Lecture 5

Organic Pharm. Chemistry for Pharmacy Students

By

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Areas of Improvement for Prodrugs

- site specificity
- protection of drug from biodegradation
- minimization of side effects

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.

Advantage of Macromolecular Drug Delivery

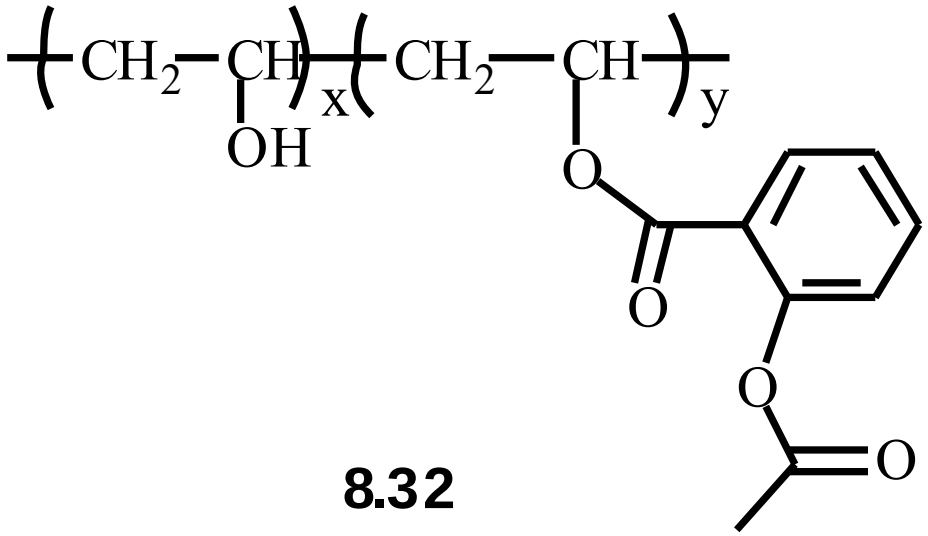
Absorption/distribution depends on the physicochemical properties of macromolecular carrier, not of the drug. Therefore, attain better targeting.

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

i. Synthetic polymers



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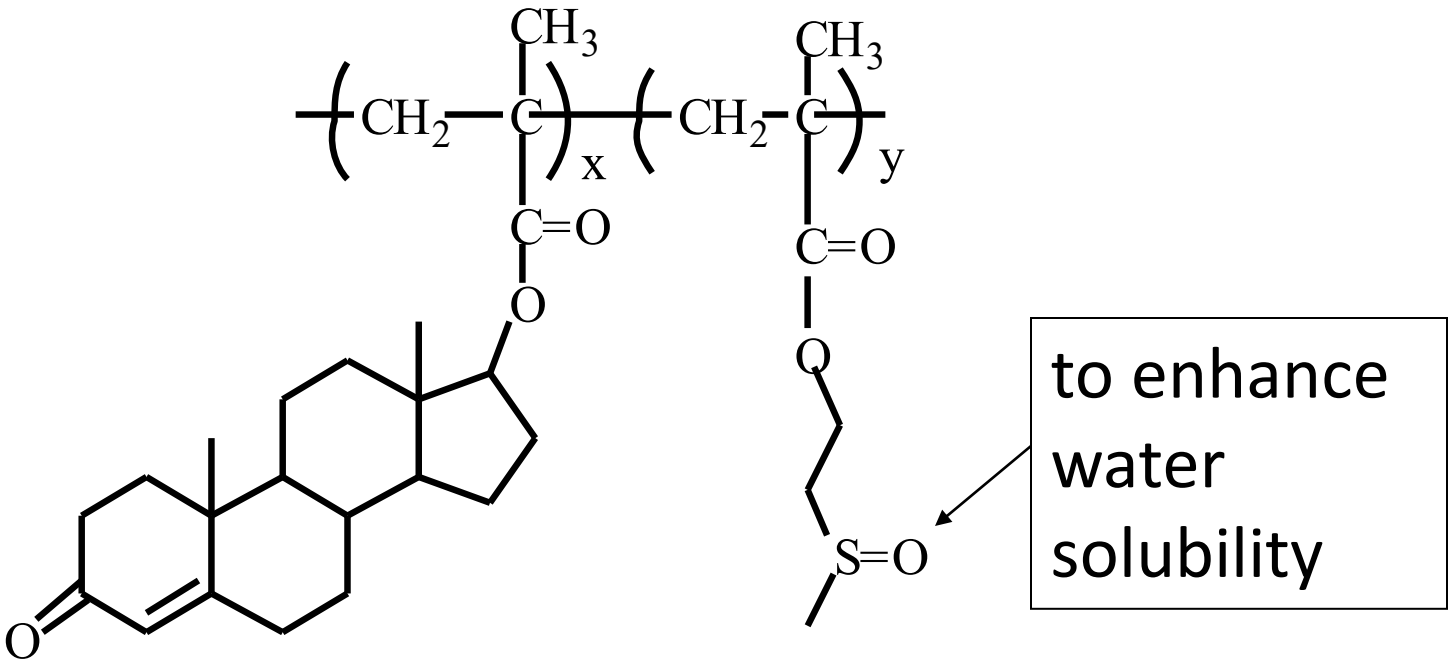
Aspirin linked to poly(vinyl alcohol) has about the same potency as aspirin, but less toxic.

