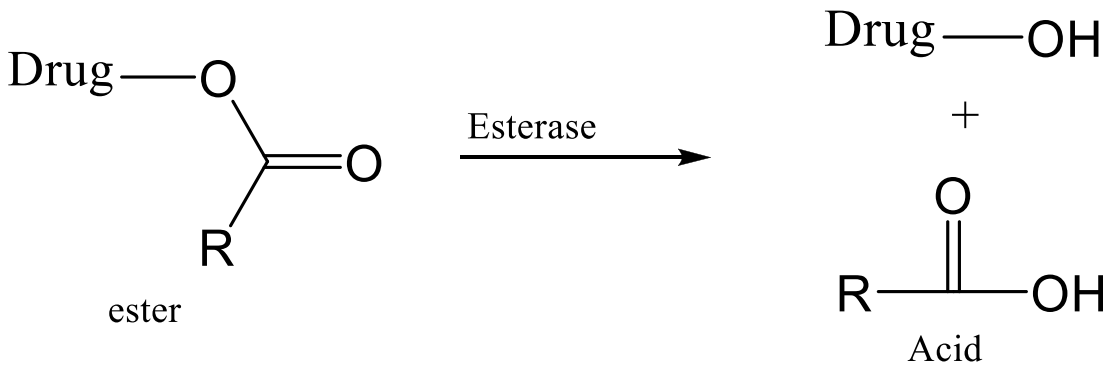
- make sterically-hindered esters
- make long-chain fatty acid esters

Synthesis of ester



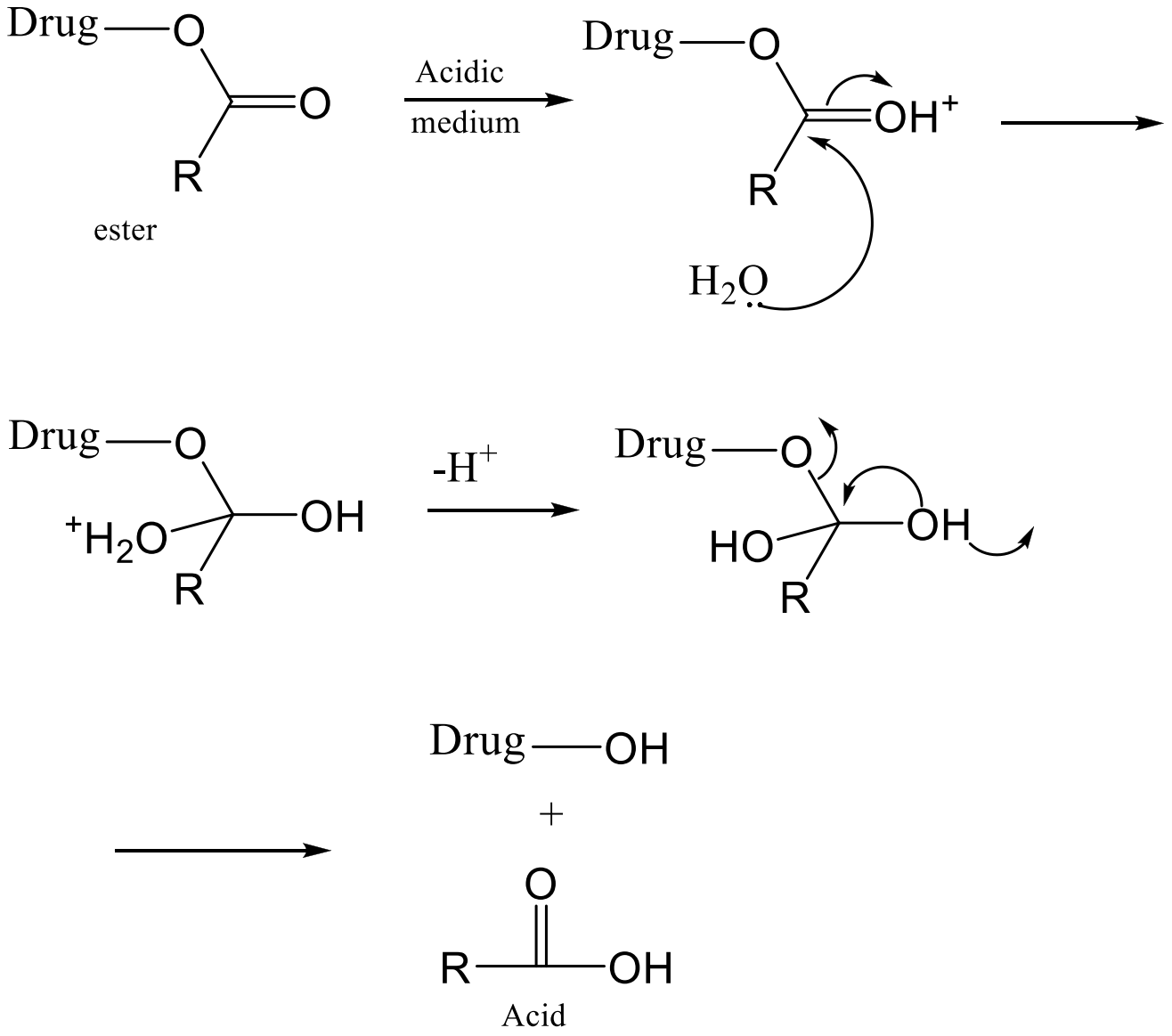
Ester hydrolysis

Enzymatic hydrolysis

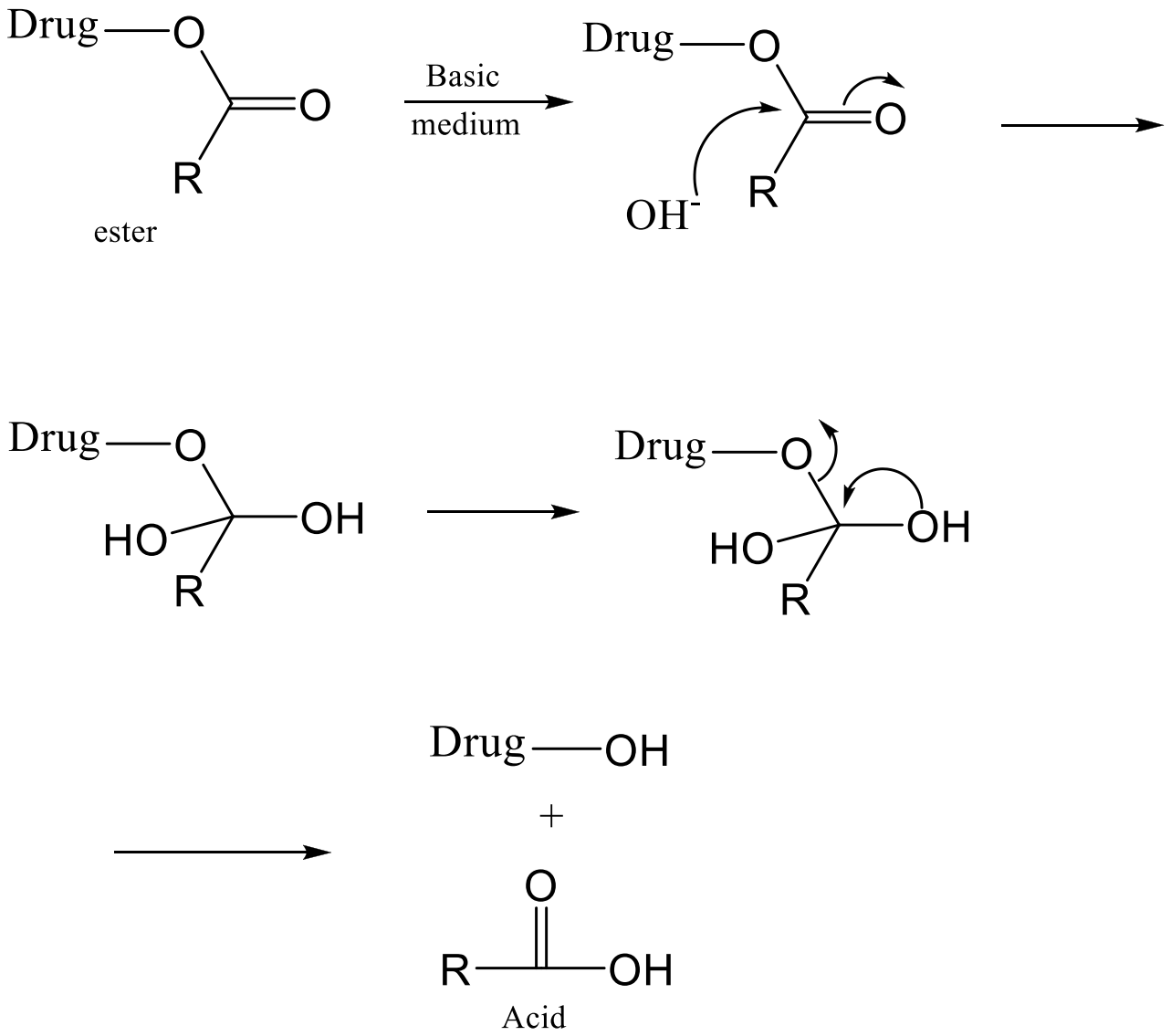


Chemical hydrolysis

Acidic hydrolysis



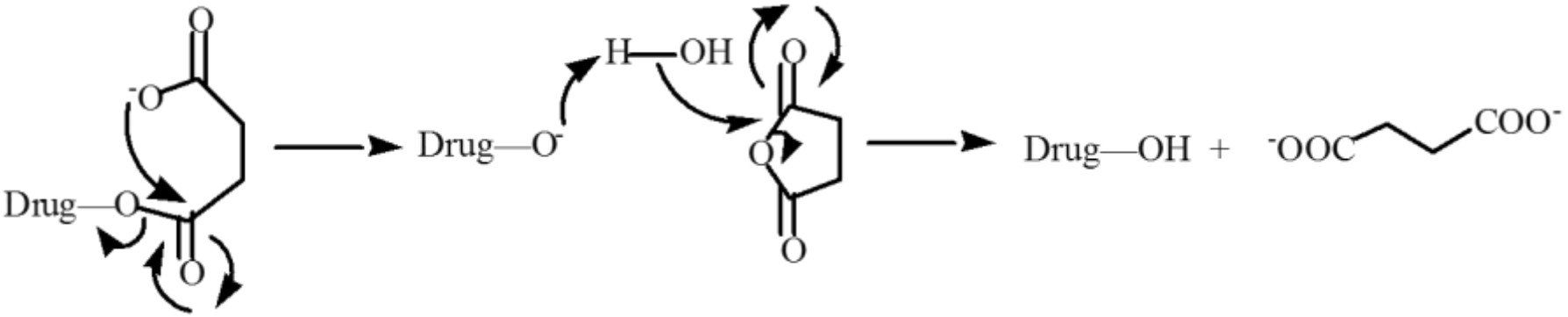
Basic hydrolysis

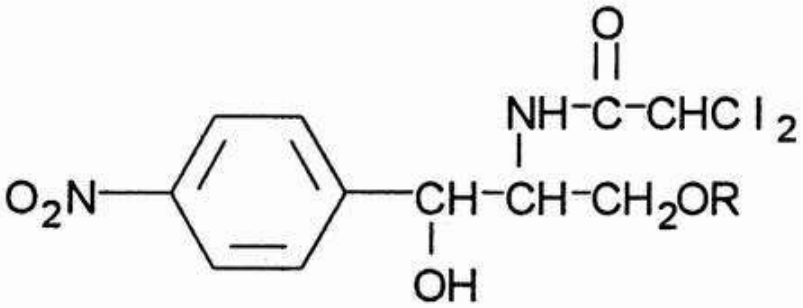


Interamolecular hydrolysis

Another Approach to Accelerate Hydrolysis

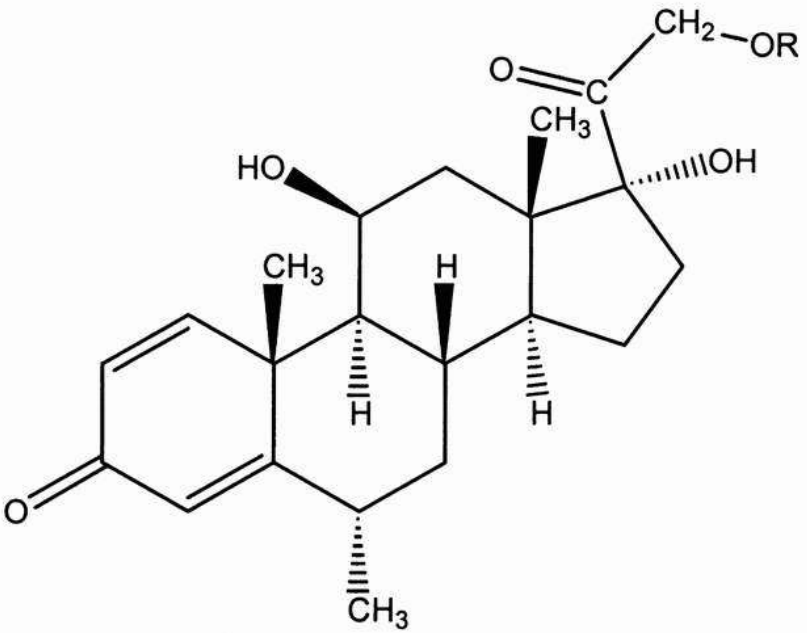
Intermolecular hydrolysis of succinate esters





Chloramphenicol: R = H

Chloramphenicol Palmitate: R = $CO(CH_2)_{14}CH_3$



Methylprednisolone: R = H

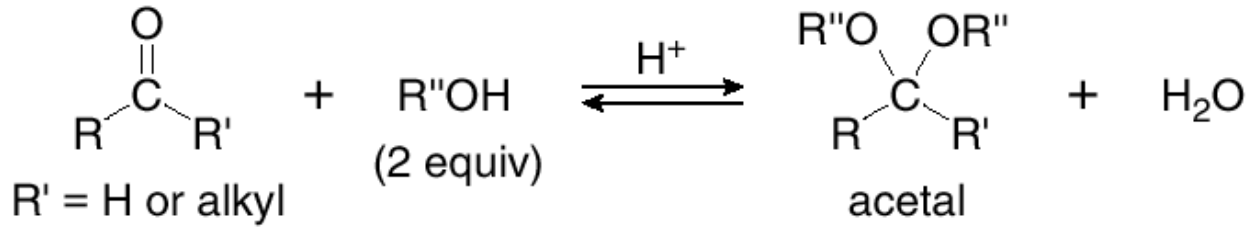
Methylprednisolone Acetate: R = $C(=O)CH_3$

Methylprednisolone Sodium Succinate: R = $C(=O)CH_2CH_2COO^-$ Na^+

Acetals or ketals can be made for rapid hydrolysis in the acidic medium of the GI tract.

Acetal and ketal Formation

Acetal formation

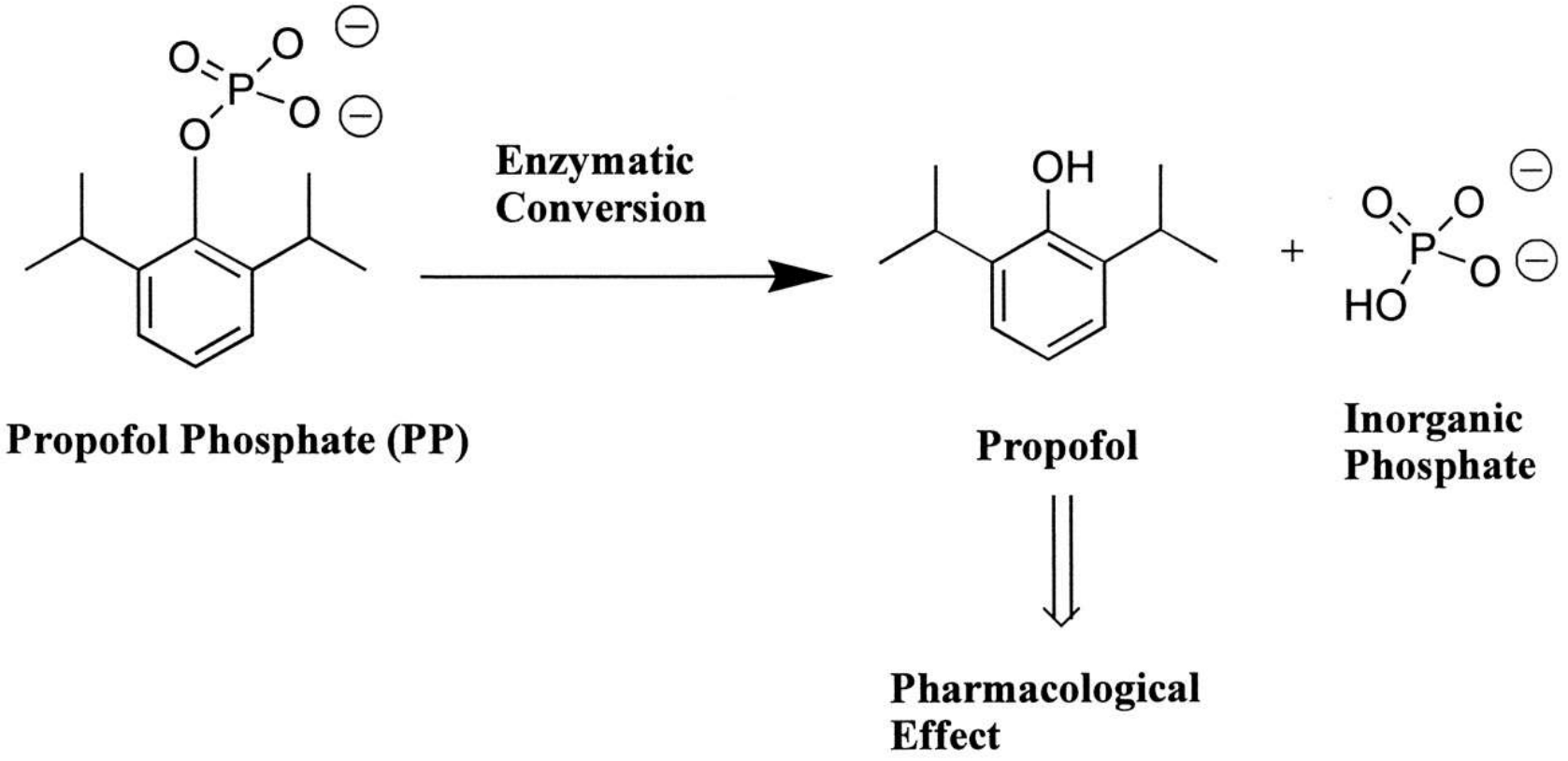


R= =Drug

Phosphate Esters

These ester use to increase water solubility of drug.

Propofol use for protection of neuronal cells from oxidative injury



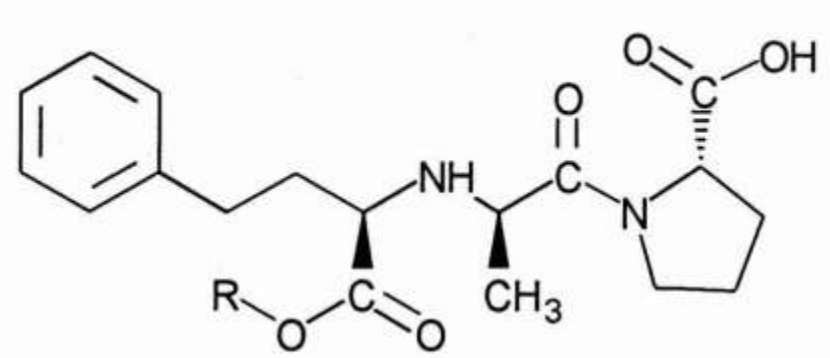
Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 3

Carboxylic Acid-Containing Groups

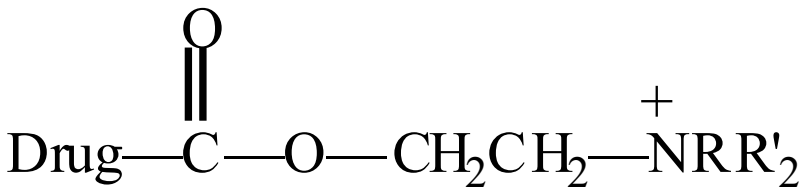
Esterify as with alcohols, by the reaction of the carboxylic group of drug with suitable alcohol.



Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

Maintaining Water Solubility of Carboxylate Prodrugs

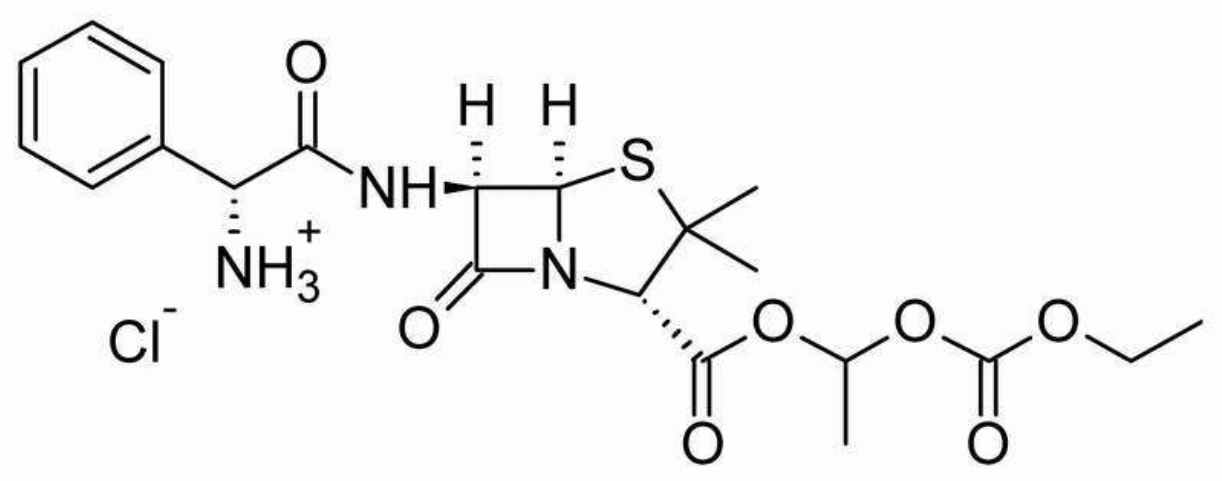


8.3

Can vary pK_a by appropriate choice of R and R′

α-Acyloxyalkyl esters (double ester)

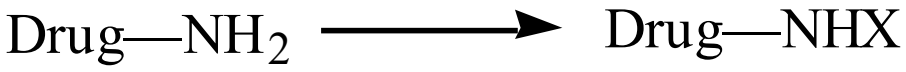
Ex.Bacampicillin Hydrochloride is acyloxyalkyl ester of ampicillin
This to improve oral bioavilability .



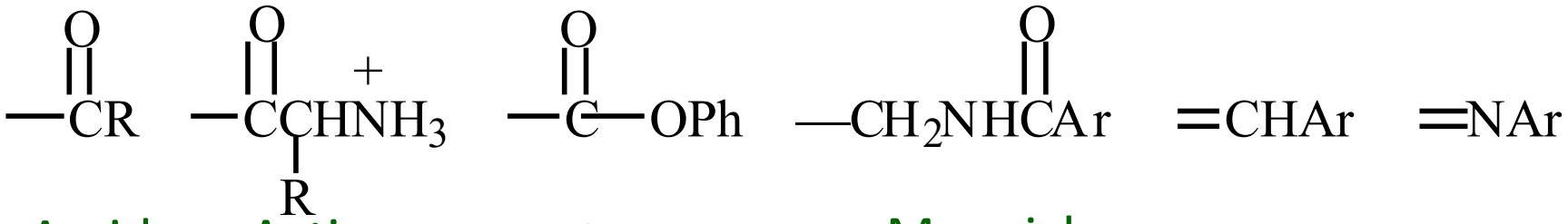
Amide derivative of carboxylic Acid

These derivative are commonly not used because of stability.

Amine Prodrugs



X



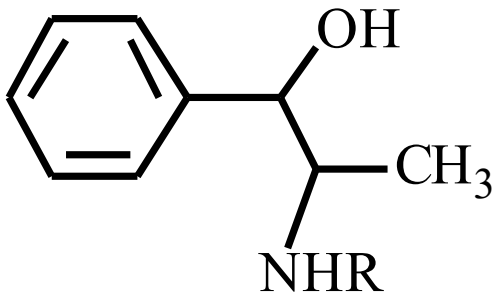
Amide | Active amide | Carbamate | Mannich base | Imine | Diazo

Amides are commonly not used because of stability

Activated amides (low basicity amines or amino acids) are effective

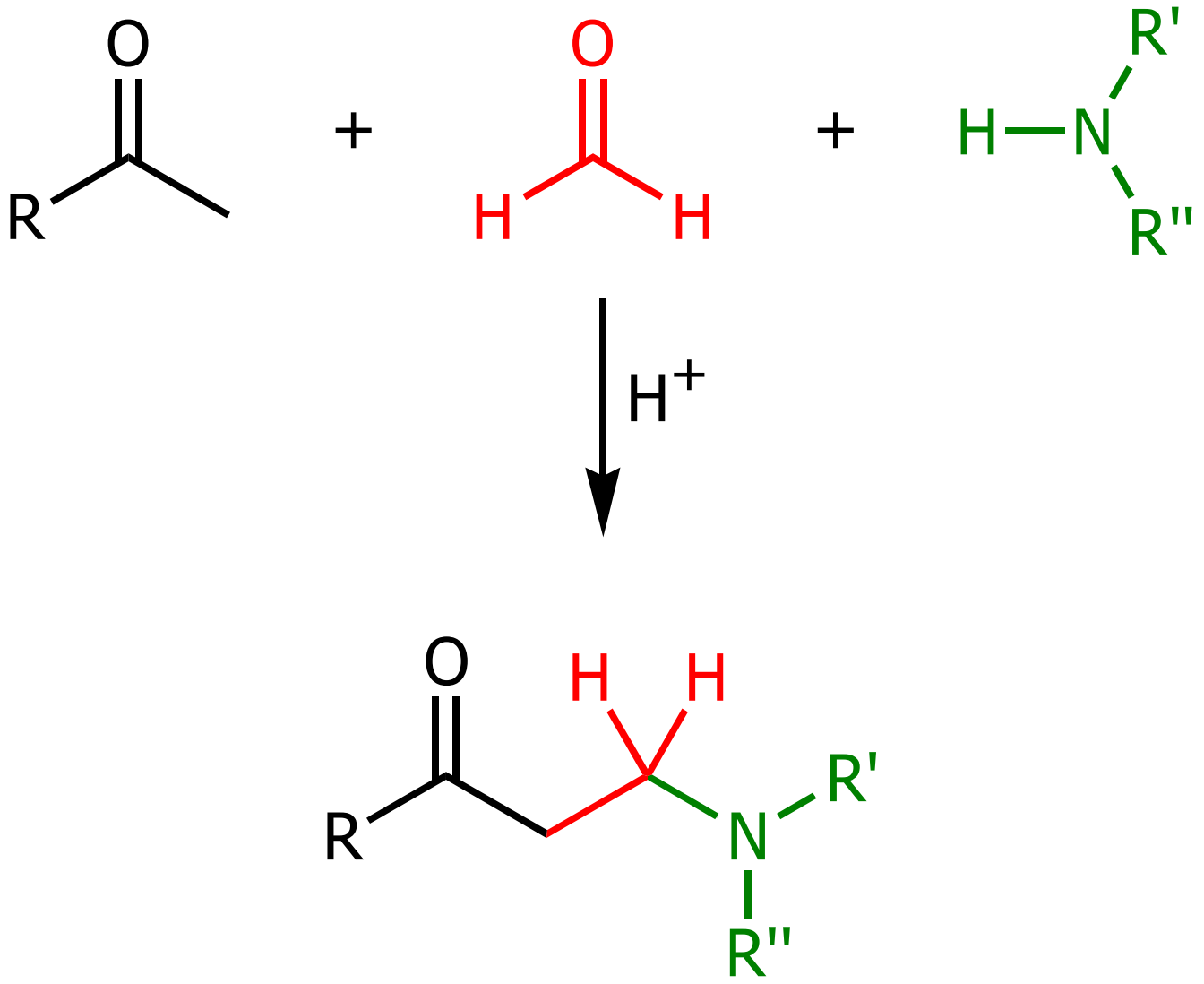
pK_a of amines can be lowered by 3 units by conversion to *N*-Mannich bases (X = CH_2CH_2COAr)

N-Mannich base (R = CH_2CH_2COPh)



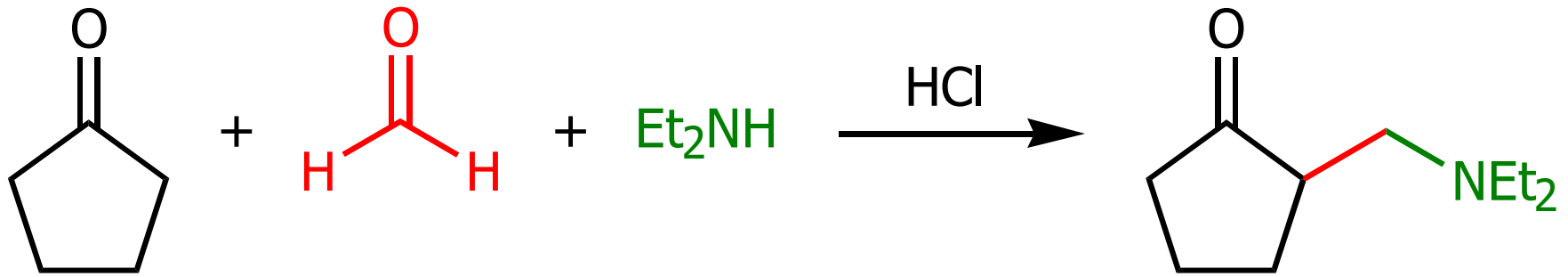
phenylpropanolamine hydrochloride (R = H HC
8.5

❖ Mannich reaction

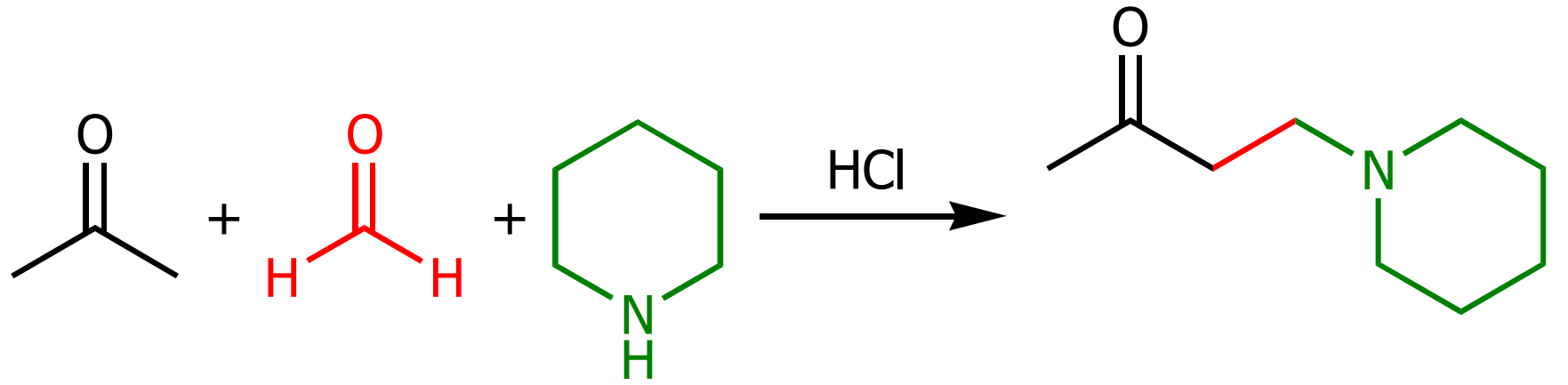


Other examples of the Mannich Reaction

(1)



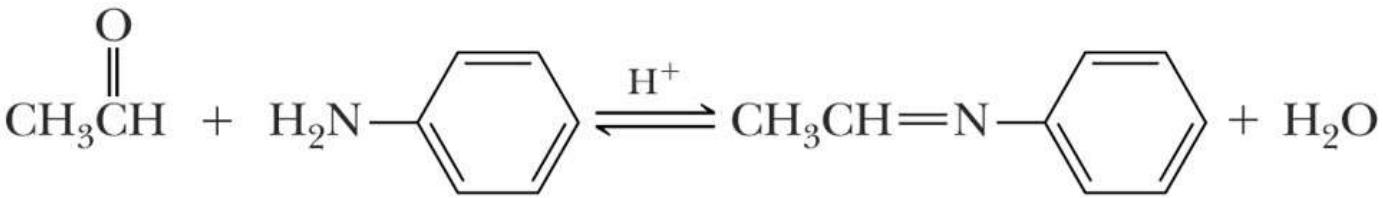
(2)



imines, Schiff bases)

Another approach to lower pK_a of amines and make more lipophilic.

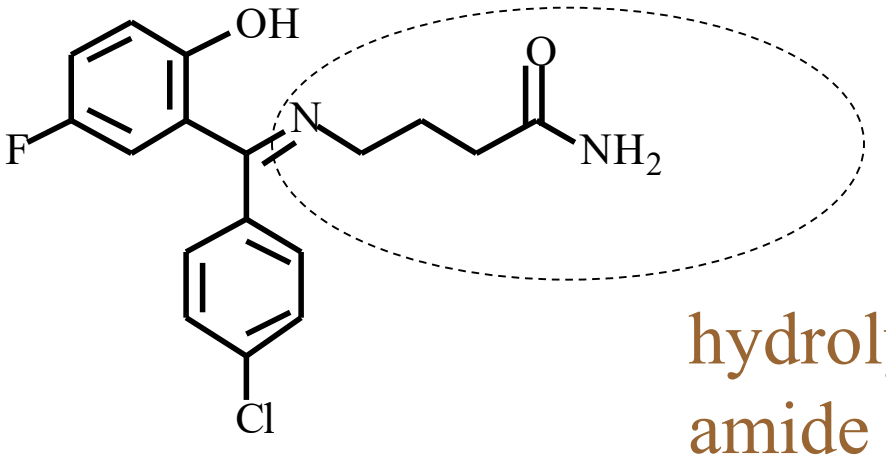
primary amines react with carbonyl compounds to give Schiff bases (imines), $RN{=}CR_2$.



Acetaldehyde Aniline An imine (a Schiff base)