Sterric Hindrance by Polymer Carrier

poly(methacrylate)

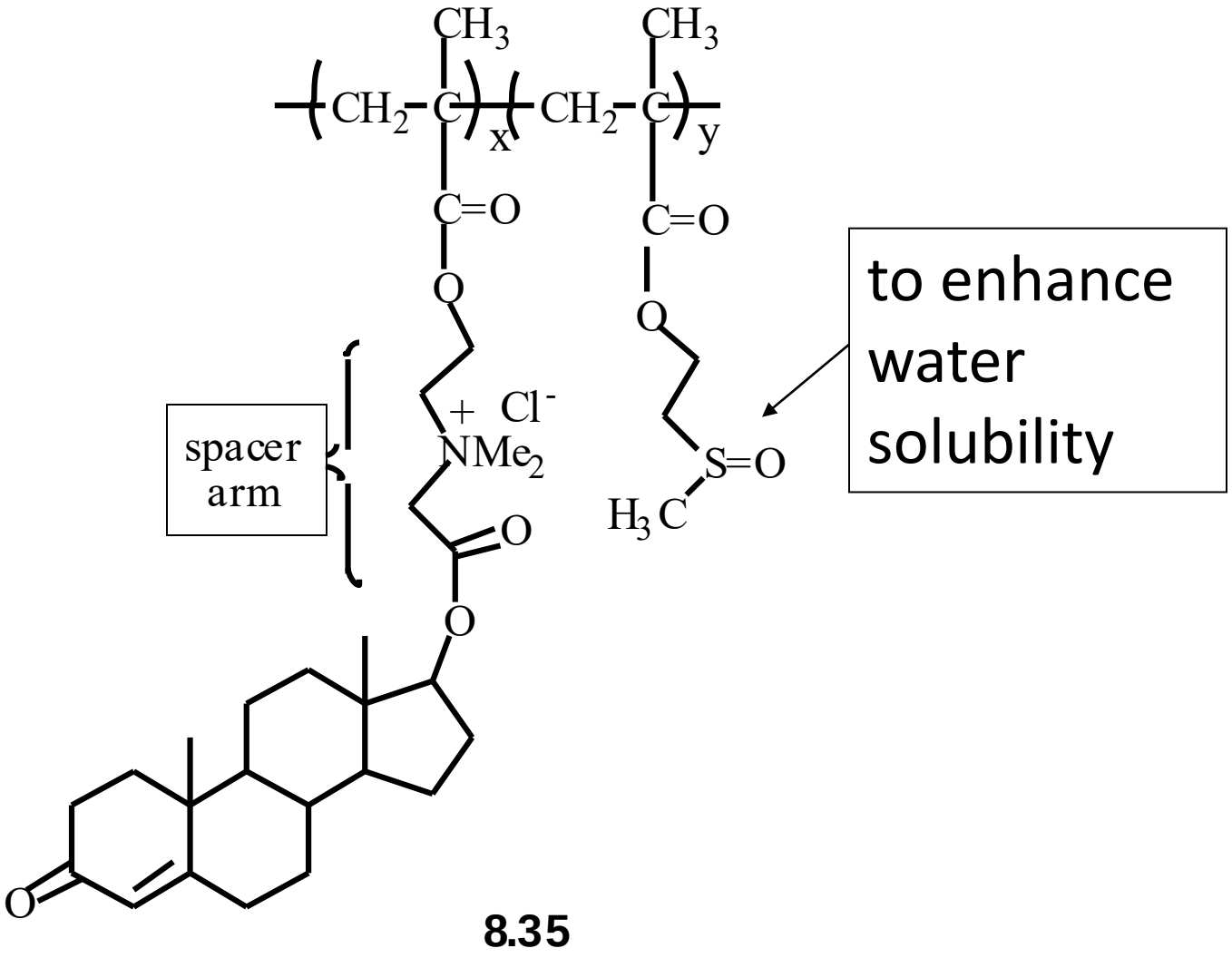


testosterone **8.34**

No androgenic effect

Polymer backbone may <u>be sterically hindering the release of the testosterone.</u>

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



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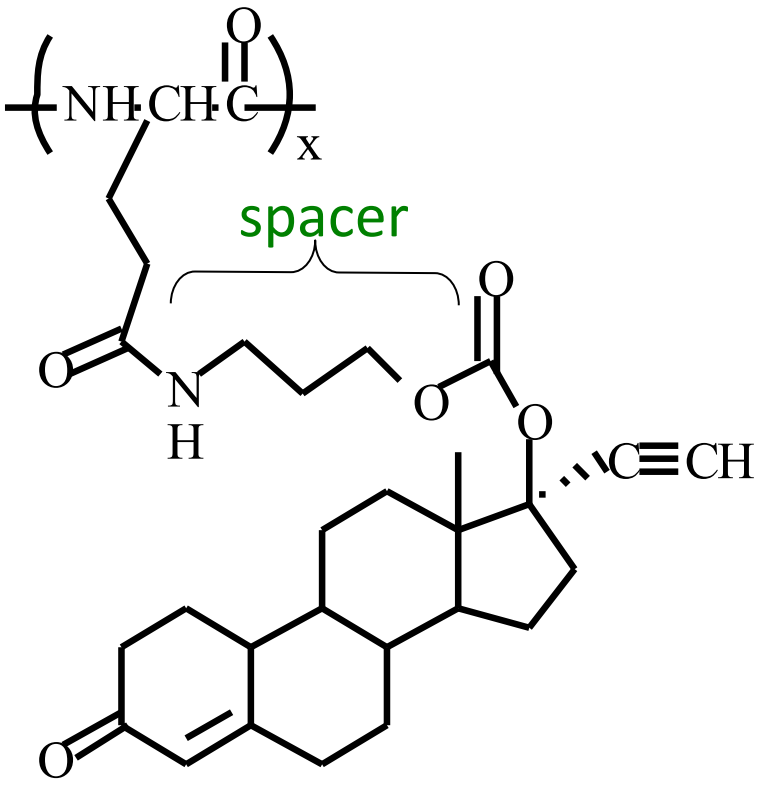
ii. Poly(α-Amino Acid) Carriers

poly(*L*-glutamine)