Primary amine

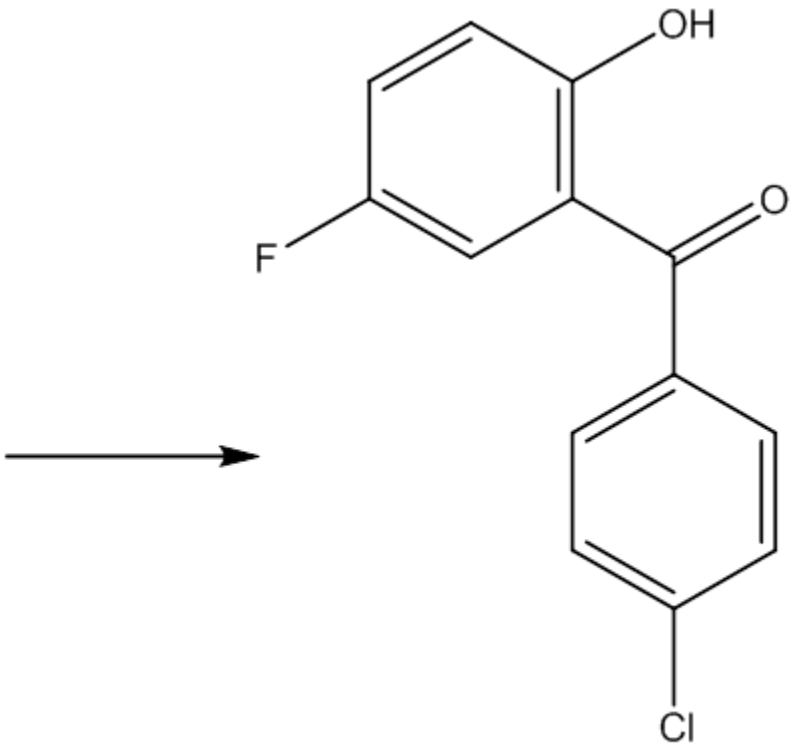
Imine (Schiff base) prodrug

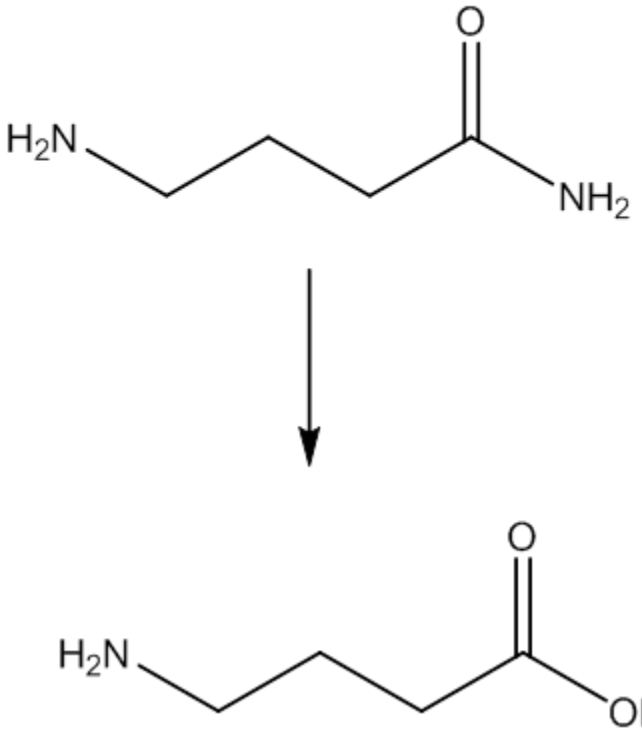


progabide
8.6

hydrolyze imine and amide to GABA inside brain

anticonvulsant

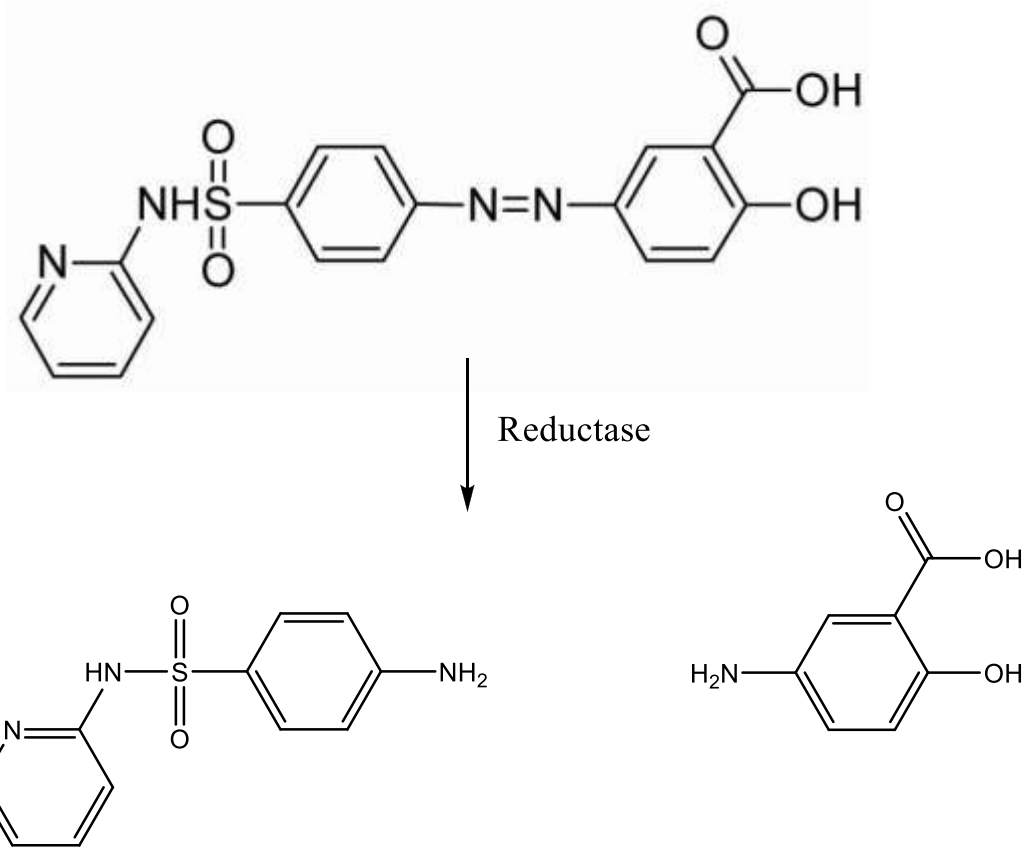


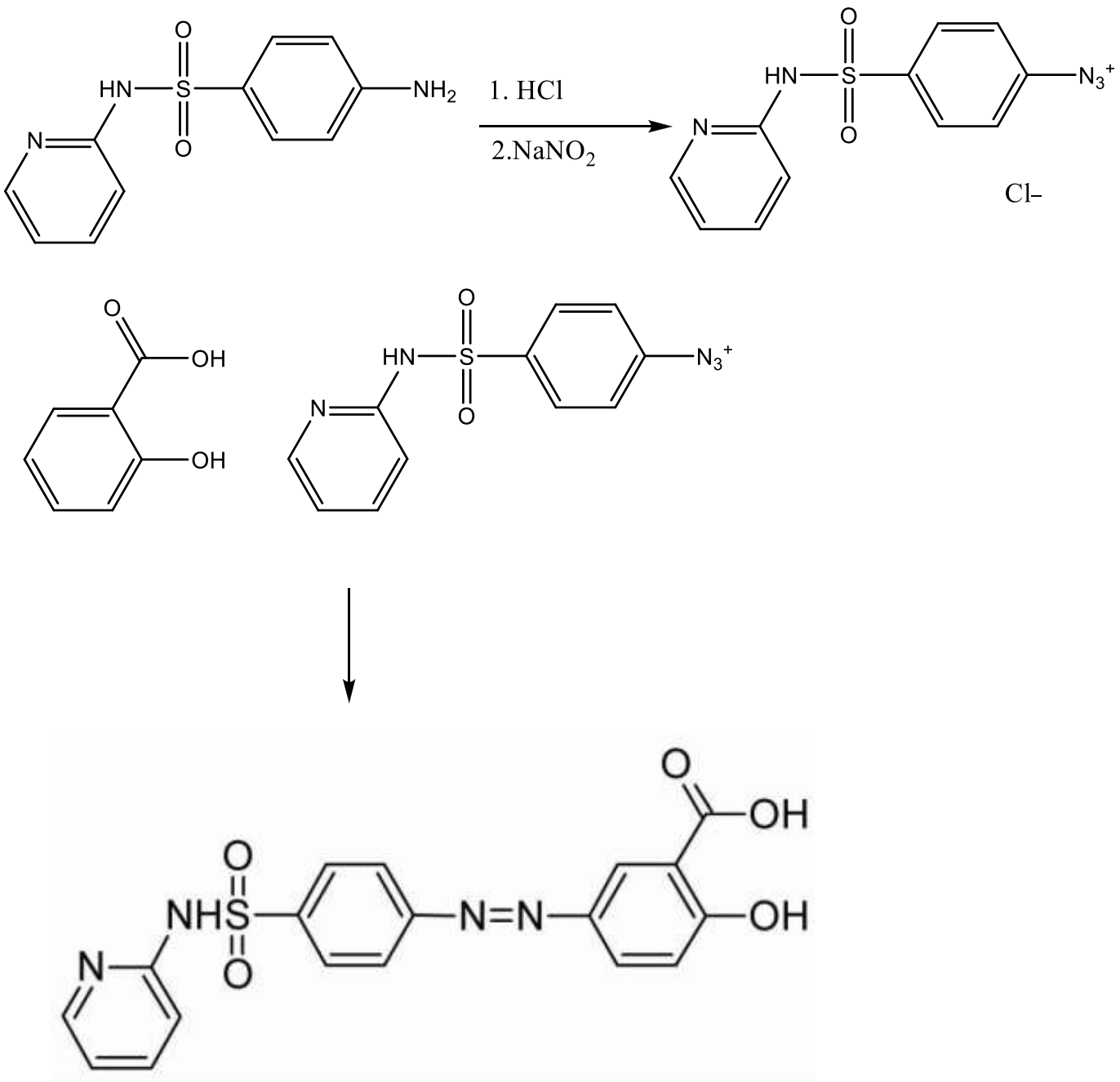


GABA

Diazo compound

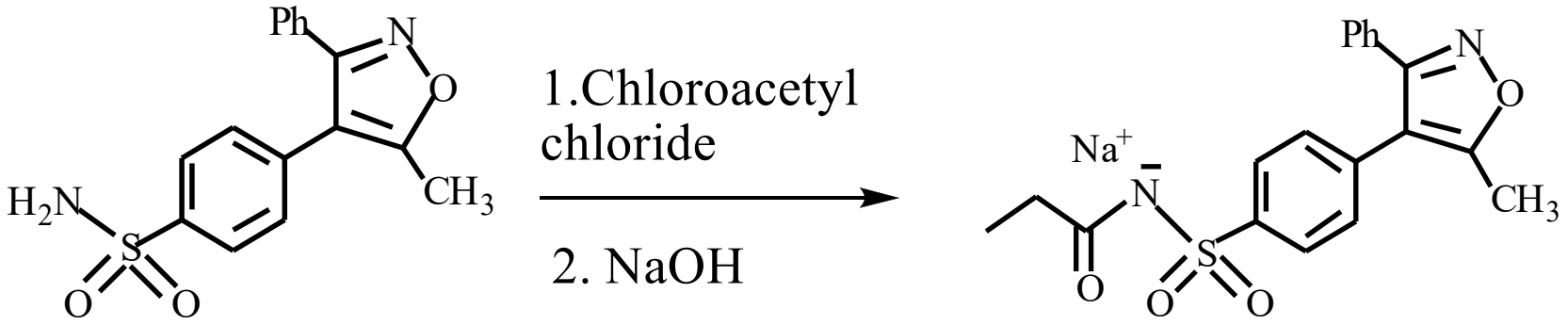
Sulfasalazine




1. HCl
2.NaNO2
Cl–

Prodrugs of Sulfonamides

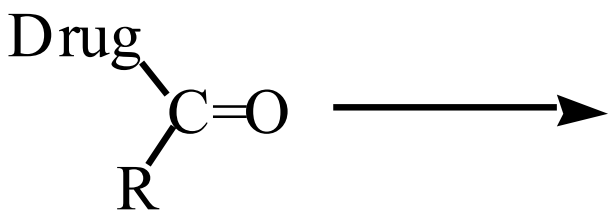
A water soluble prodrug of the anti-inflammatory drug valdecoxib (**8.9**) has been made (**8.10**).

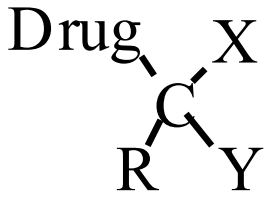


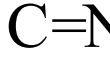
valdecoxib
8.9

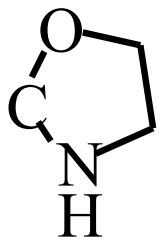
parecoxib sodium
8.10

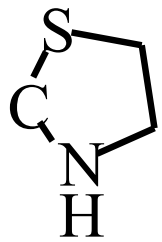
Prodrug Analogs of Carbonyl Compounds





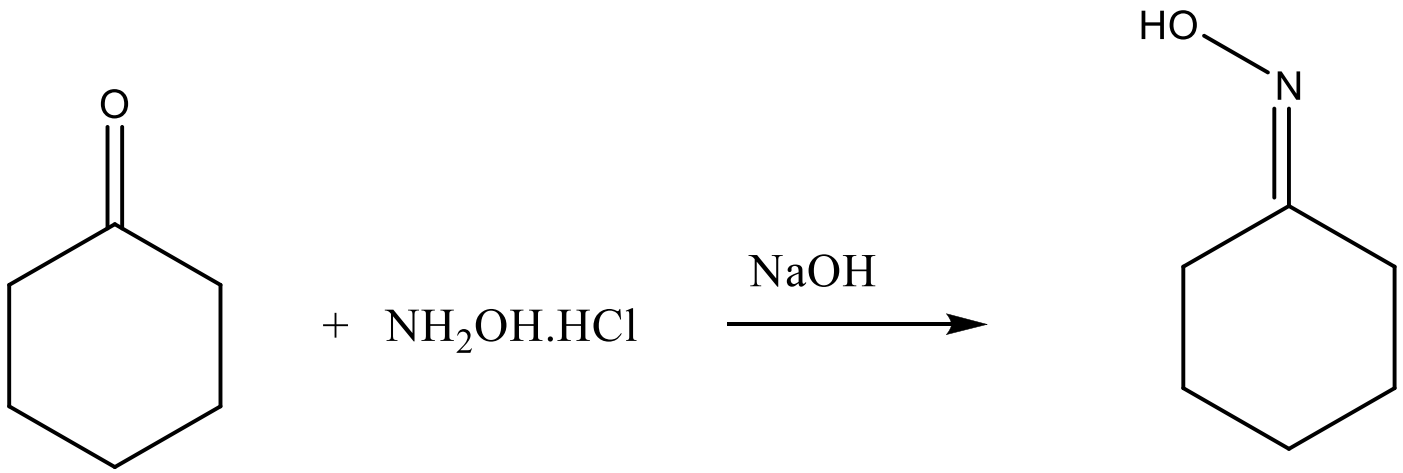




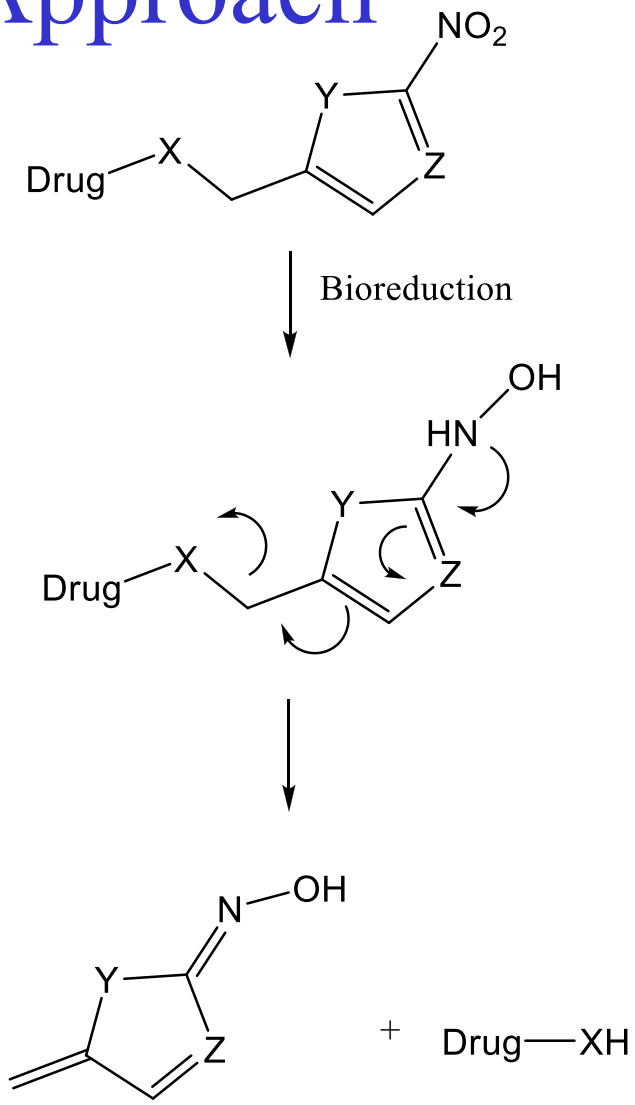


imines oximes ketals Tetrahydro oxazole Tetrahydro thiozaole

Oxime synthsis



A Reductive Carrier-Linked Prodrug Approach



X= O or NH or S
Y= O or S
Z= N

Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 4

Prodrug approaches for enhancing administration, permeability or absorption

Bipartate prodrugs

Prodrugs with increased aqueous solubility

Poor aqueous solubility is considered as a serious problem limiting the therapeutic use of numerous drugs

One frequently employed means of improving the aqueous solubility of a drug is by the use of

1. Phosphate derivatives
2. Esters derivatives
3. Hemisuccinate derivatives

1. Phosphate

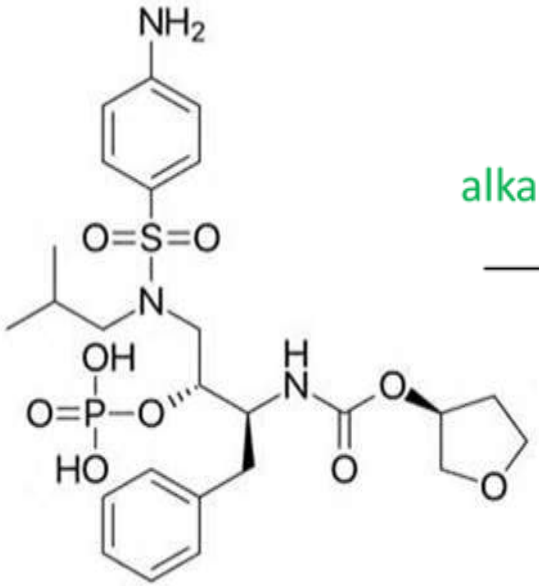
Due to the ionic nature of the phosphate group

Phosphate derivatives display high chemical stability, often even higher than the parent compound.

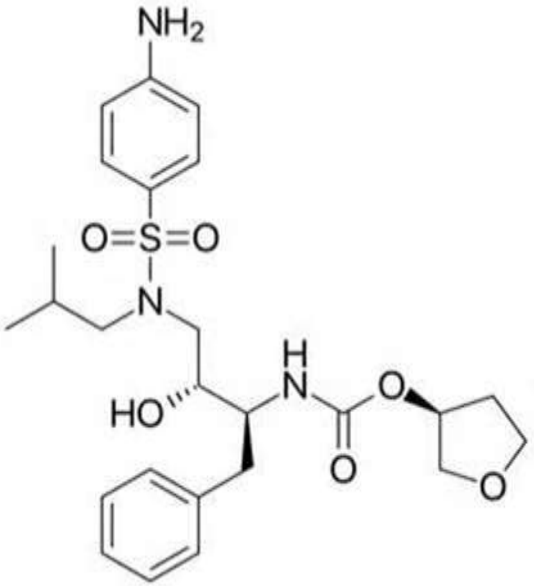
Under physiological conditions phosphate prodrugs undergo rapid biotransformation by endogenous phosphatases, such as alkaline phosphatase, of the intestine, plasma, and the liver

Fosamprenavir; phosphate ester of amprenavir
a HIV protease inhibitor.
Antiviral, HIV infections.

Bioconverted by alkaline phosphatases to amprenavir,



alkaline phosphatases



Fosamprenavir

amprenavir

Estramustine phosphate ; phosphate ester of estramustine

Bioconverted by alkaline phosphatases to estramustine,.
Antimitotic drugs.

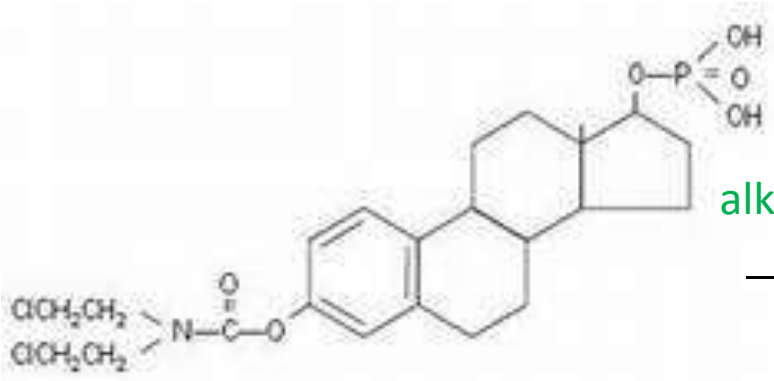


Figure 1. Estramustine Phosphate

alkaline phosphatases

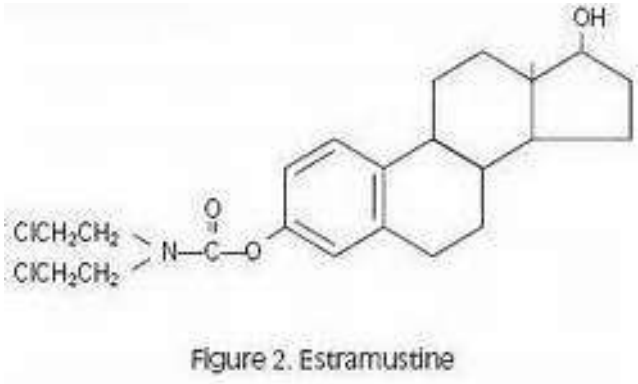
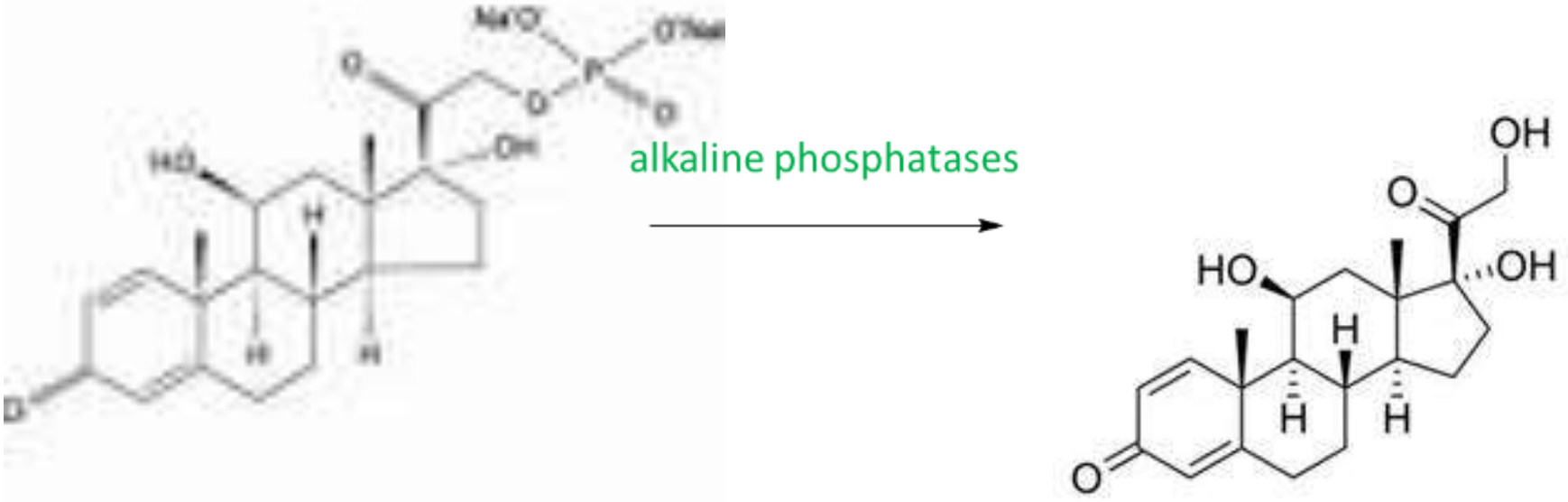


Figure 2. Estramustine

Prednisolone disodium phosphate; phosphate ester of prednisolone

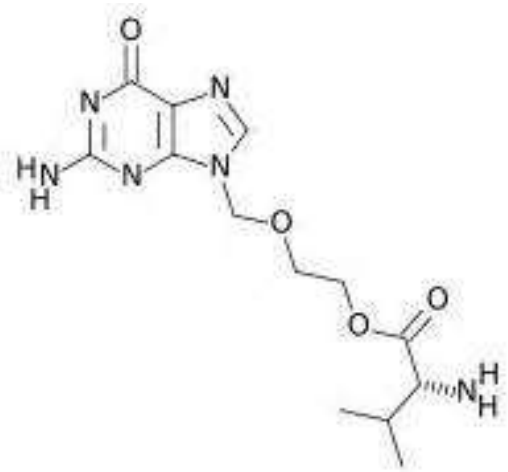
Bioconverted by alkaline phosphatases to prednisolone.

Anti-inflammatory, antialergic.



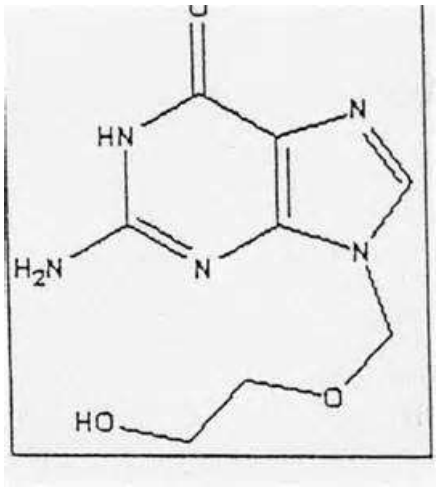
2-Another approach to increase absorption is esterification with amino acids.

valacyclovir which is valine esters of the antiviral drugs acyclovir
are substrates for PEPT1 (a specific transport system for amino acid)



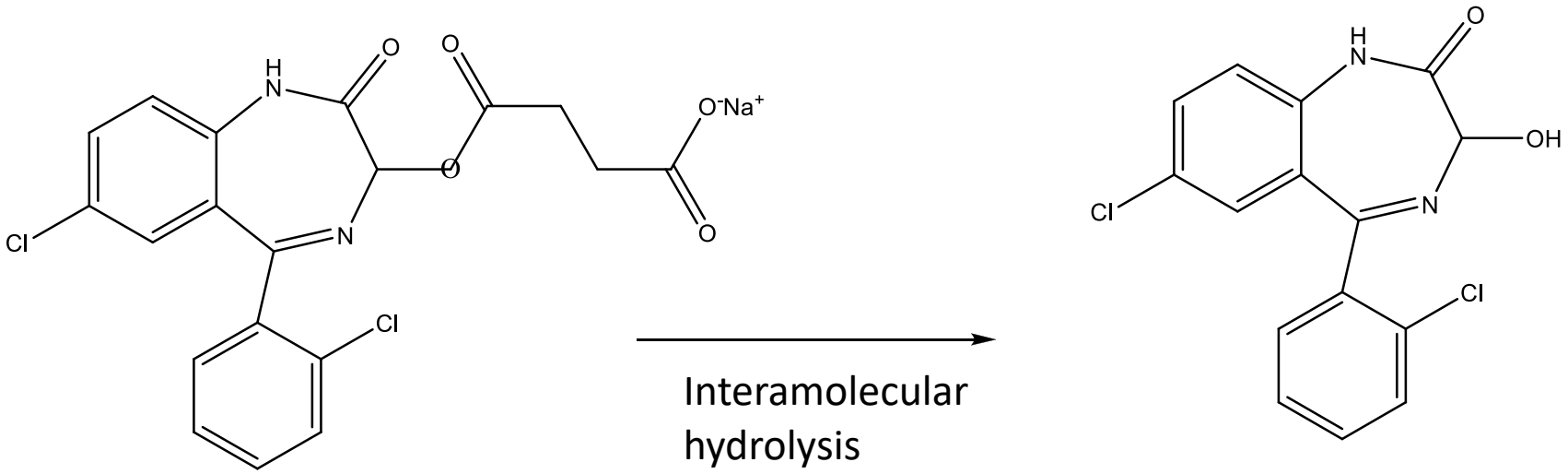
Valaciclovir

esterase



3-A hemisuccinate group can be conveniently used to increase water solubility, as it contains a free carboxylic group, which is suitable for the formation of dissociated salts.

hemi succinate esters is cinazepam, a novel benzodiazepine anxiolytic drug suitable for intravenous injections



Prodrugs with increased lipid solubility

1- Oral preparation

In order to improve lipophilicity, and thus passive transport through biological membranes, compounds containing polar or ionizable groups can be converted into ester prodrugs

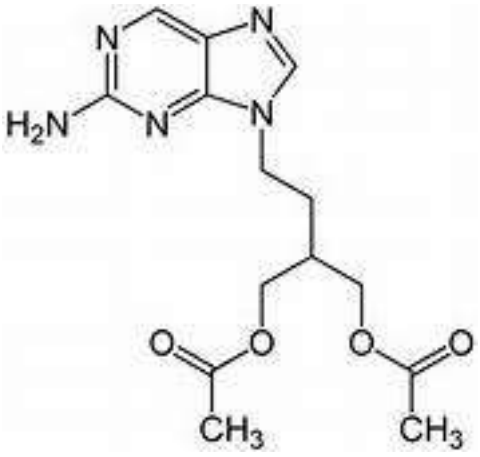
Enalapril In the liver bioconverted by esterases to enalaprilic acid, an angiotensin-converting enzyme inhibitor. Used in the treatment of hypertension, ischemic heart disease

Enalapril

enalaprilic acid

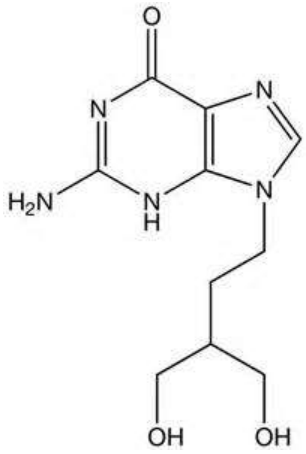
Famciclovir dimethyl ester of penciclovir

Bioconverted by esterases and aldehyde oxidase to penciclovir – inhibitor of Herpes DNA synthesis. Antiviral.



Famciclovir

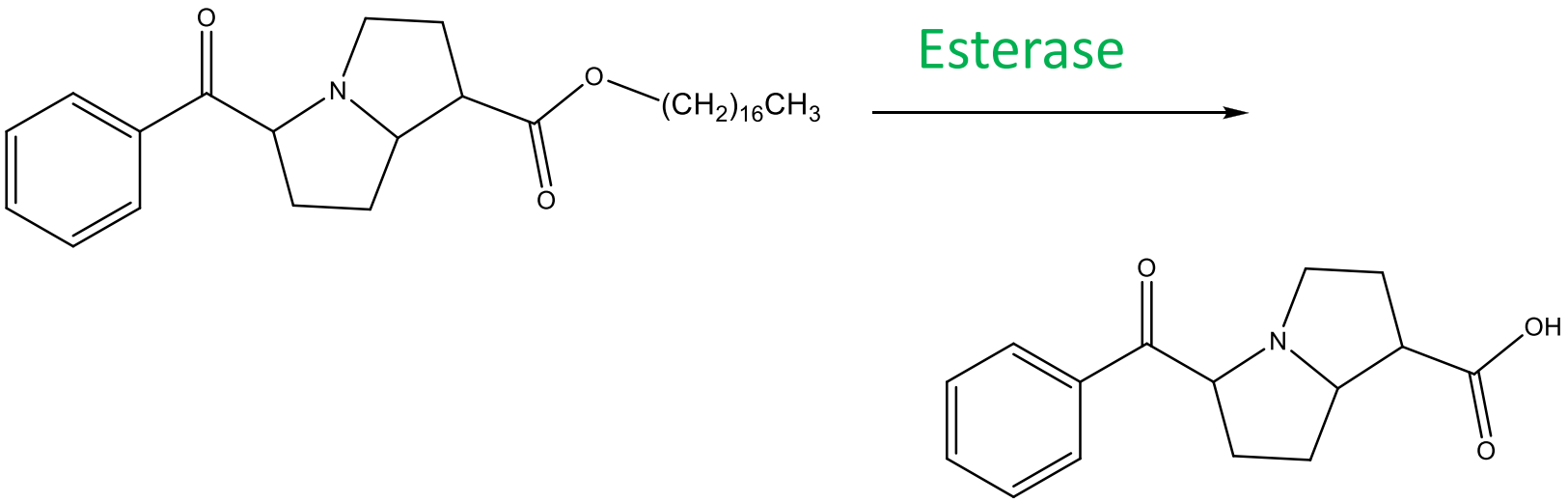
esterases and
aldehyde oxidase



penciclovir

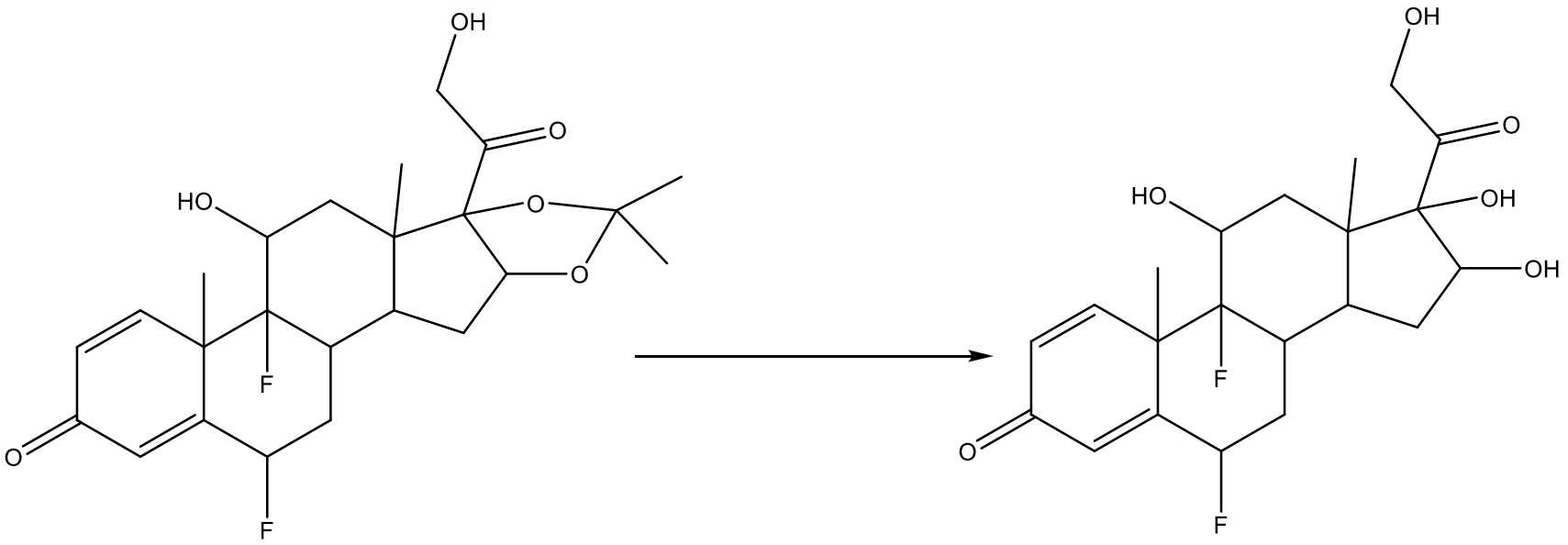
2-Prodrugs with increased lipophilicity are also designed for topical administration

Esters of ketolac (a non-steroidal anti-inflammatory drug with potent analgesic activity) and fatty acids (stearic acid) allow the drug to accumulate in the skin with concomitant low skin permeation, leading to increased therapeutic efficiency and reduced side effects of the parent drug



fluocinolone acetonide is highly lipid soluble

corticosteroids prodrug used for inflammation, allergic, pruritic of skin conditions



fluocinolone acetonide

fluocinolone

latanoprost prodrugs of prostaglandin F2a (PGF2a) analogs, applied as eye drops for the treatment of glaucoma. molecules which are relatively polar and hydrophilic due to their carboxylic acid moiety and several hydroxyl groups. They penetrate through biological membranes poorly.

This problem has been solved by a modification of the chemical structure of PGF2a analogs. Latanoprost isopropyl esters of latanoprost acid penetrate easily through the corneal epithelium due to their increased lipophilicity, where they are then hydrolyzed to active carboxylic acids

latanoprost

latanoprost acid

Tripartate prodrugs
(Self-immolative Prodrugs)

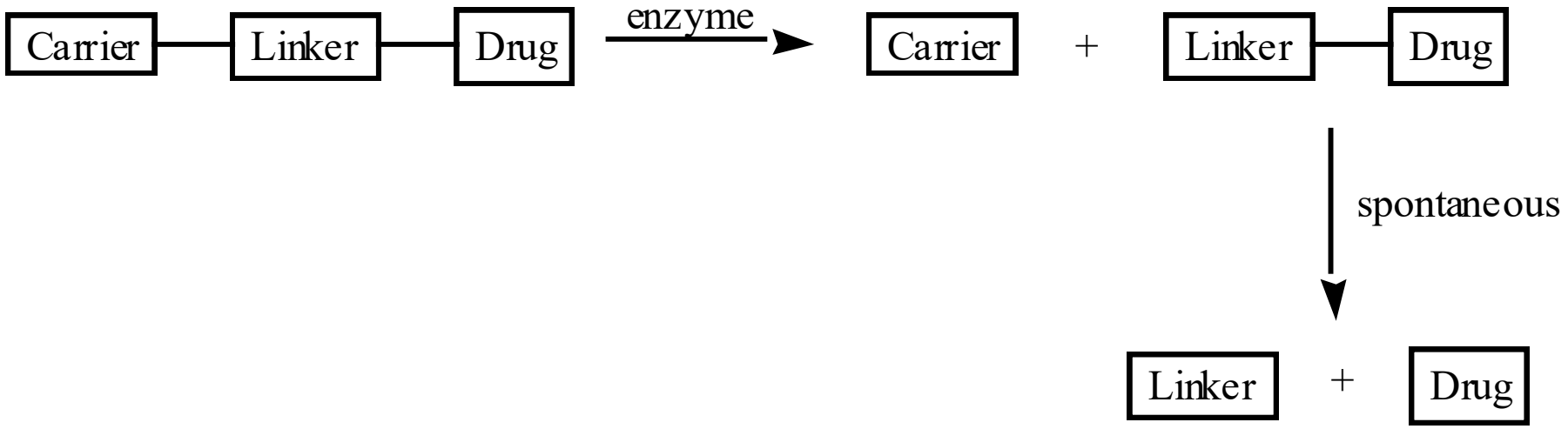
A bipartate prodrug may be ineffective because the linkage is too labile or too stable.

In a tripartate prodrug, the carrier is not attached to the drug; rather, to the linker.

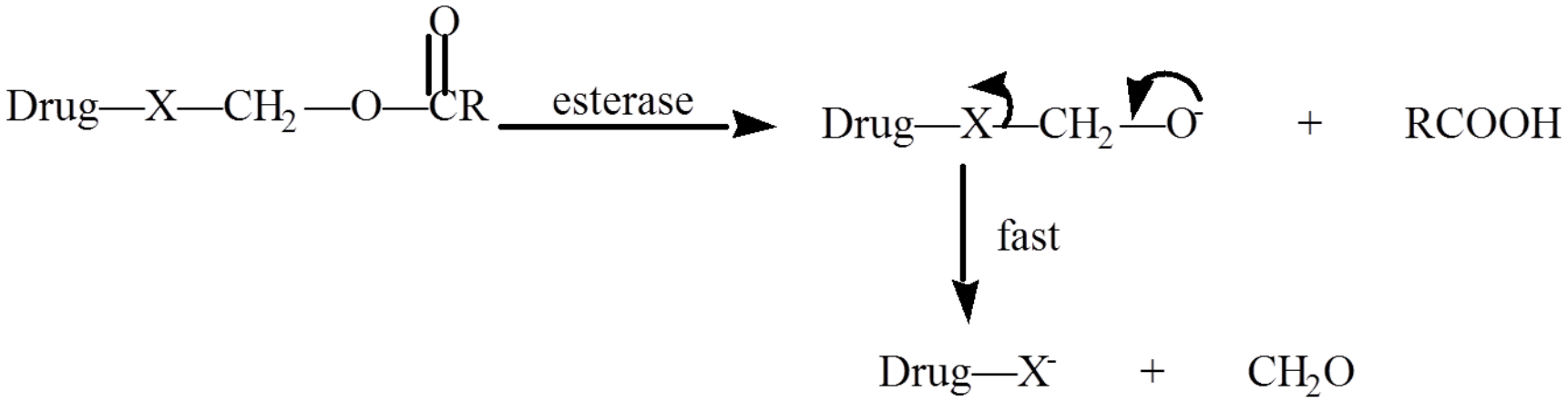
Therefore, more flexibility in the types of functional groups and linkages that can be used, and it moves the cleavage site away from the carrier.

The linker-drug bond must cleave spontaneously (i.e., be self-immolative) after the carrier-linker bond is broken.

Tripartate Prodrugs



Typical Approach

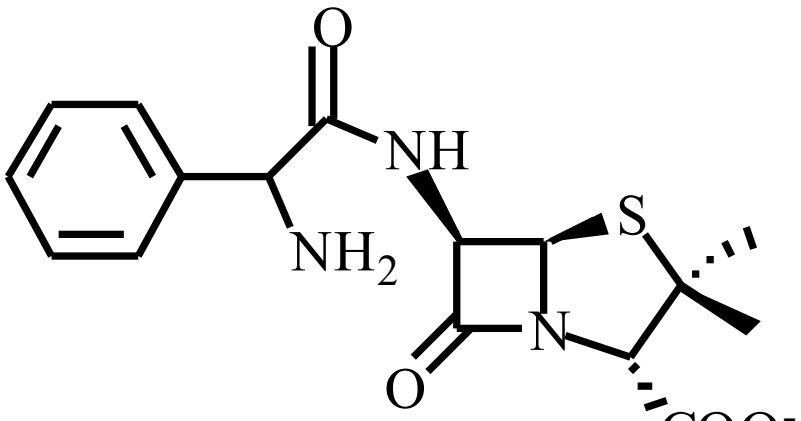


Tripartate Prodrugs of Ampicillin

Poor oral absorption (40%)

Excess antibiotic may destroy important intestinal bacteria used in digestion and for biosynthesis of cofactors.

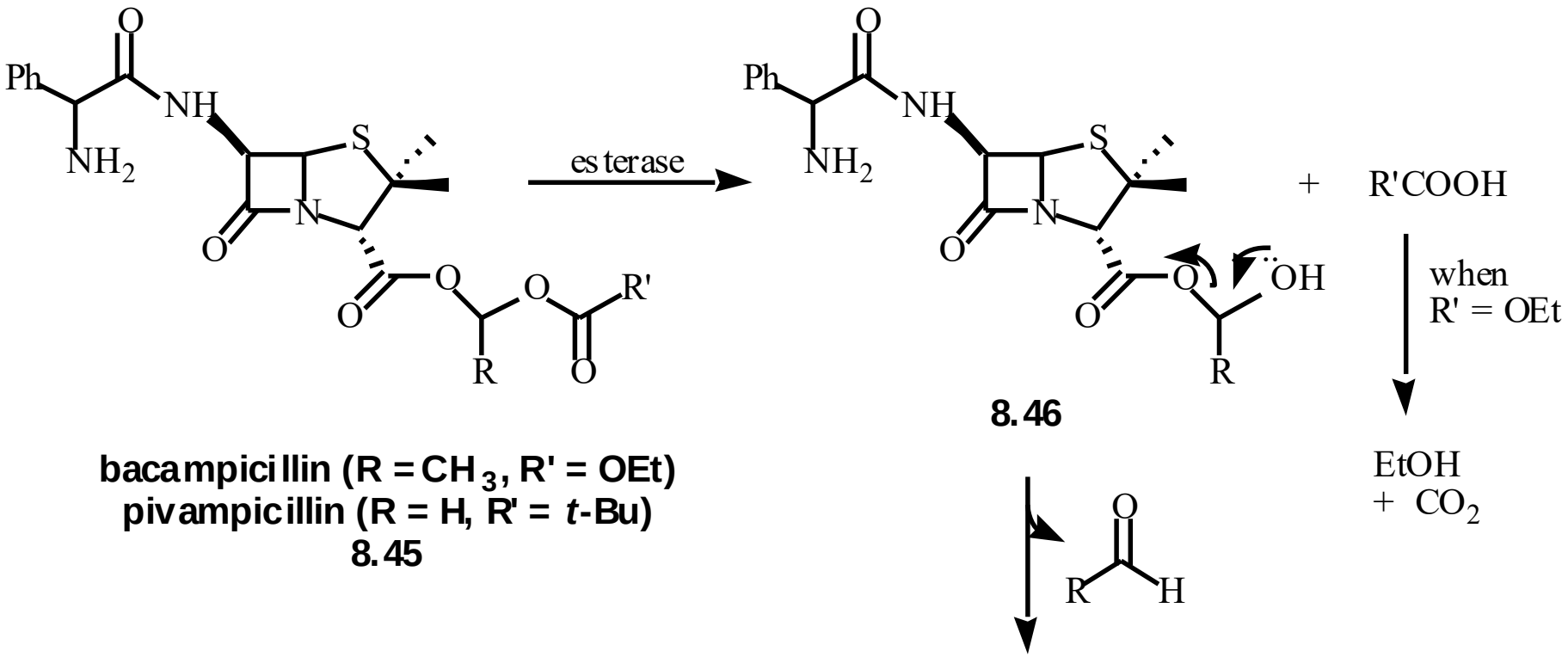
Also, more rapid onset of resistance.



antibacterial
ampicillin
8.44

Various esters made were too stable in humans thought the thiazolidine ring sterically hindered the esterase.

Tripartate Prodrugs of Ampicillin



bacampicillin (R = CH_3, R' = OEt)
pivampicillin (R = H, R' = *t*-Bu)
8.45

8.46

8.44

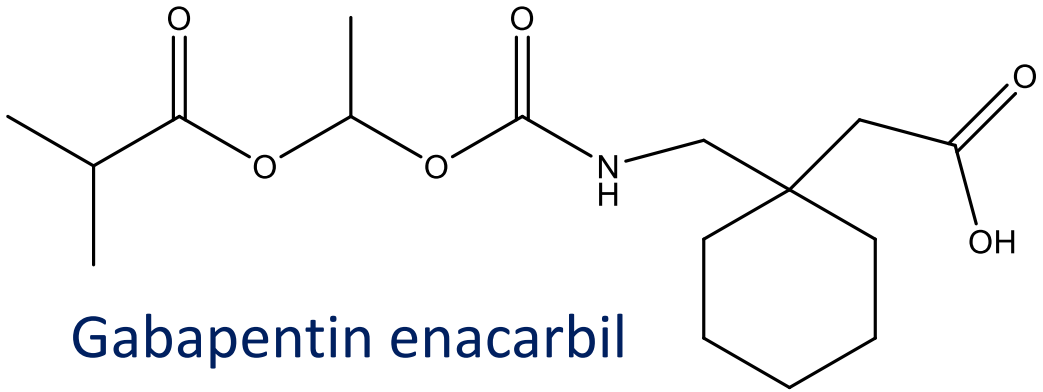
98-99% absorbed

Ampicillin is released in < 15 minutes

Tripartate Prodrugs as substrates for GI membrane transporters

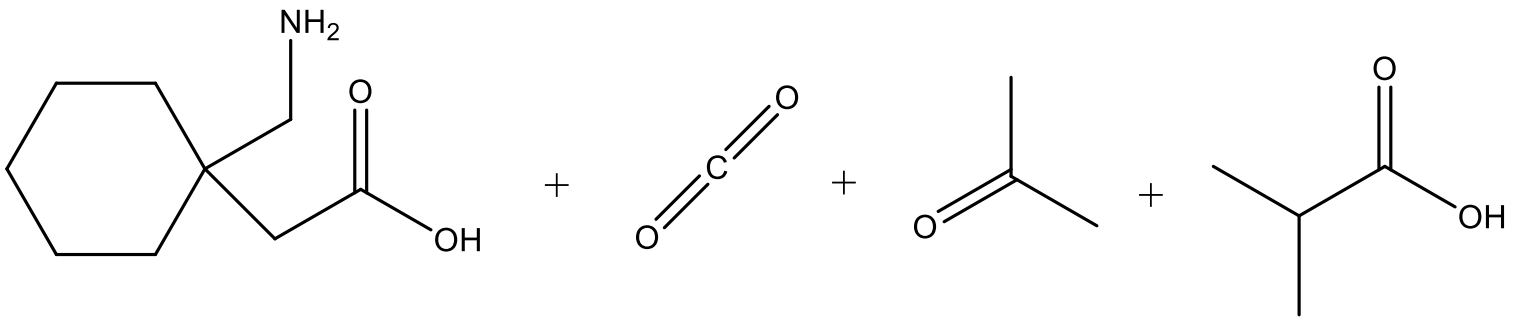
Gabapentin enacarbil a prodrug of gabapentin absorb by monocarboxylic acid transporter-1 (MCT-1) and sodium-dependent multivitamin transporter (SMVT), distributed throughout the intestine.

gabapentin enacarbil has better absorption, bioavailability, and pharmacokinetic properties compared with gabapentin. Gabapentin is approved for the treatment of epilepsy and postherpetic neuralgia



Gabapentin enacarbil

Esterase



Gabapentin

Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 5

Prodrug approaches for the CNS delivery

One of the major difficulties in the development of drugs acting at the central nervous system (CNS) is the inability of many therapeutically compounds to cross the blood-brain barrier (BBB).

transport of molecules across the BBB is achieved either through diffusion as a passive process, or with the aid of special carrier systems involving intrinsic transporter proteins

The BBB restricts the passage of neurotoxic substances and peripheral immune cells from entering the brain, while selectively facilitating the transport of nutrients into the brain. In addition, it prevents central neurotransmitters and neuromodulators from reaching the circulatory system

Three basic prodrug strategies have been used to facilitate the transport of drugs into the CNS:

(1) Increasing passive diffusion by masking polar groups on the parent drug (so-called lipidization of molecules)

(2) increasing carrier-mediated or receptor mediated transport through the BBB

(3) Decreasing the active efflux of the drug from the brain into the blood.