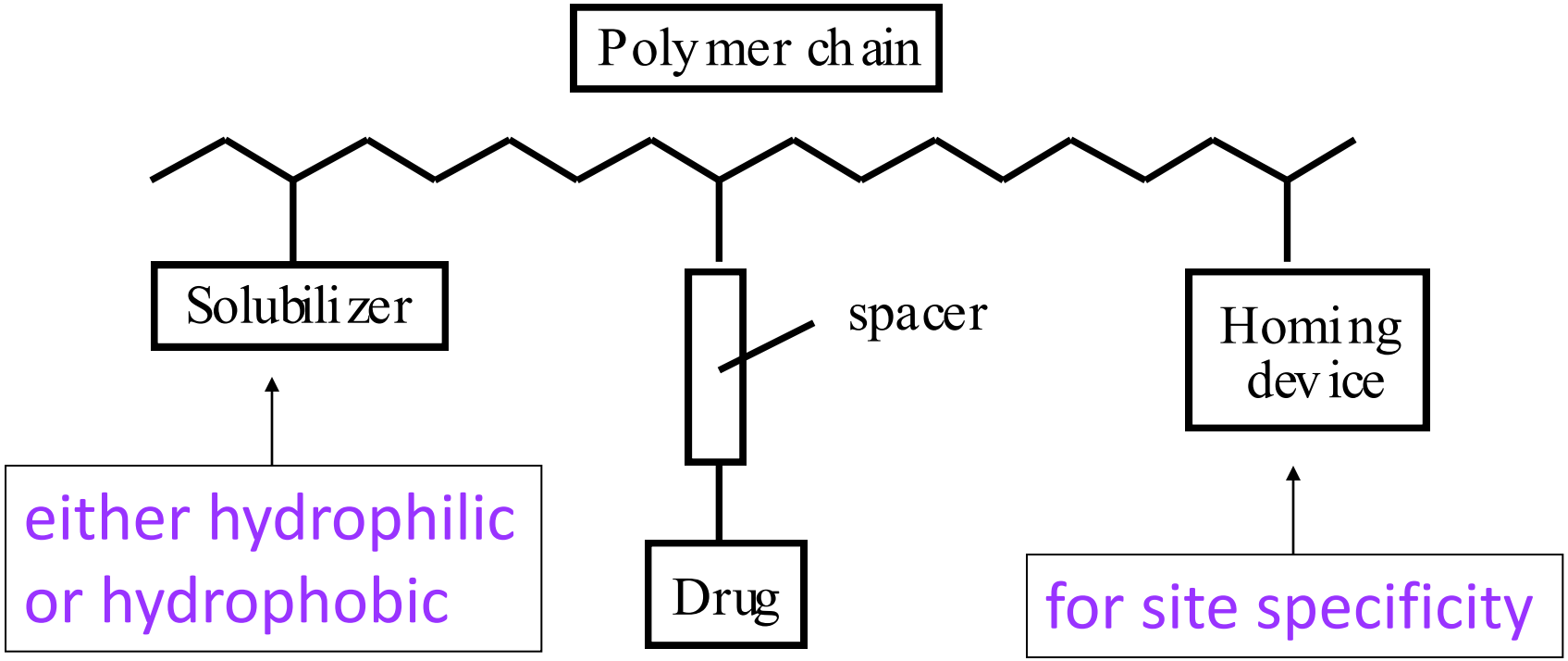


8.37

norethindrone - contraceptive

Slow release over nine months in rats

General Site-Specific Macromolecular Drug Delivery System



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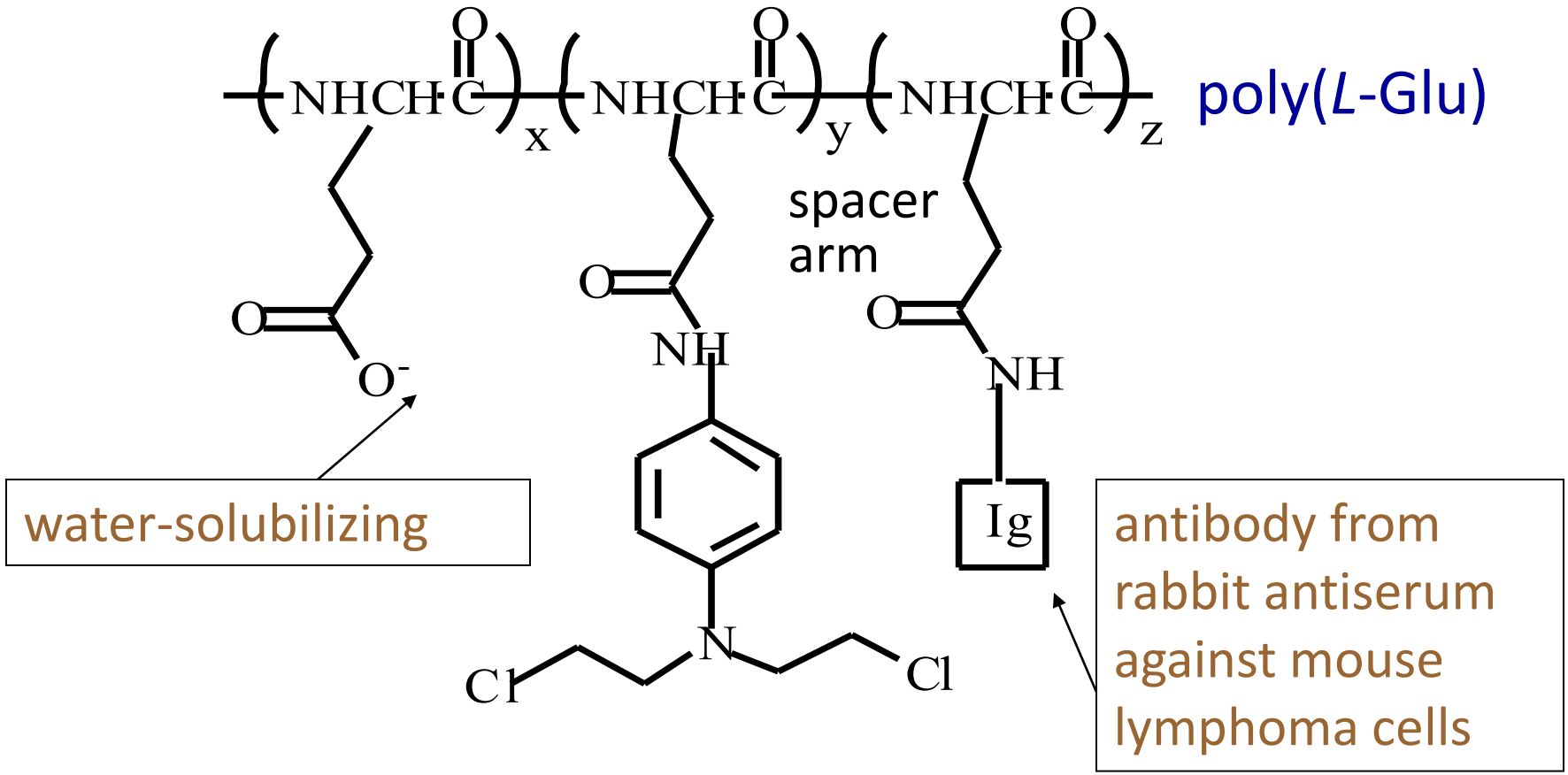
Example: Site-Specific Delivery of a Nitrogen Mustard



8.39

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

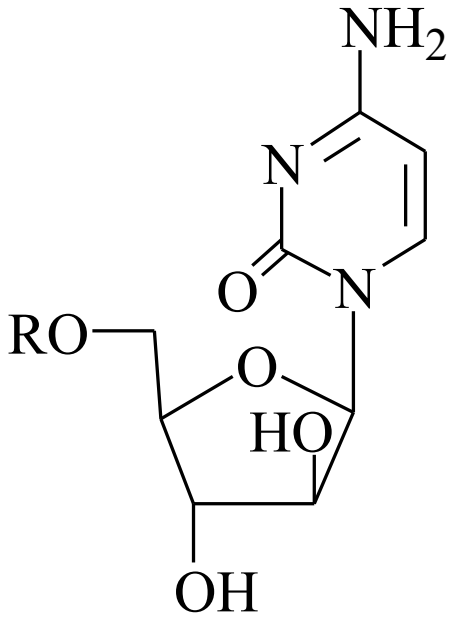
Also, therapeutic index greatly enhanced (40 fold).

Tumor Cell Selectivity

Drug attached to albumin (R = albumin)
(Drug-protien binding)

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

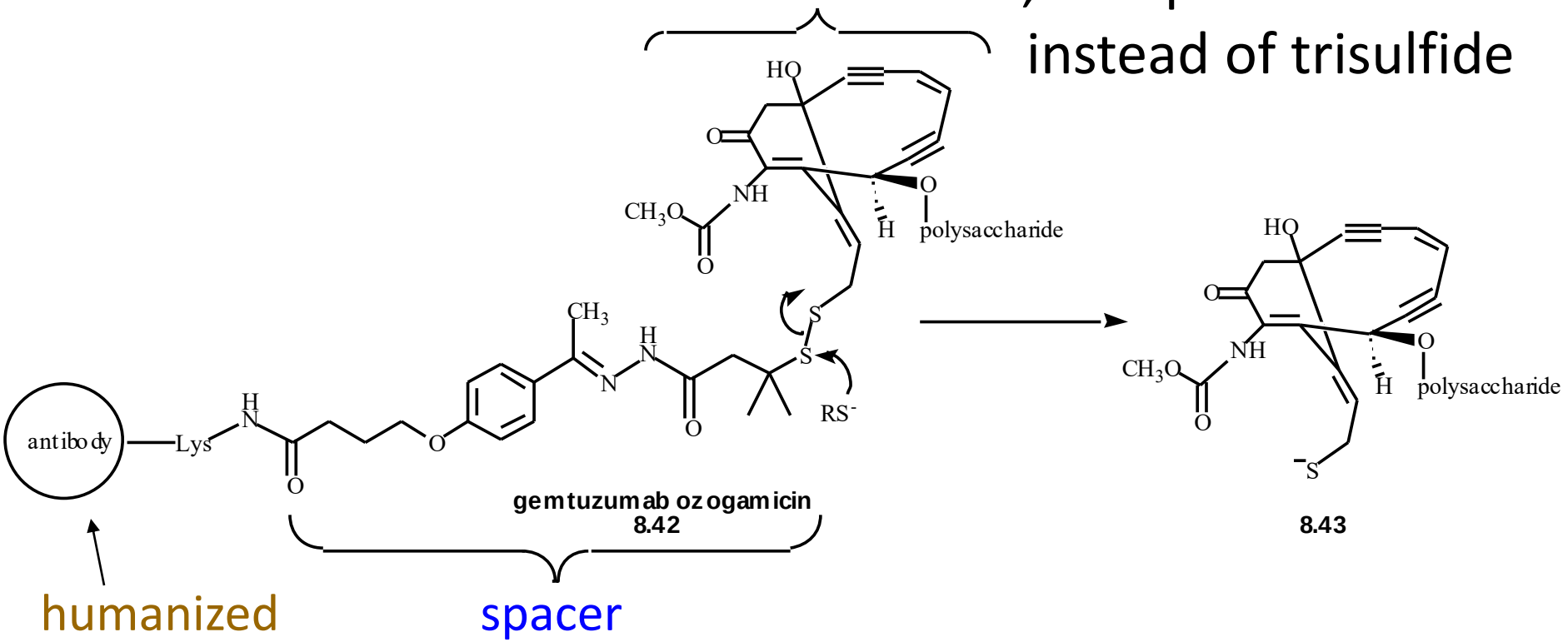
Shown to inhibit growth of *Ectomelia* virus in mouse liver, whereas free inhibitor did not.