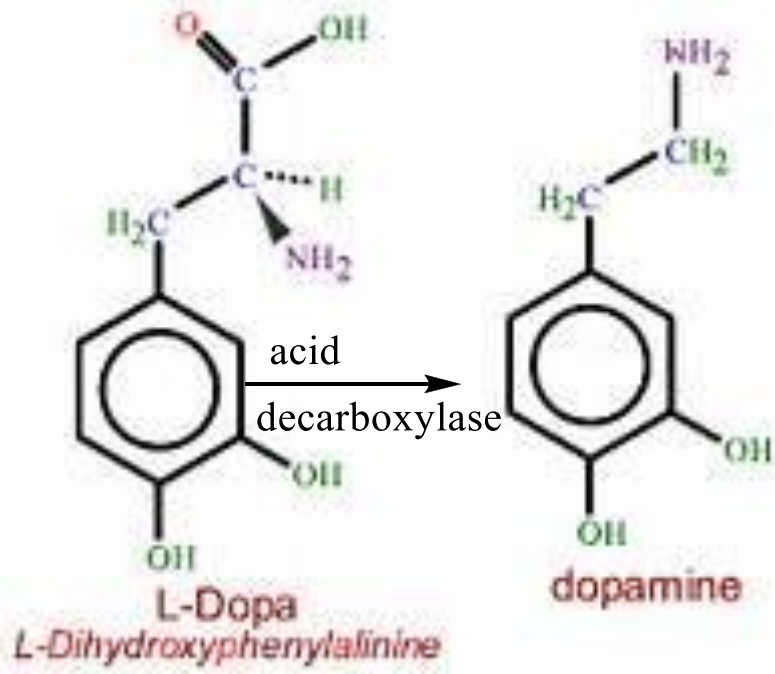
In order to achieve therapeutically effective doses in the CNS, the process of prodrug biotransformation should be slow in the peripheral tissues but fast in the brain itself.

Although dopamine is unable to cross the BBB due to its hydrophilic nature, L-DOPA, its amino acid analog and precursor, crosses the BBB via LAT1. The drug is then decarboxylated by amino acid decarboxylase (AADC) to dopamine.

Additionally, catechol-*O*-methyltransferase (COMT) converts L-DOPA to 3-*O*-methyl DOPA. To minimize the metabolism of L-DOPA outside the CNS and to increase its half-life time, the drug is given in combination with peripheral inhibitors of AADC (carbidopa)

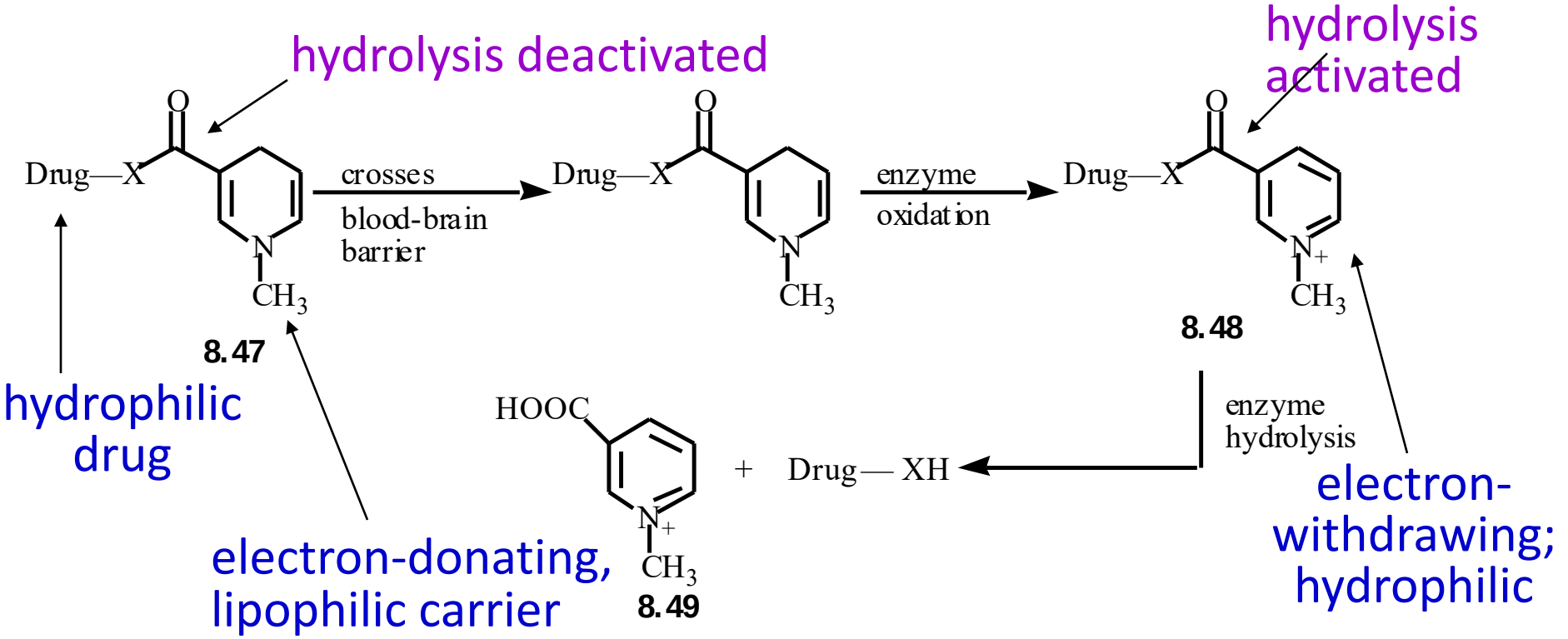
Prodrugs with a very close structural resemblance to endogenous substrates of the BBB influx transporters will be recognized by them and transported across the BBB into the brain, where the release of an active drug will take place.

L-DOPA, a dopamine prodrug used in the treatment of Parkinson's disease, is an example of compounds transported into the brain with the aid of influx transporters.



Reversible Redox Drug Delivery System to the CNS

By use 1-methyl-1,4-dihydropyridine-3-carboxylic acid

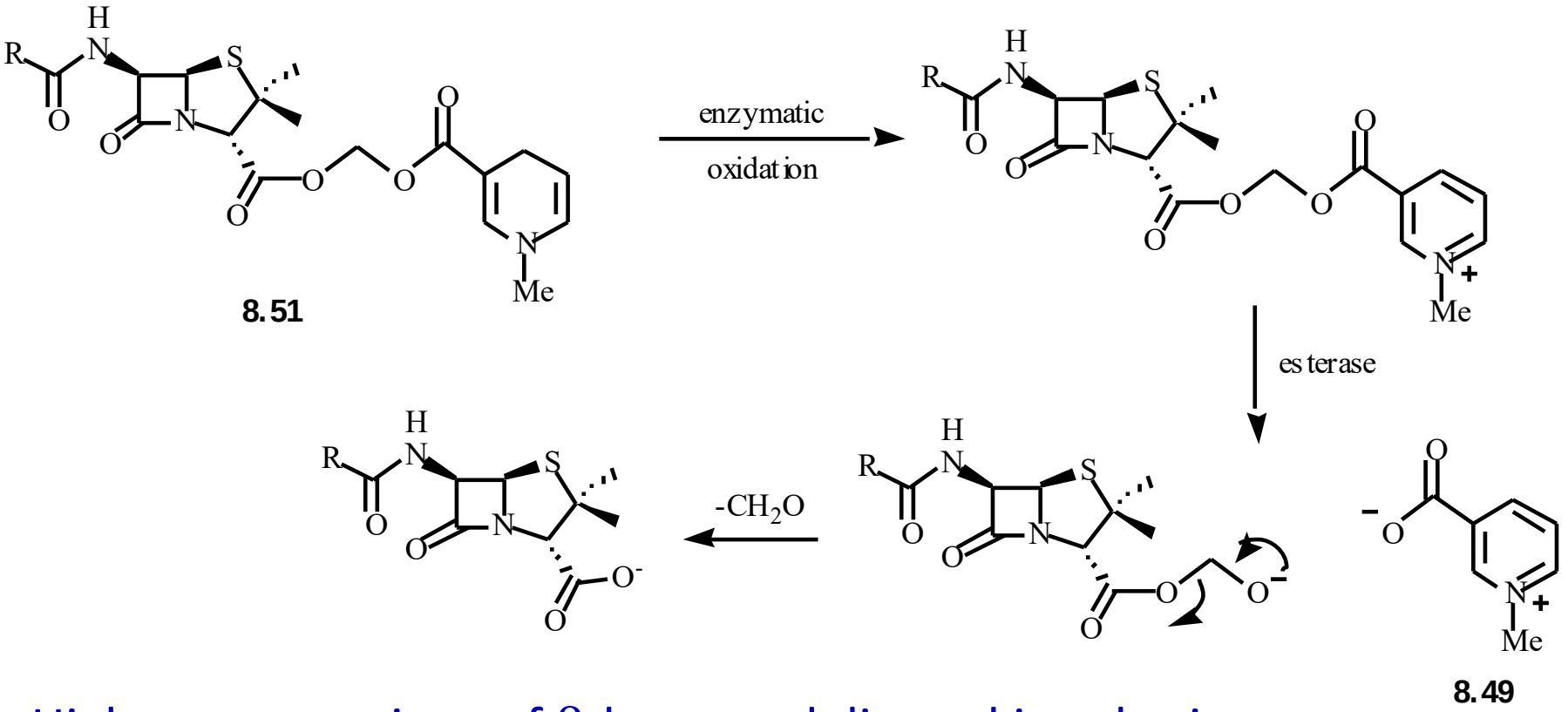


Passive diffusion of **8.47** into the brain; active transport of **8.49** out of the brain

XH of the drug is NH_2, OH, or SH

If oxidation occurs before it gets into the brain, it cannot cross the blood-brain barrier.

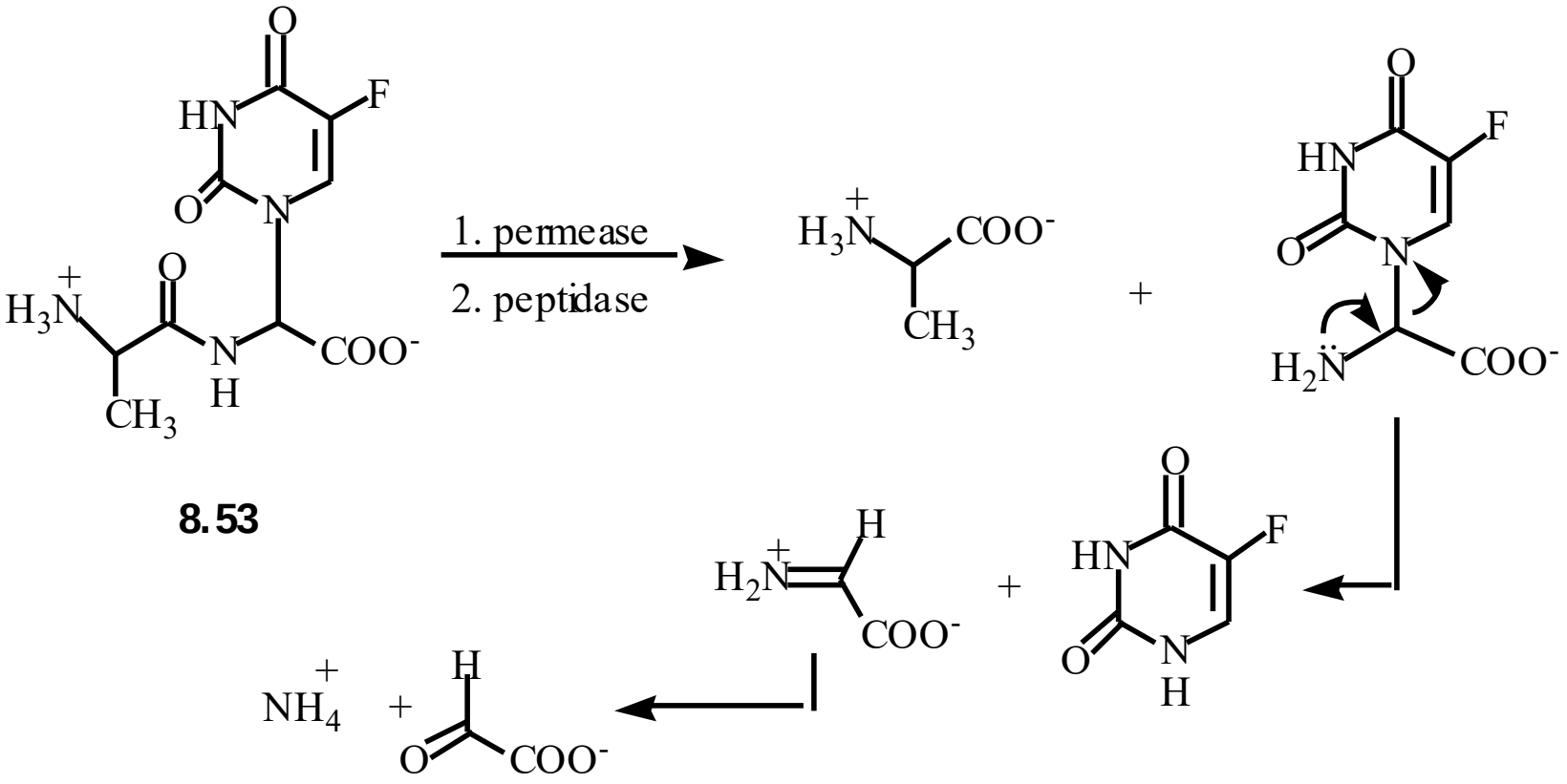
Antibody generation in the brain is not significant.β-Lactams are too hydrophilic to cross the blood-brain barrier effectively. So the reversible redox Drug delivery system can be used to increase the penetration of antibiotic into CNS



High concentrations of β-lactams delivered into brain.

Tripartate Prodrug for Delivery of Antibacterials

Permeases are bacterial transport proteins for uptake of peptides.



8.53

Only *L*,*L*-dipeptides are active

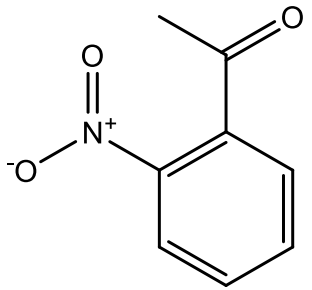
Prodrug for Stability
protection from first-pass effect

Naltrexone(R=H), opiod addiction

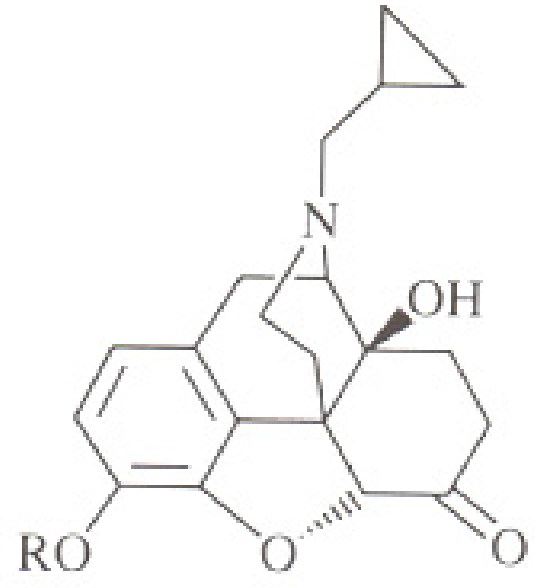
Not stable, it effected by the first pass

R= **Naltrexone-2-nitrobenzoate**, bioavailability 45X times

R=



2-nitrobenzoate



Prodrugs for Slow and Prolonged Release

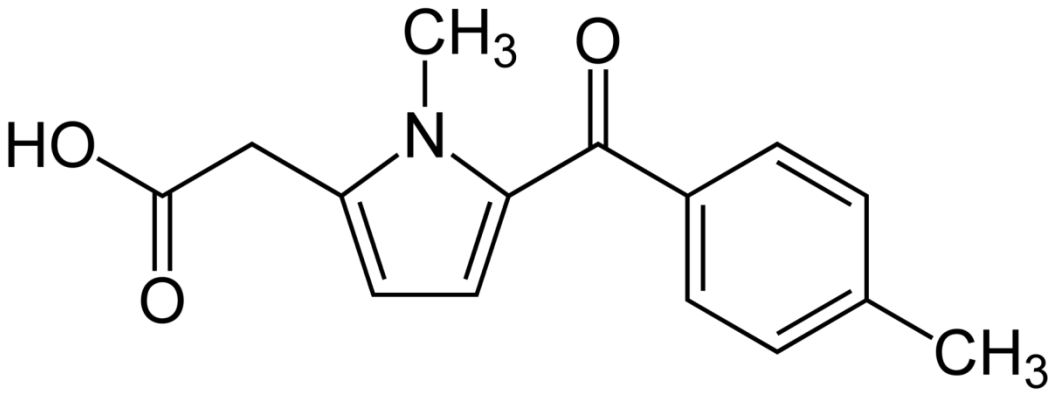
Advantages:

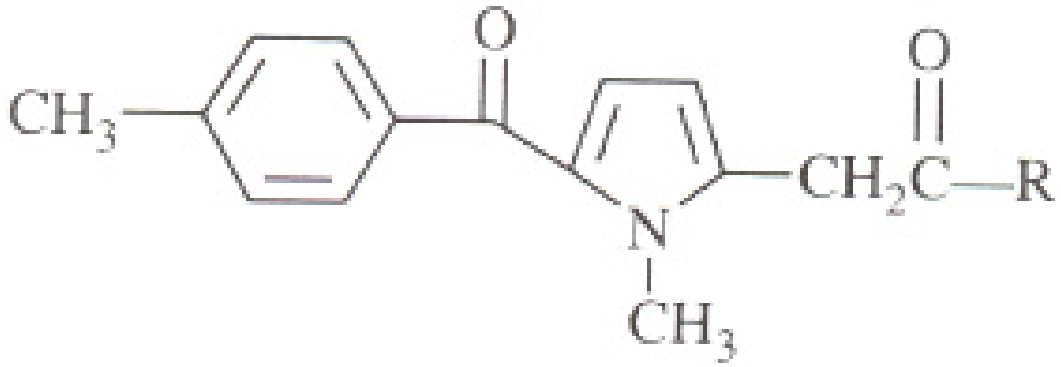
1. To reduce the number and frequency of doses
2. To eliminate night time administration
3. To minimize patient noncompliance
4. To eliminate peaks and valleys of fast release (relieve strain on cells)
5. To reduce toxic levels
6. To reduce GI side effects

Tolmetin sodium(R=O-Na+), antiarthritis

Peak concentration duration: 1 hr.

R= NHCH2COOH, peak duration: 9 hrs.