cytosine arabinoside (R = H)
8.41
antitumor

Antibody-Targeted Chemotherapy

Scheme 8.7



Does not release calicheamicin nonenzymatically.

Exhibits no immune response.

Tripartate Drugs

(Self-immolative Prodrugs)

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

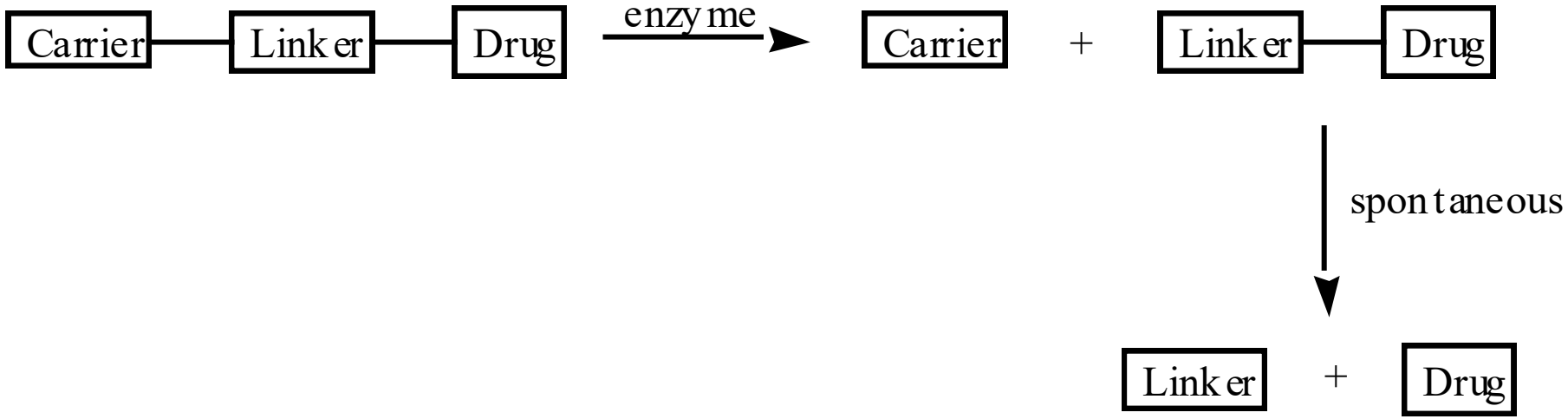
In a tripartate prodrug, the carrier is not attached to the drug; rather, to the linker.

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.