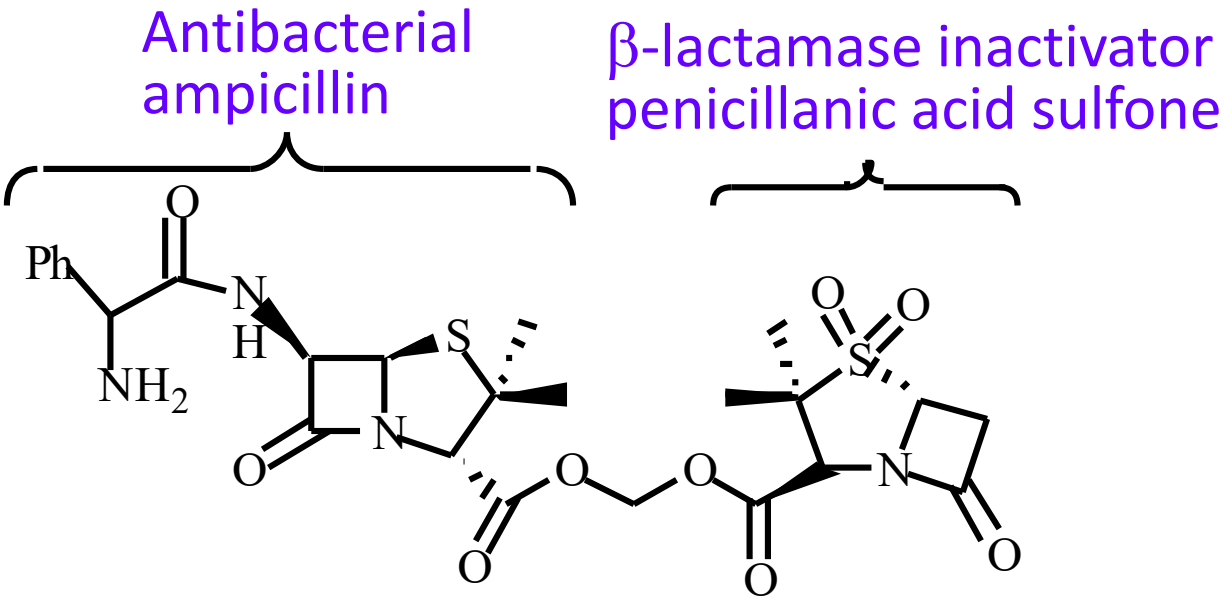
Mutual Prodrugs

Ideal mutual prodrugs properties

- Well absorbed
- Both components are released together and quantitatively after absorption
- Maximal effect of the combination of the two drugs occurs at 1:1 ratio
- Distribution/elimination of components are similar

Mutual Prodrugs

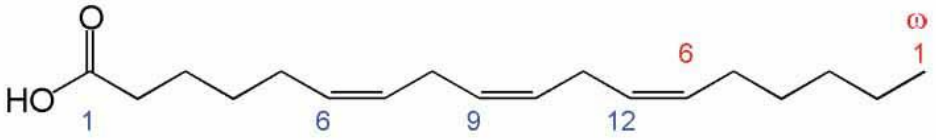
A bipartate or tripartate prodrug in which the carrier is a synergistic drug with the drug to which it is linked.



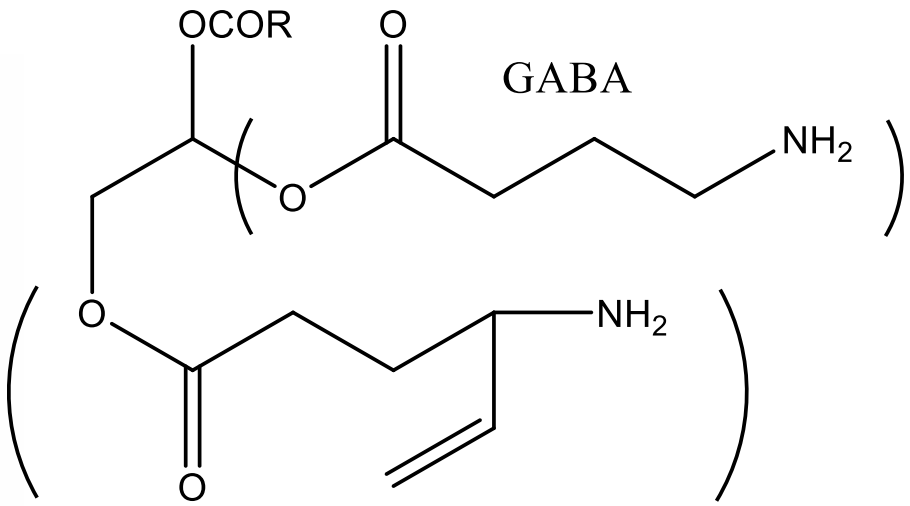
sultamicillin
8.59

Hydrolysis gives 1:1:1 ampicillin : penicillanic acid sulfone : formaldehyde

The blood-brain barrier prevents hydrophilic molecules from entering the brain, unless actively transported. The anticonvulsant drug vigabatrin crosses poorly. A glyceryl lipid (R = linolenoyl) containing one GABA ester and one vigabatrin ester was 300 times more potent in vivo than vigabatrin.



R=



vigabatrin

Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 6

prodrugs to improve targetability and efficacy of chemotherapeutic agents?

Chemotherapy is a primary treatment for cancer

majority of anticancer drugs currently in use exert their oncostatic actions by inhibiting proliferation or by arresting cell cycle at a certain phase

As oncostatic drugs are characterize with poor selectivity, they affect not only neoplastic cells but also rapidly proliferating normal cells, such as, bone marrow, gut epithelia, hair follicles, lymphatic cells and gametes.

The lack of selectivity of anticancer drugs, and associated toxicity, hampers their effectiveness and long term use.

One of the promising approaches to achieve this goal is prodrug technology

An anticancer prodrug should be transported to neoplastic cells, where it will undergo transformation to a cytotoxic parent drug by native or recombinant enzymes

Capecitabine a prodrug of 5-fluorouracil approved for the therapy of solid tumors including breast cancer and colorectal cancer, may be considered a pioneer of chemotherapy prodrugs

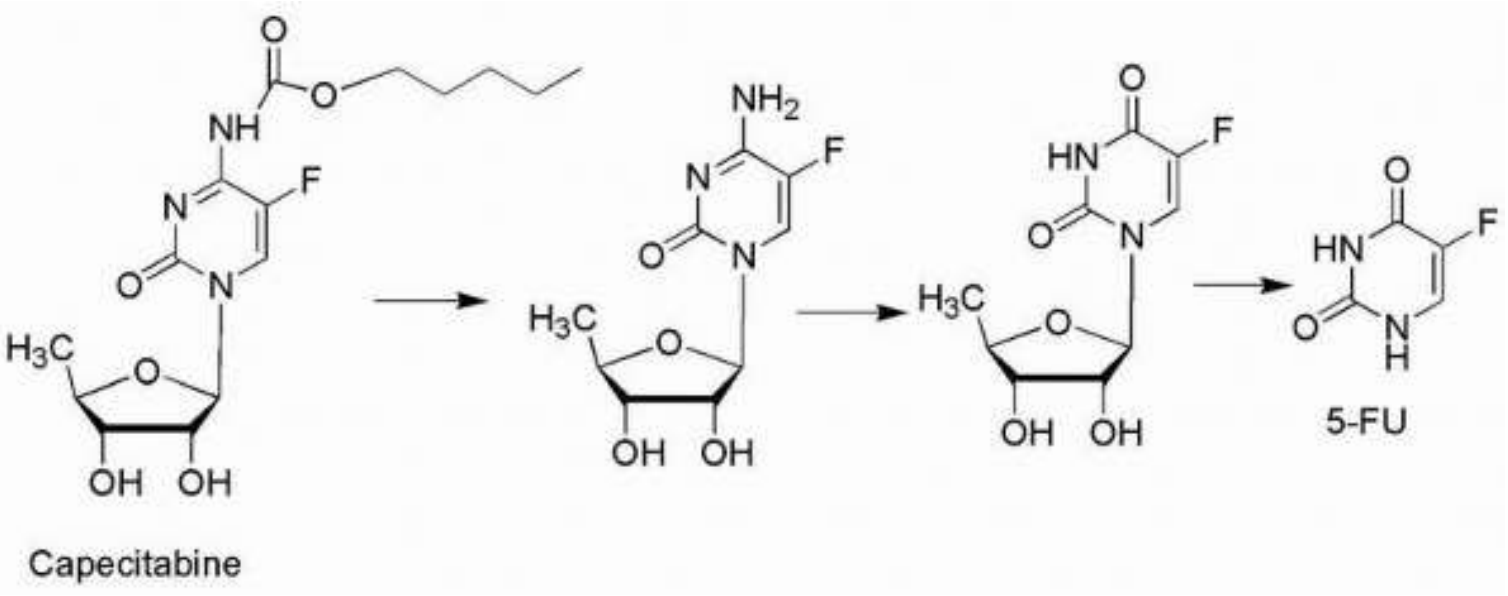
Following oral administration, capecitabine is rapidly and extensively absorbed.

Capecitabine

1. carbamate hydrolysis (carboxylesterase)

2. De-amination (cytosine deaminase)

3. Hydrolysis of the sugar moiety to yield 5-FU (kinase) take Place in cancer tissue



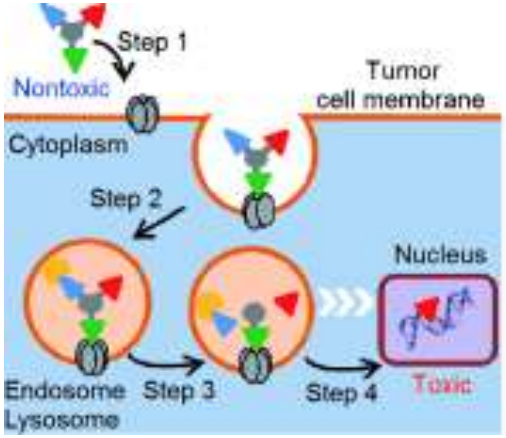
Anticancer prodrugs can be designed to target specific molecules (enzymes, peptide transporters, antigens) that are overexpressed in tumor cells in comparison to normal cells.

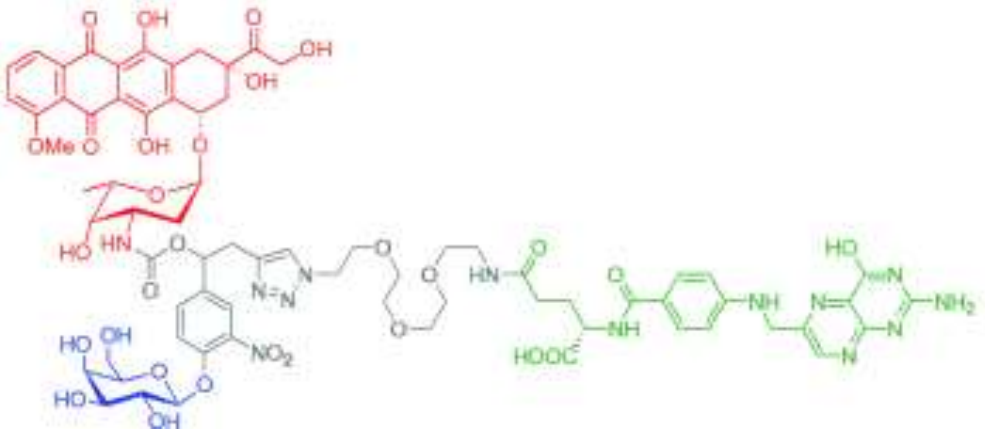
Folates are low-molecular-weight vitamins required by all eukaryotic cells for one-carbon metabolism and *de novo* nucleotide synthesis

Most cells rely on a low-affinity membrane-spanning protein that transports reduced folates directly into the cell, a few cells also express a high-affinity receptor, generally referred to as the folate receptor (FR)

This receptor preferentially mediates the uptake of oxidized forms of the vitamin (eg, folic acid) by receptor-mediated endocytosis. FR is expressed on the surfaces of many malignant cells and is fully accessible to parenterally administered folate-drug conjugates.

Several chemotherapeutic agents have also been conjugated to folic acid for FR-targeted chemotherapy


Step 1
Nontoxic
Tumor
cell membrane
Cytoplasm
Step 2
Nucleus
Endosome
Lysosome
Step 3
Step 4
Toxic



≡


Drug
Linker
Targetin
ligand
Trigger

Enzyme-Prodrug Therapies

For selective activation of prodrugs in tumor cells

Two steps:

1. Incorporate a prodrug-activating enzyme into a target tumor cell

2. Administer a nontoxic prodrug which is a substrate for the exogenous enzyme that incorporated

Criteria for Success with Enzyme-Prodrug Therapies

1. The prodrug-activating enzyme is *either nonhuman or a human protein expressed poorly in normal human cells.*

2. The prodrug-activating enzyme must have high *catalytic activity.*

3. The prodrug must be a *good substrate* for the incorporated enzyme and *not for other endogenous enzymes.*

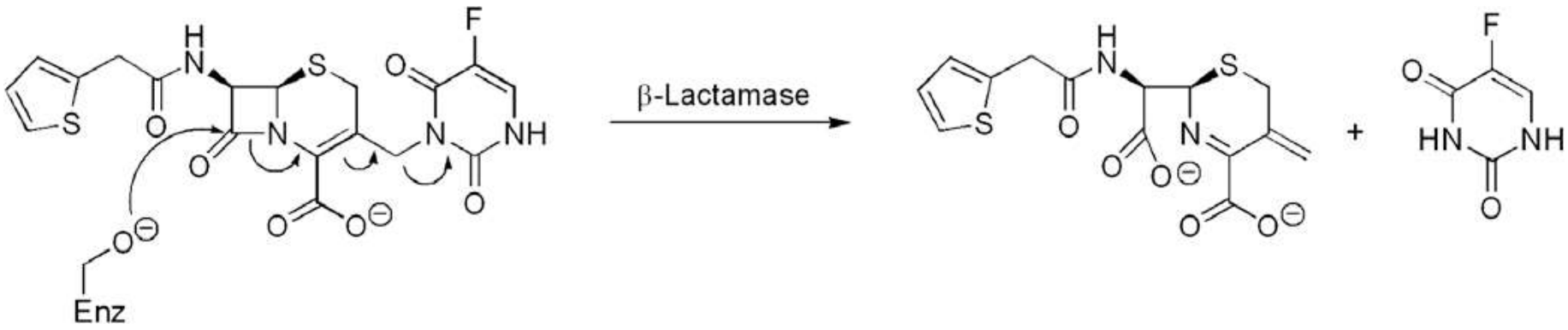
4. The prodrug must be able to *cross tumor* cell membranes.

5. The prodrug should have no or *low cytotoxicity and the drug high cytotoxicity.*

6. The activated drug should be highly *diffusible to kill neighboring non expressing cells* (bystander killing effect).

7. The half-life of the *active drug is long enough for bystander killing effect but short enough to avoid leaking out of tumor cells.*

Example of Enzyme-Prodrug Therapies is the incorporation of the β-lactamase into the cancer cell and then administer the anticancer-cephalosporin pordrug to be selectively hydrolyzed in the cancer tisuue.



Antibody-Directed Enzyme Prodrug Therapy (ADEPT)

An approach for site-specific delivery of cancer drugs.

Phase One: An antibody-enzyme conjugate is administered which binds to the surface of the tumor cells. The antibody used has been targeted for the particular tumor cell. The enzyme chosen for the conjugate is one that will be used to cleave the carrier group off of the prodrug administered in the next phase.

Phase Two: After the antibody-enzyme has accumulated on the tumor cell and the excess conjugate is cleared from the blood and normal tissues, the prodrug is administered. The enzyme conjugated with the antibody at the tumor cell surface catalyzes the conversion of the prodrug to the drug when it reaches the tumor cell.

ADEPT

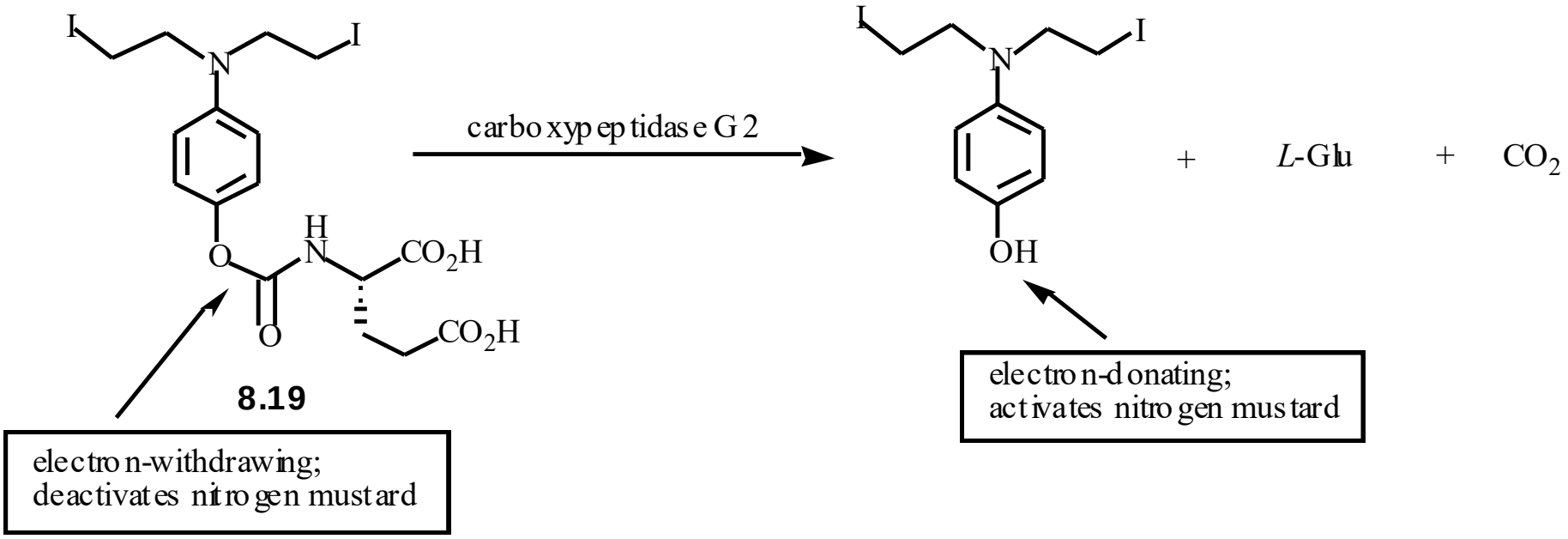
Advantages:

1. Increased selectivity for targeted cell
2. Each enzyme molecule converts many prodrug molecules
3. The released drug is at the site of action
4. Demonstrated to be effective at the clinical level
5. Concentrates the drug at the site of action

Disadvantages:

1. Immunogenicity and rejection of antibody-enzyme conjugate
2. Complexity of the two-phase system and i.v. administration
3. Potential for leak back of the active drug

An example is c*arboxypeptidase G2 or alkaline phosphatase* linked to an antibody to activate a nitrogen mustard prodrug.



Note the *prodrug-activating enzyme is a bacterial enzyme.*

Antibody-Directed Abzyme Prodrug Therapy (ADAPT)

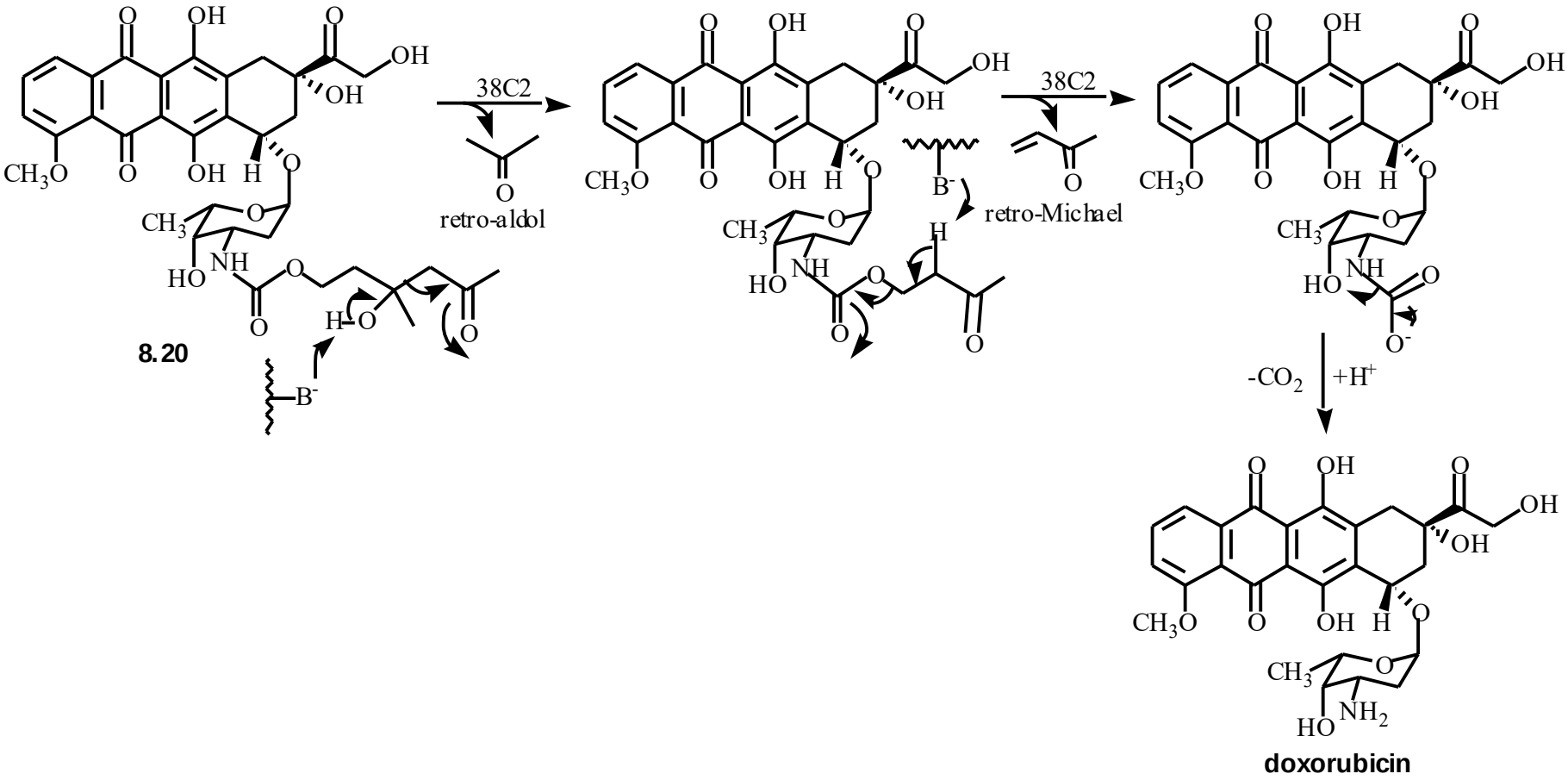
Instead of using a prodrug-activating enzyme, a humanized prodrug-activating catalytic antibody (abzyme) can be used.