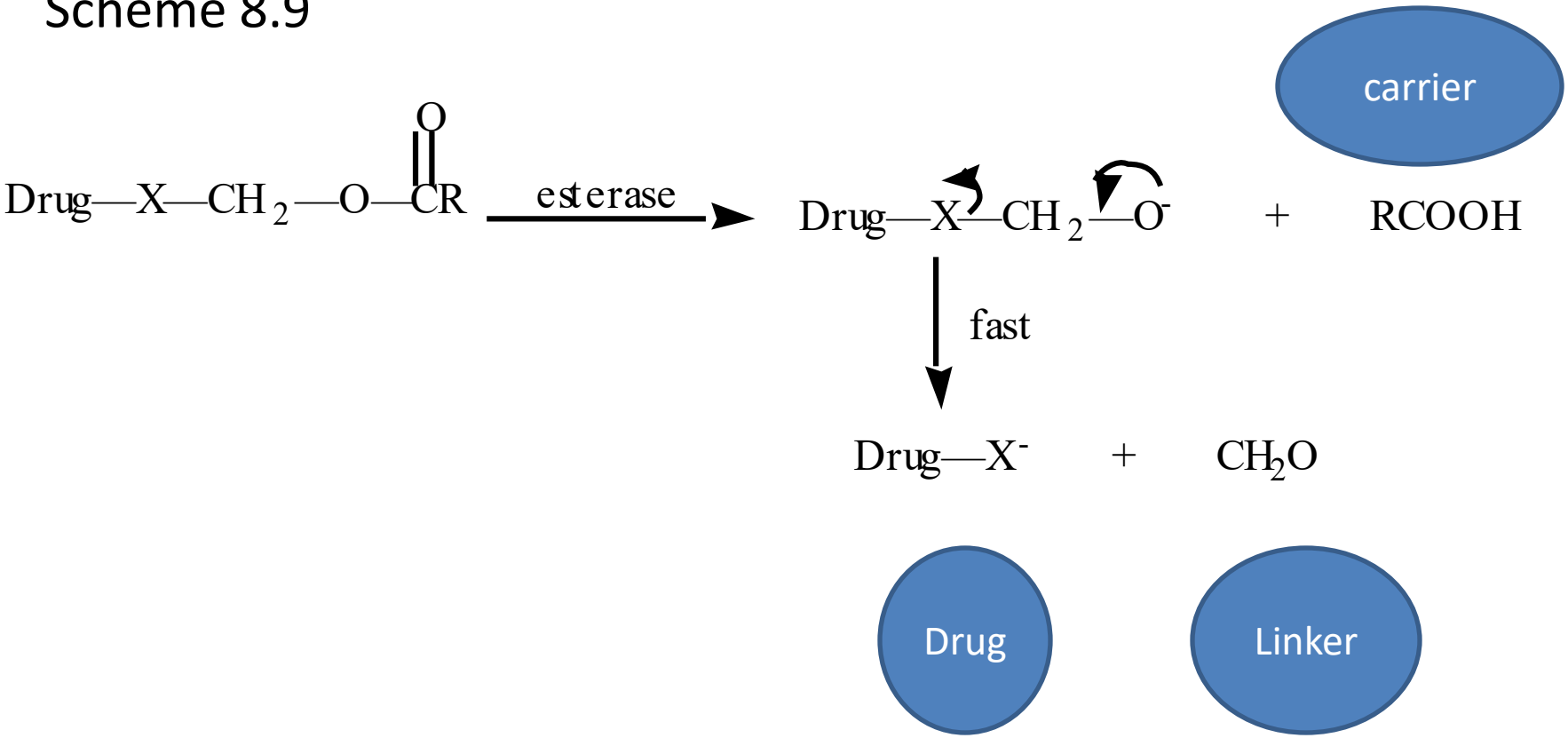
Tripartate Prodrugs

Scheme 8.8



Typical Approach

Scheme 8.9

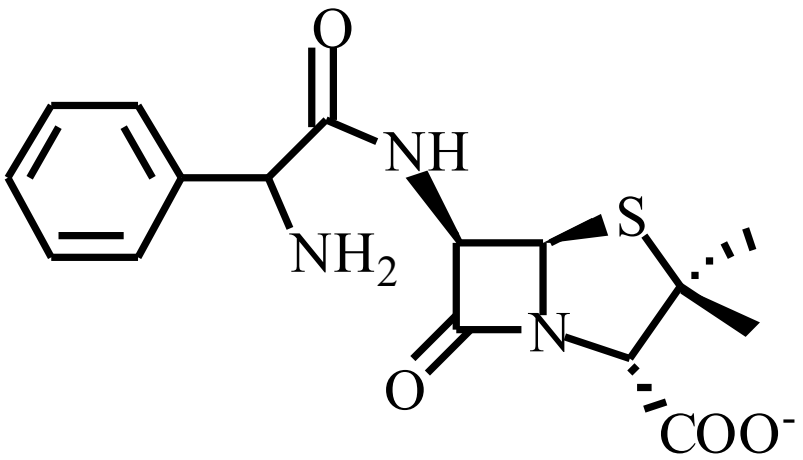


Tripartate Prodrugs of Ampicillin

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.