Ideally, the abzyme catalyzes a reaction not known to occur in humans, so the only site where the prodrug could be activated is at the tumor cell where the abzyme is bound.

Antibody 38C2 catalyzes sequential retro-aldol and retro-Michael reactions not catalyzed by any known human enzyme.

Found to be long-lived in vivo, to activate prodrugs selectively, and to kill colon and prostate cancer cells.

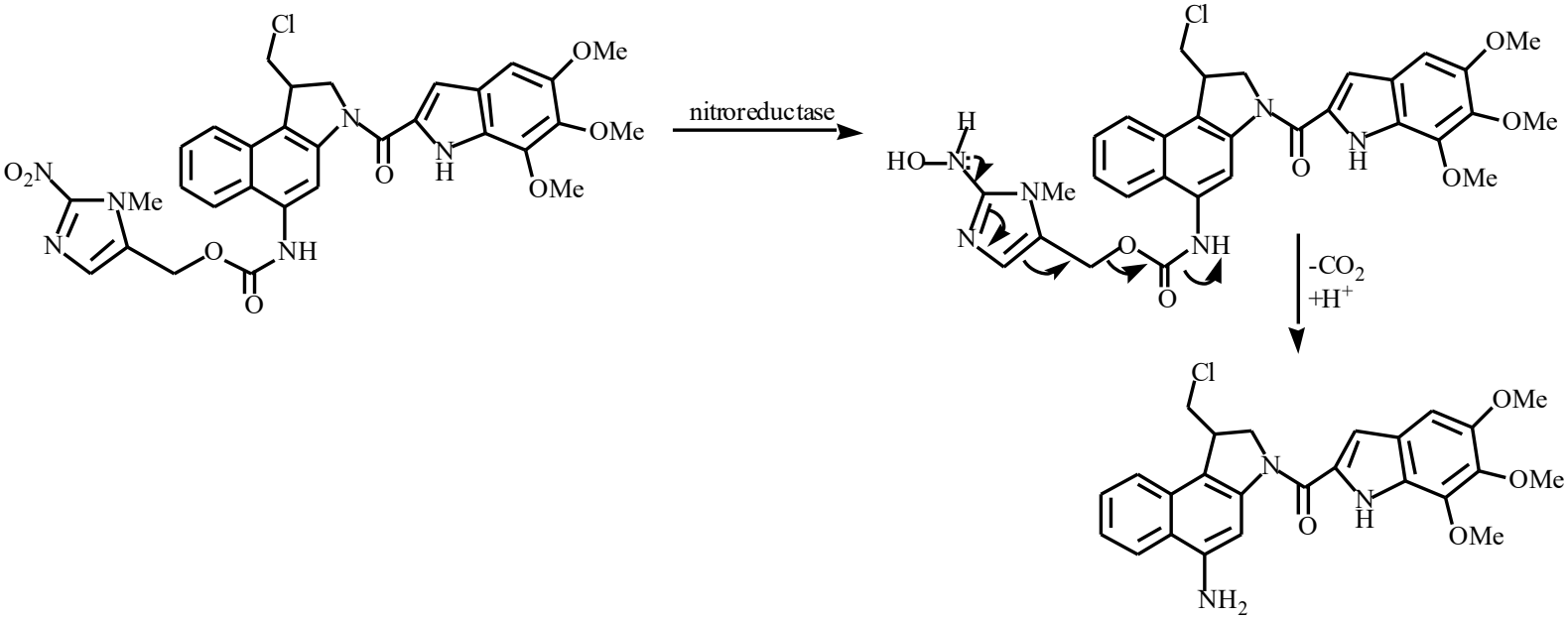
Abzyme 38C2 Activation of a Doxorubicin Prodrug



Gene-Directed Enzyme Prodrug Therapy (GDEPT)

Also known as suicide gene therapy

A gene encoding the prodrug-activating enzyme is expressed in target cancer cells under the control of tumor-selective promoters or by viral transfection. These cells activate the prodrug as in ADEPT.



amino-*seco*-CBI-TMI

8.21

Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 7

Macromolecular Drug Delivery

A bipartate or tripartate carrier-linked prodrug in which the drug is attached to a macromolecule, such as a synthetic polymer, protein, lectin, antibody, cell, etc.

Advantage

1. Absorption/distribution depends on the physicochemical properties of macromolecular carrier, not of the drug. Therefore, attain better targeting.

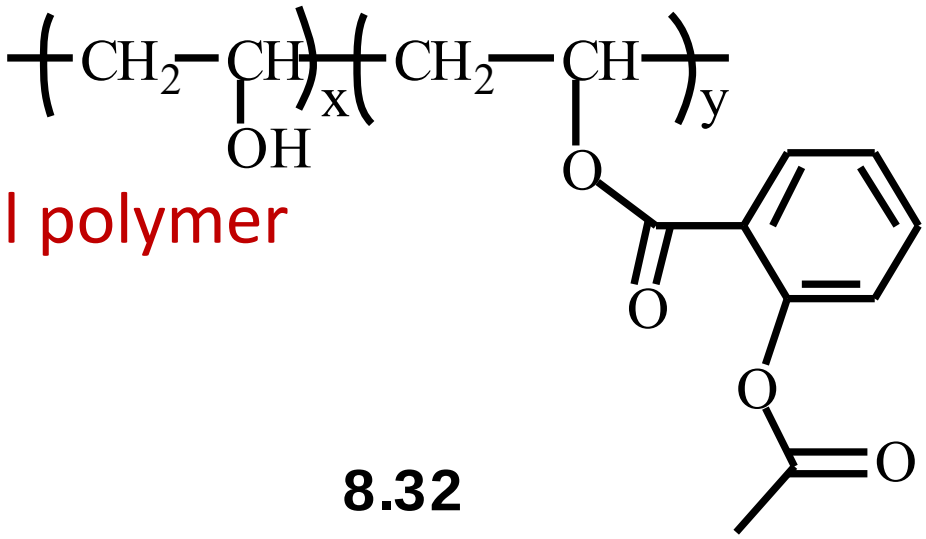
2. Minimize interactions with other tissues or enzymes.
3. Fewer metabolic problems; increased therapeutic index.

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



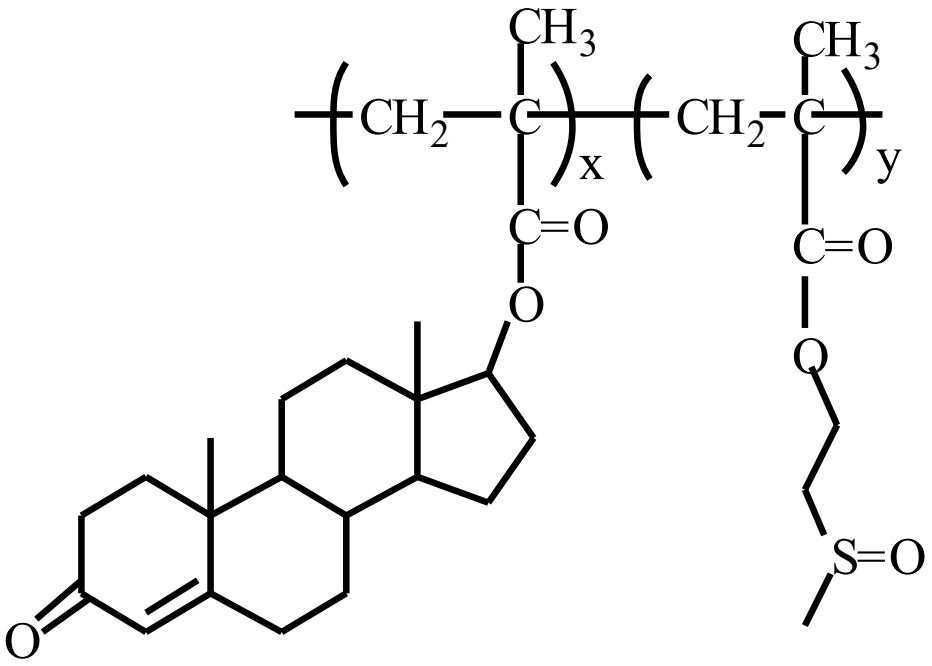
vinyl alcohol polymer

8.32

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

Steric Hindrance by Polymer Carrier

poly(methacrylate)polymer



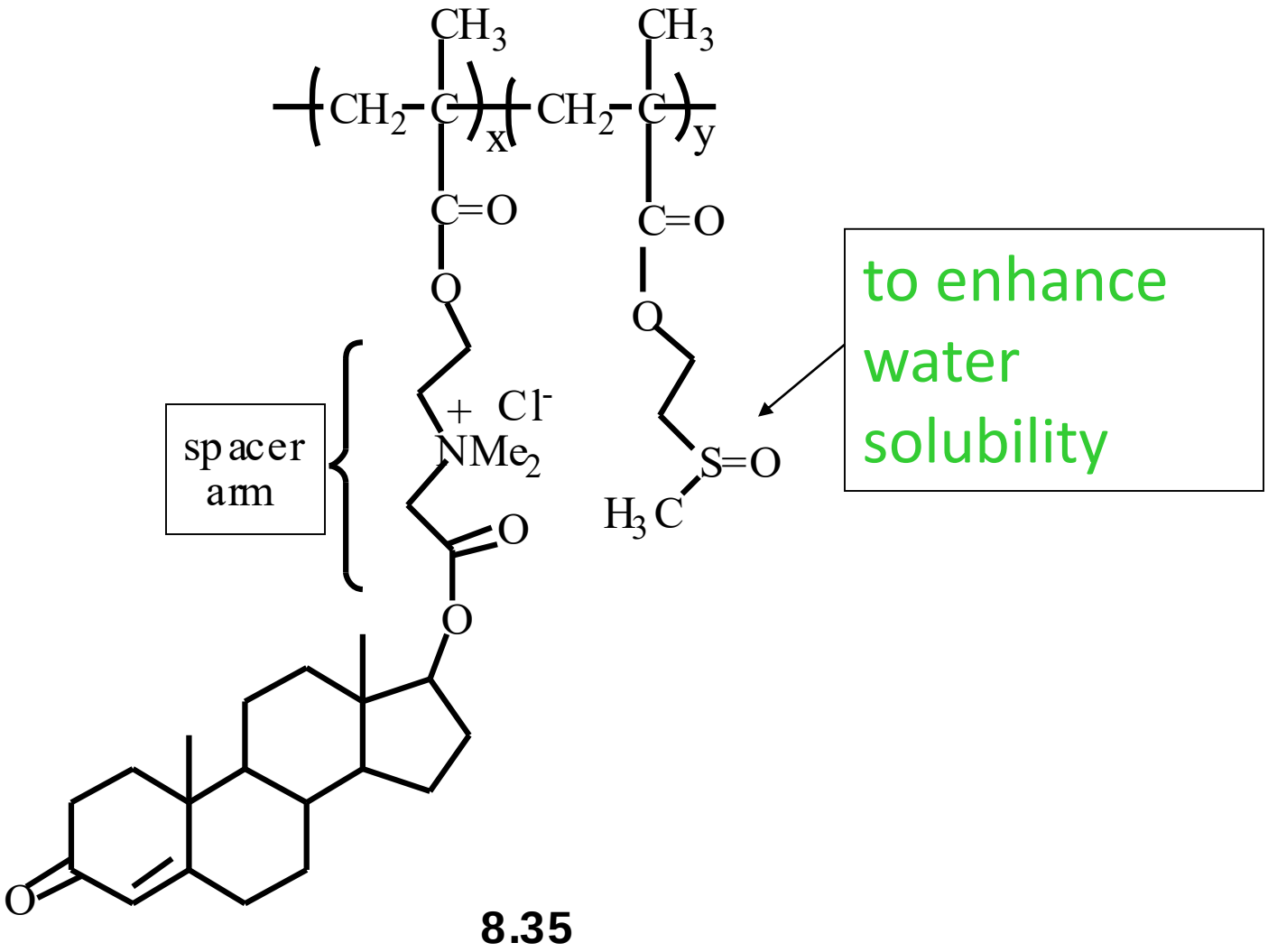
testosterone **8.34**

to enhance water solubility

No androgenic effect

Polymer backbone may be sterically hindering the release of the testosterone.

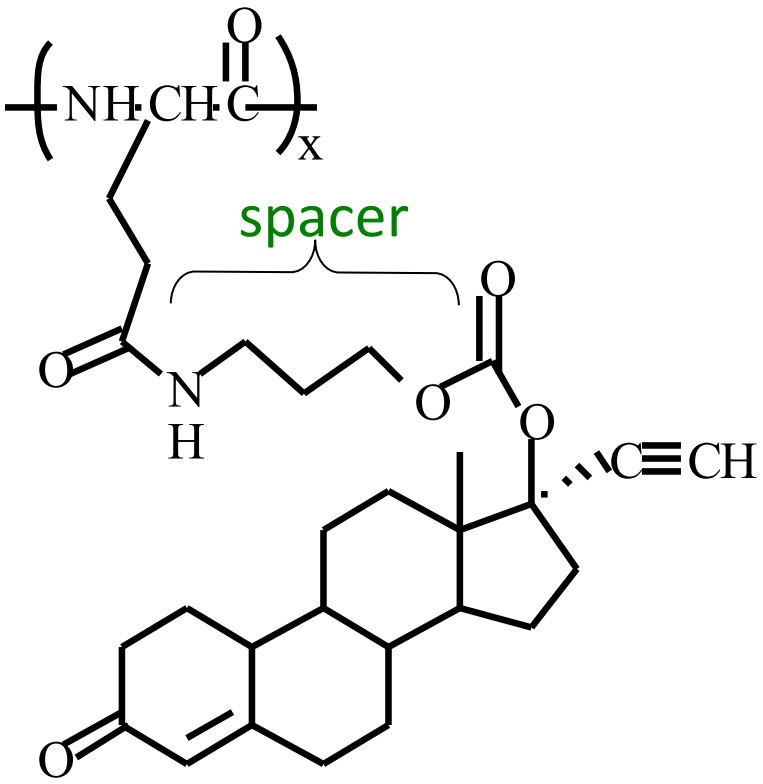
A spacer arm was added, and it was as effective as testosterone.



8.35

Poly(α-Amino Acid) Carriers

poly(*L*-glutamine)

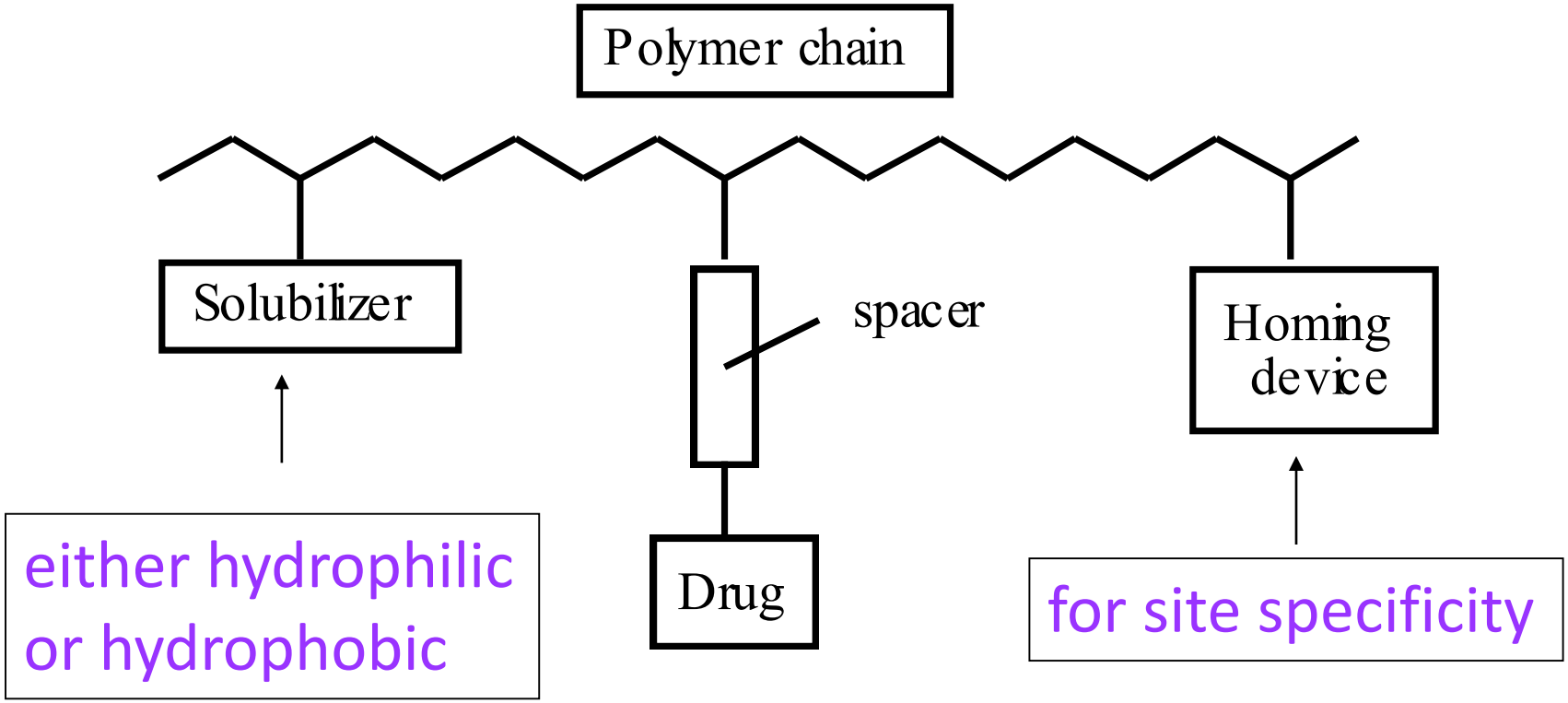


8.37

norethindrone - contraceptive

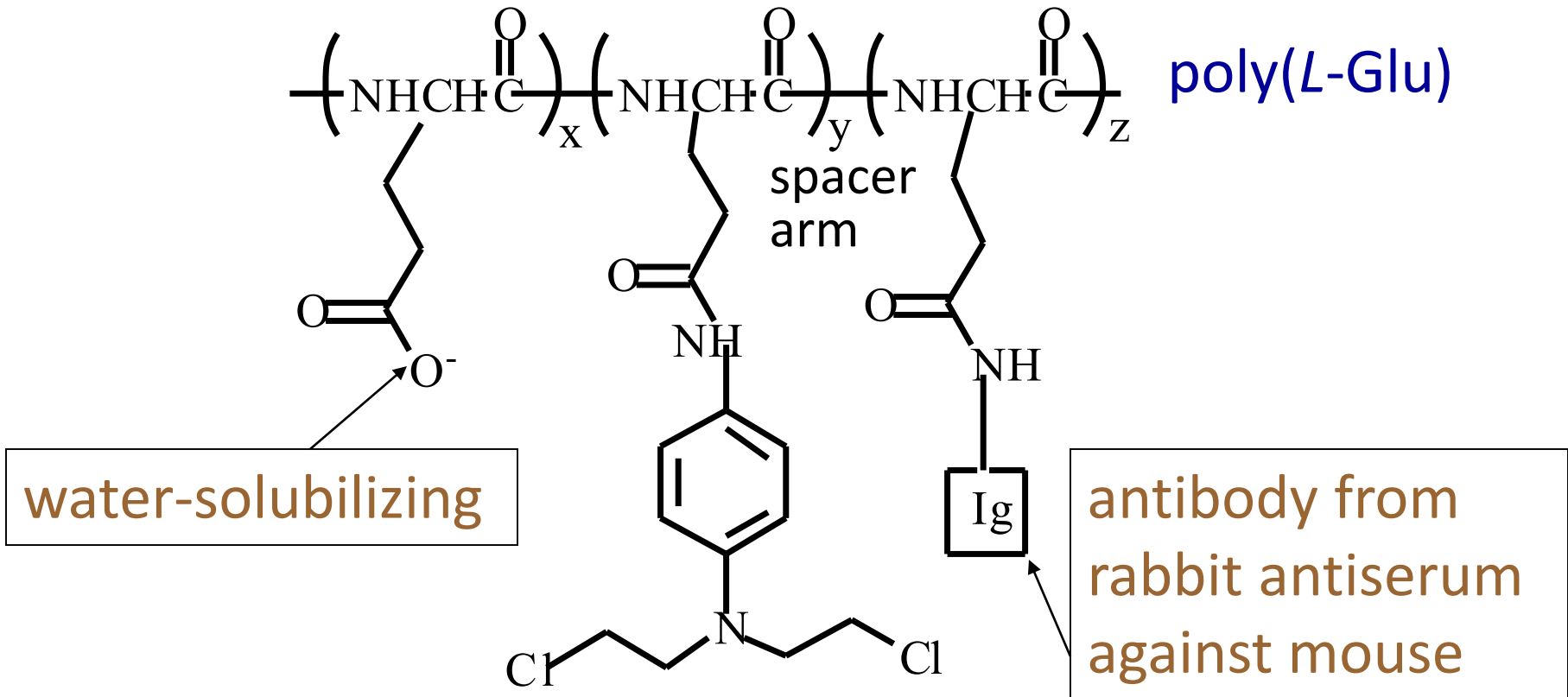
Slow release over nine months in rats

General Structure of Site-Specific Macromolecular Drug Delivery System



8.38

Site-Specific Delivery of a Nitrogen Mustard



8.39

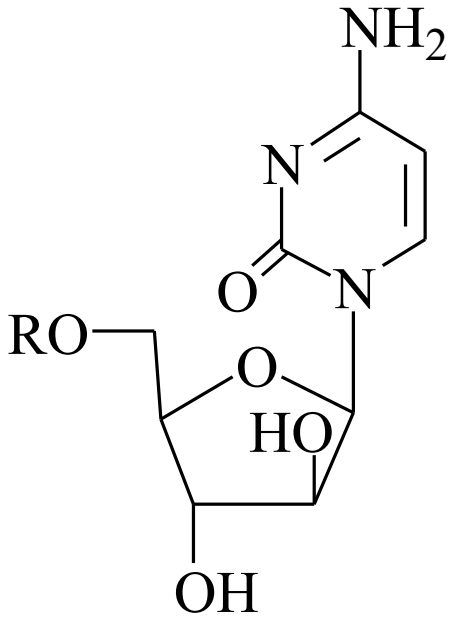
All 5 mice tested were alive and tumor free after 60 days (all controls died).