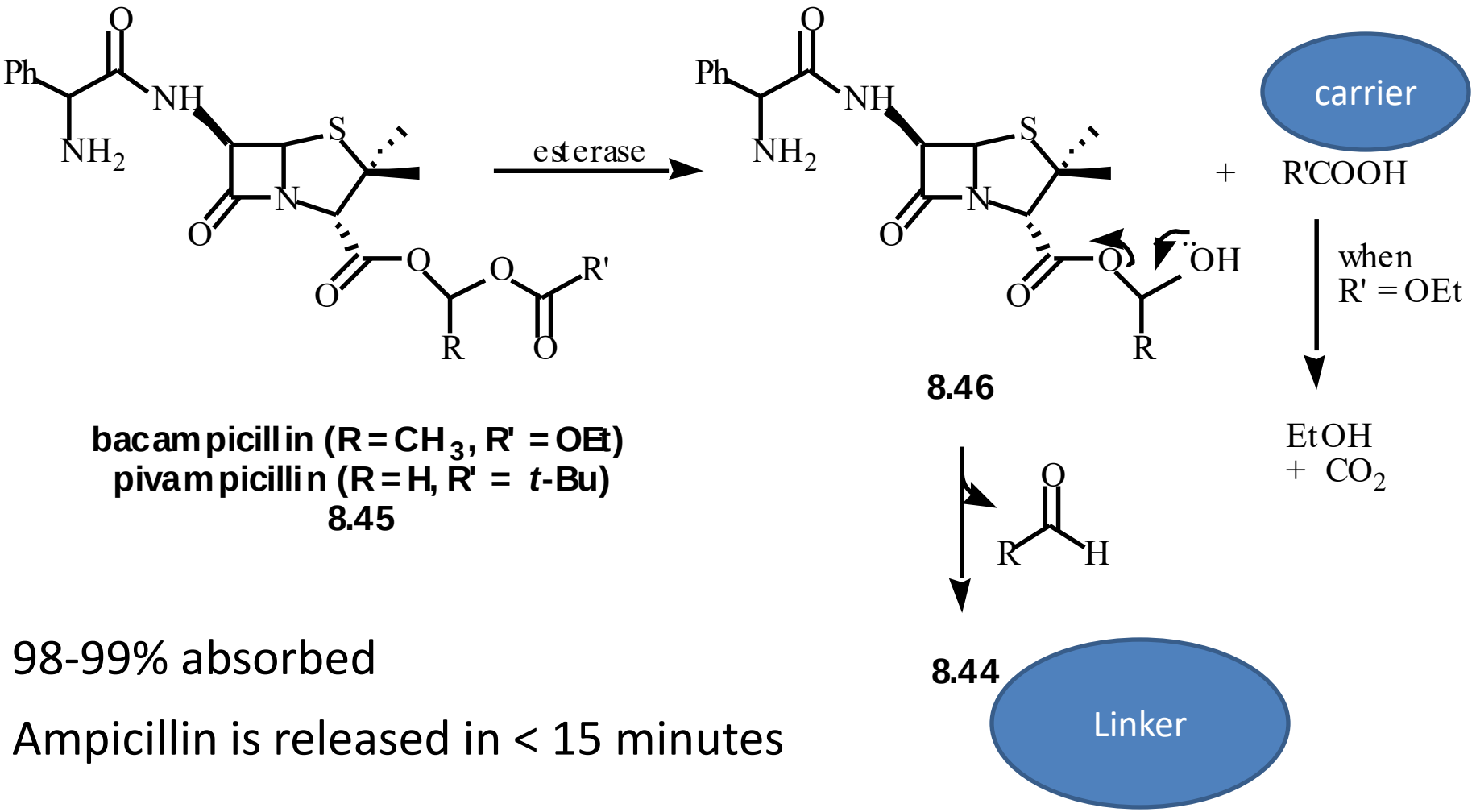


ampicillin
8.44
antibacterial

Various esters made were too stable in humans (although they were hydrolyzed in rodents) - thought the thiazolidine ring sterically hindered the esterase.

Tripartate Prodrugs of Ampicillin

Scheme 8.10



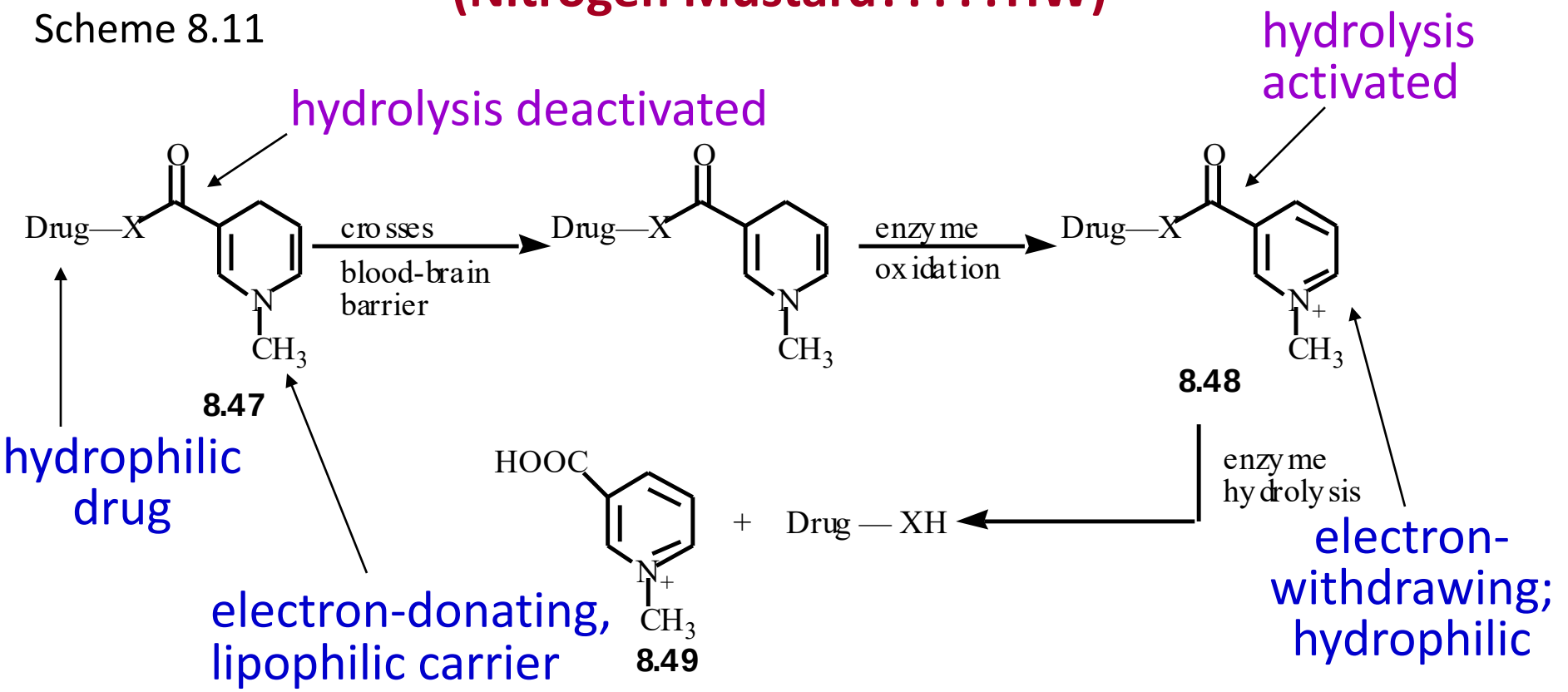
bacampicillin (R = CH_3, R' = OEt)
pivampicillin (R = H, R' = *t*-Bu)
8.45

98-99% absorbed

Ampicillin is released in < 15 minutes

Reversible Redox Drug Delivery System to the CNS (Nitrogen Mustard?????HW)