Also, therapeutic index greatly enhanced (40 fold).

Tumor Cell Selectivity

Drug attached to albumin (R = albumin)

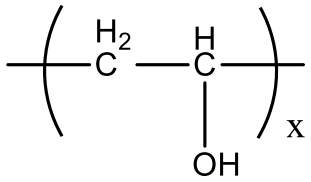
Tumor cells take up proteins rapidly. Proteins broken down inside cells, releasing the drug.



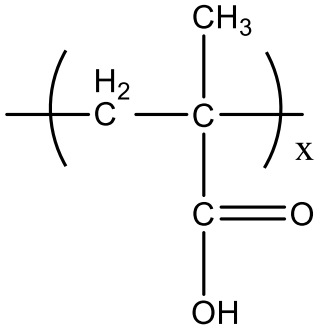
cytosine arabinoside (R = H)
8.41

antitumor

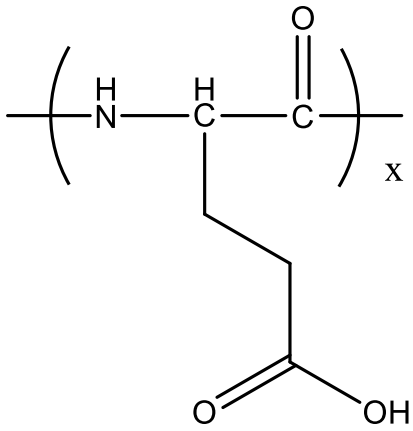
Type of polymers



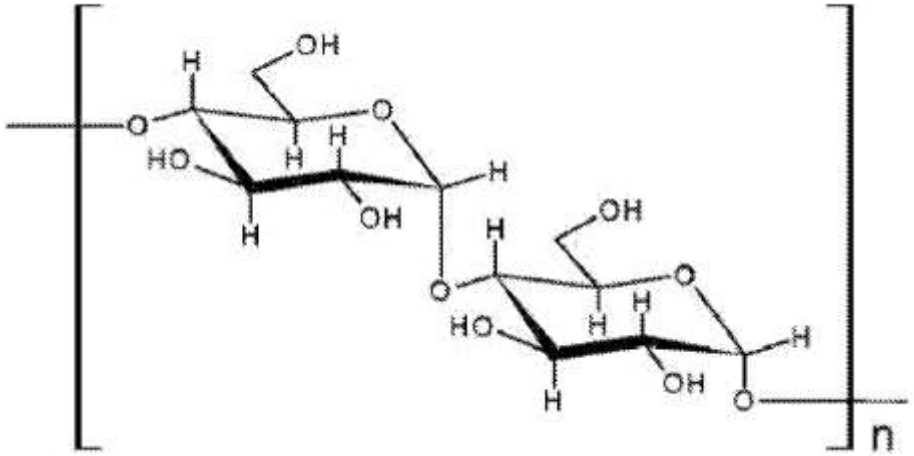
Polyvinyl alcohol



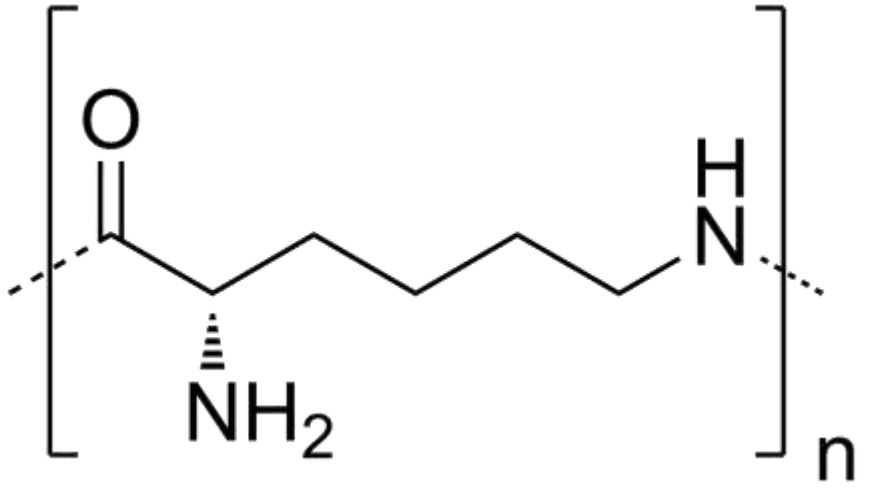
poly(methacrylate)polymer



poly(L-glutamine)

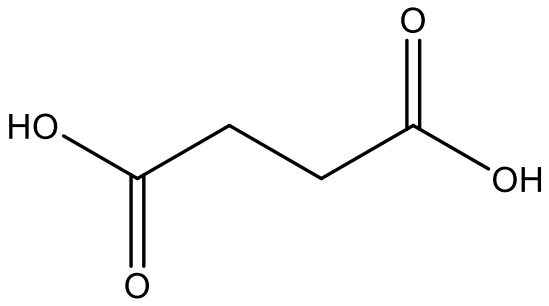


Dextran polymers

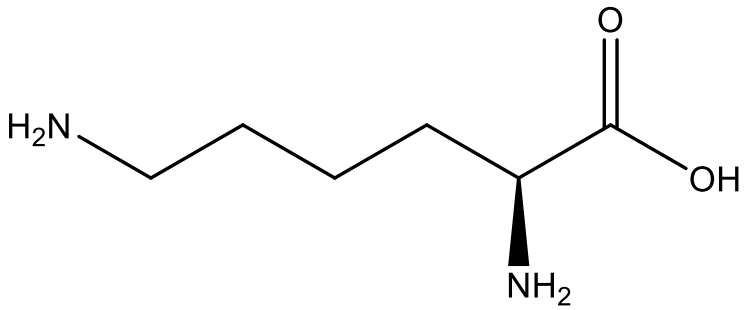


polylysinpolymers

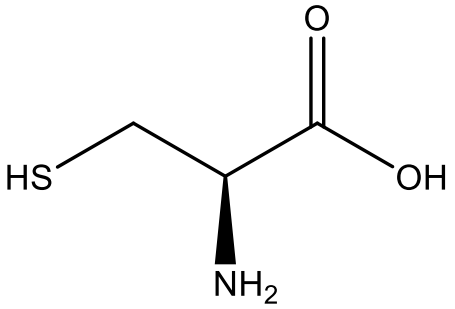
Type of spacer (linker)



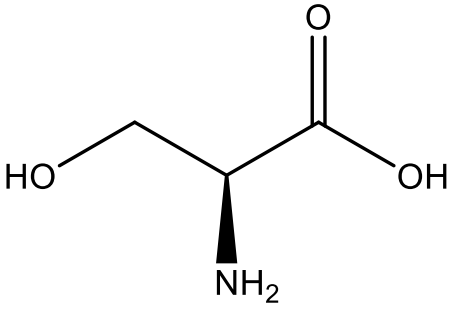
succinic acid



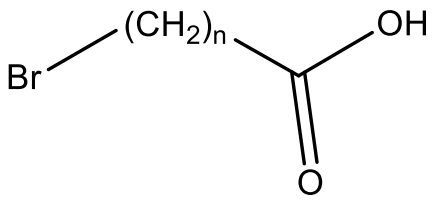
lysin



cystein



serine



Bromo caboxylic acid

Use suitable polymer and spacer (linker) for design polymeric prodrug for the following drug.

1. Drug-OH to improve water solubility
2. Drug-SH to improve lipid solubility
3. Drug-COOH
4. Drug- NH_2
5. Drug-(C=O)-CH_3

Prodrugs and Drug Delivery Systems

Assis.Prof.Dr.Mohammed Hassan

Lecture 8

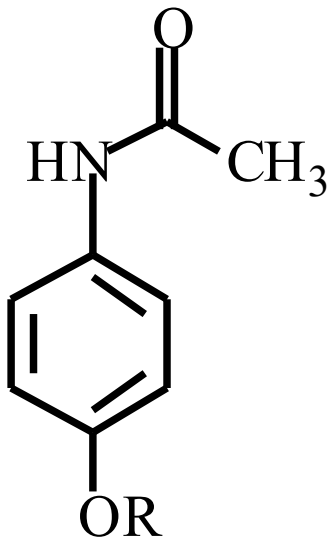
Bioprecursor Prodrugs

Carrier-linked prodrugs largely use hydrolytic activation

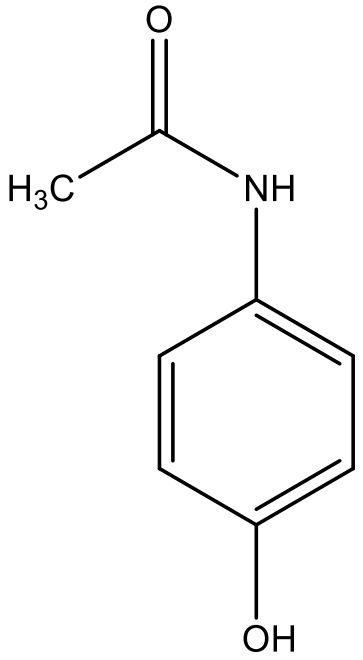
Bioprecursor drugs mostly use oxidative or reductive activation

O-Dealkylation

Analgesic activity of phenacetin is a result of *O*-dealkylation to acetaminophen.



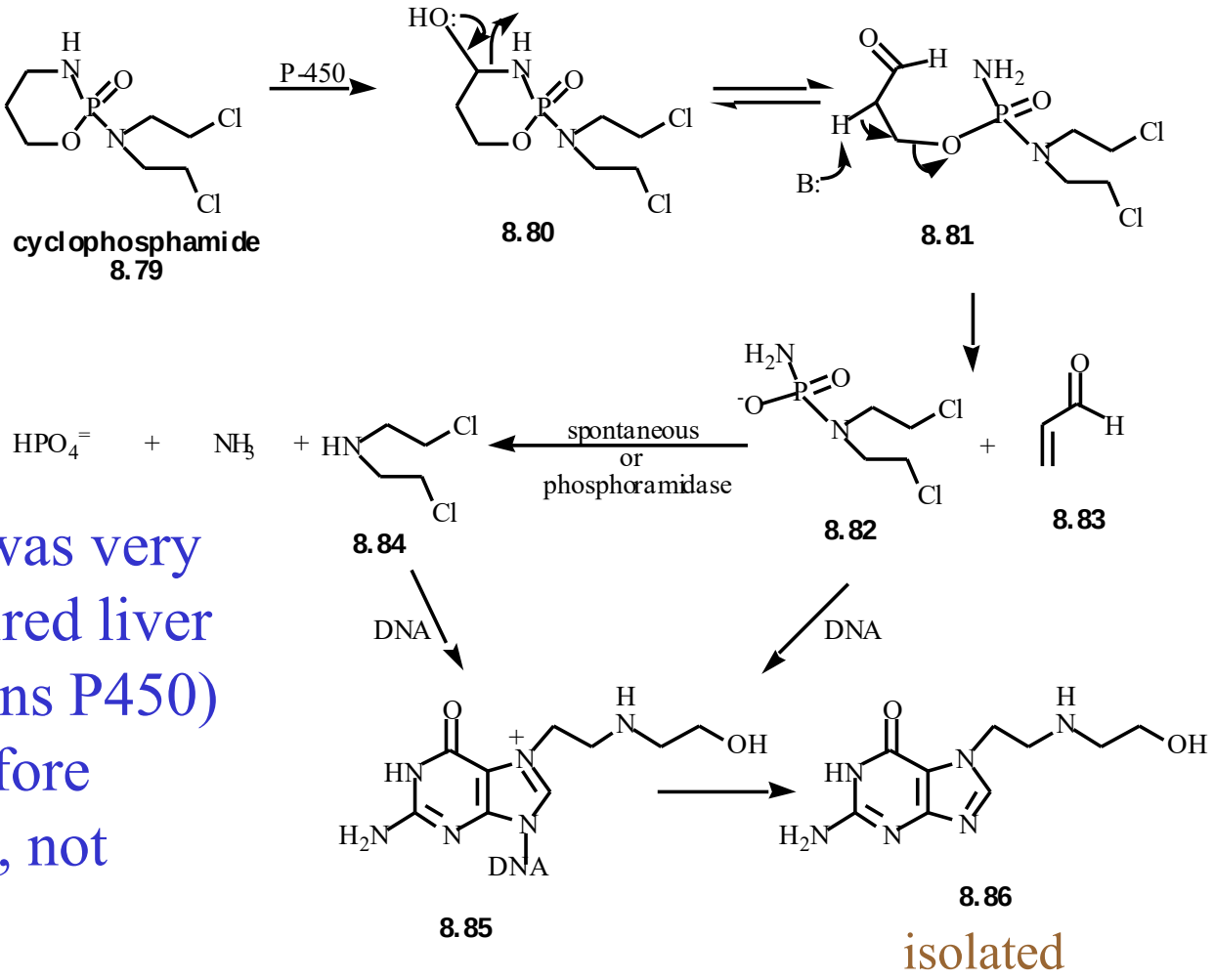
phenacetin (R = CH_2CH_3)
acetaminophen (R = H)
8.78



Acetaminophen

Oxidative Deamination

Neoplastic (cancer) cells have a high concentration of phosphoramidases, so hundreds of phosphamide analogs of nitrogen mustards were made for selective activation in these cells.



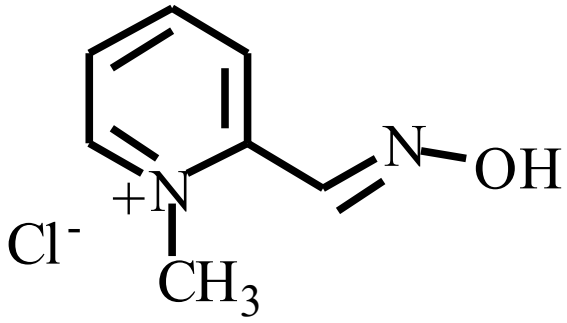
Cyclophosphamide was very effective, but it required liver homogenates (contains P450) for activation. Therefore oxidation is required, not hydrolysis.

isolated

N-Oxidation

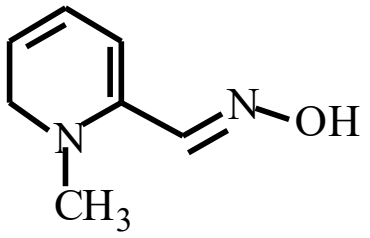
Pralidoxime chloride is an antidote for nerve poisons.

It reacts with acetylcholinesterase that has been inactivated by organophosphorus toxins.



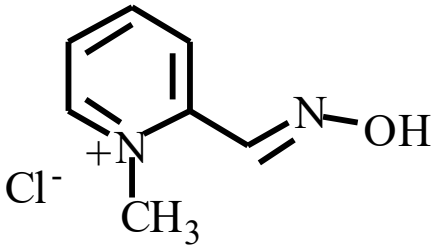
pralidoxime chloride
8.91

To increase the permeability of pralidoxime into the CNS, the pyridinium ring was reduced



8.92

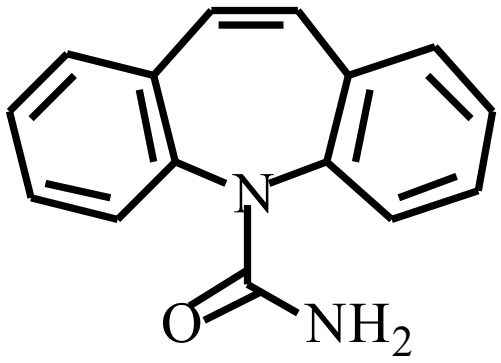
oxidation into brain



pralidoxime chloride
8.91

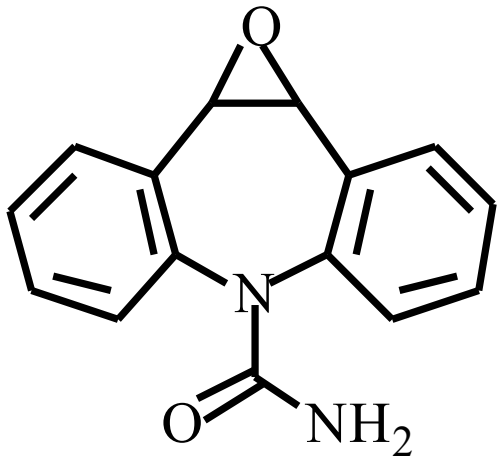
Similar to the reversible redox drug delivery strategy for getting drugs into the brain by attaching them to a dihydronicotinic acid, hydrophobic crosses the blood-brain barrier; oxidation to prevents efflux from brain.

Alkene Epoxidation



carbamazepine
8.102

Epoxidase



8.103

active anticonvulsant agent

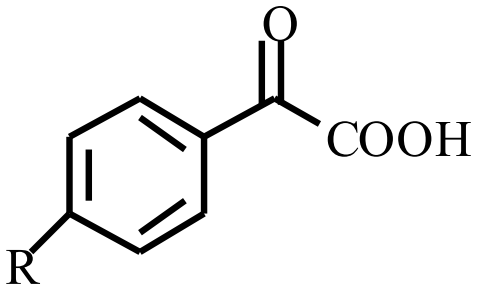
Transamination

Stimulation of pyruvate dehydrogenase results in a change of myocardial metabolism from fatty acid to glucose utilization.

Glucose metabolism requires less O_2 consumption.

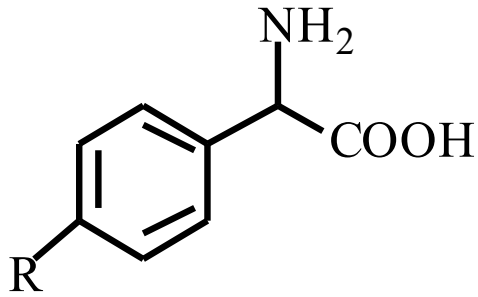
Therefore, utilization of glucose metabolism would be beneficial to patients with ischemic heart disease (arterial blood flow blocked; less O_2 available).

Arylglyoxylic acids (**8.104**) stimulate pyruvate dehydrogenase, but have a short duration of action.



8.104

Oxfenicine (**8.105**, R = OH) is actively transported and is transaminated (aminotransferase) in the heart to **8.104** (R = OH).



oxfenicine (R = OH)
8.105