Scheme 8.11



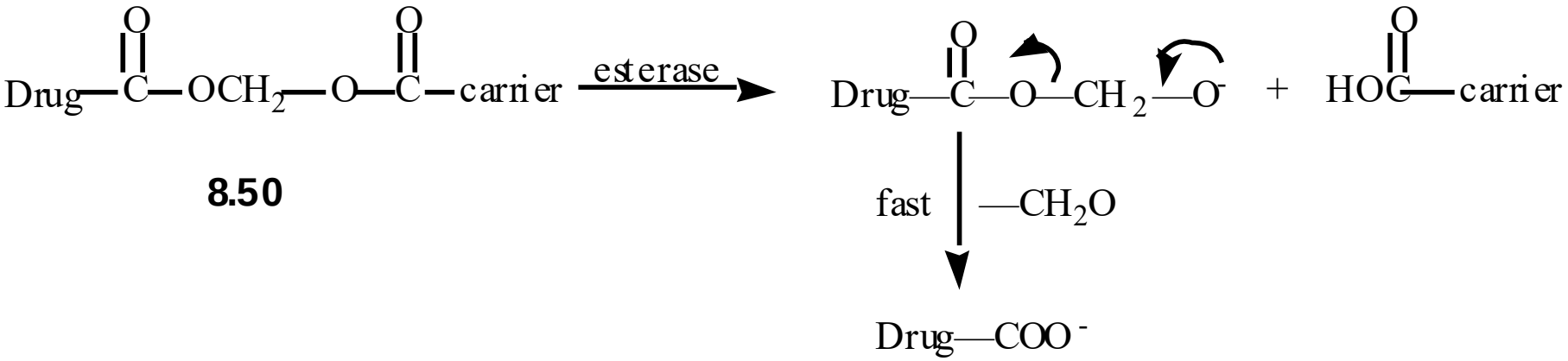
Passive diffusion of **8.47** into the brain; active transport of **8.49** out of the brain

XH of the drug is NH_2, OH, or COOH

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

When the drug is a carboxylic acid, a self-immolative reaction also can be used.

Scheme 8.12



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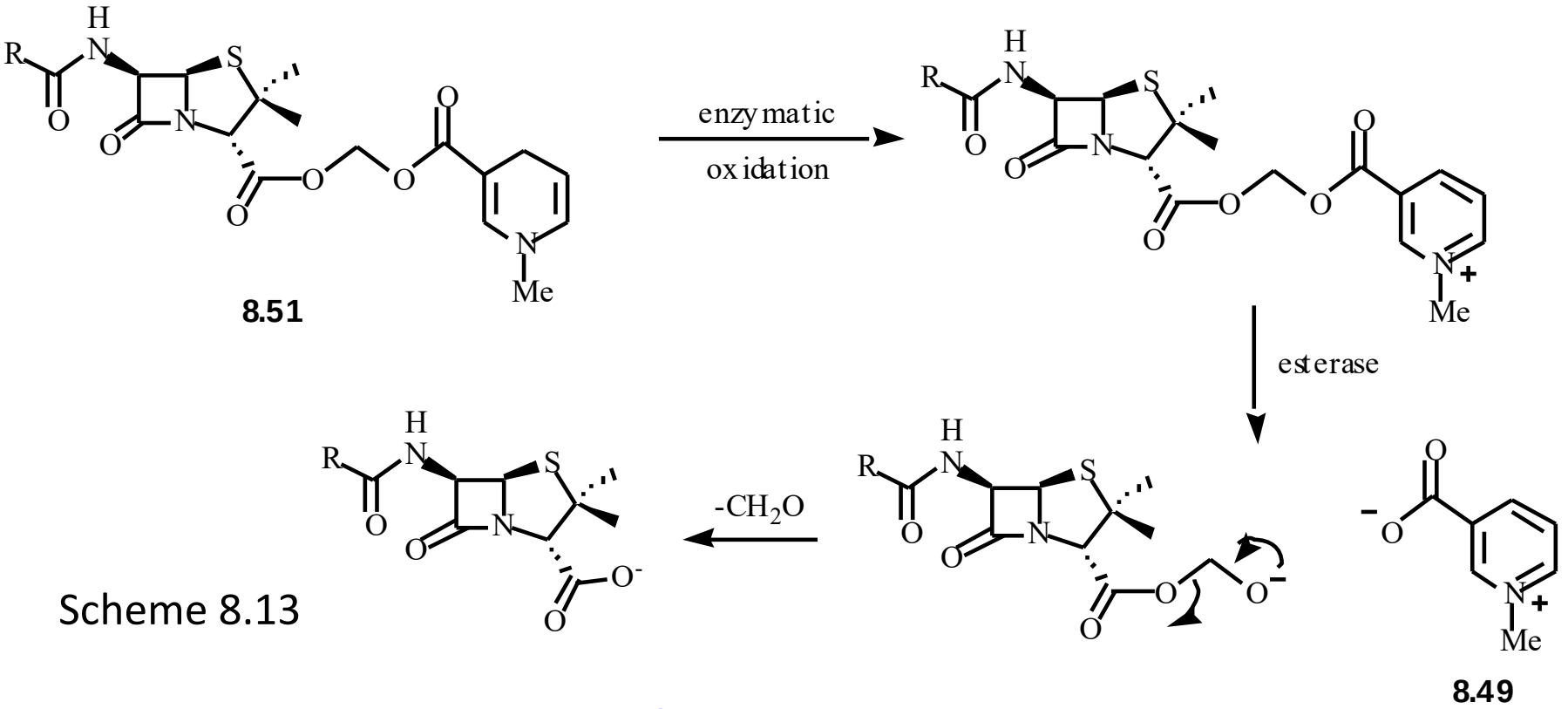
Example of Redox Drug Delivery

Antibody generation in the brain is not significant.

β-Lactams are too hydrophilic to cross the blood-brain barrier effectively.



8.51

8.49

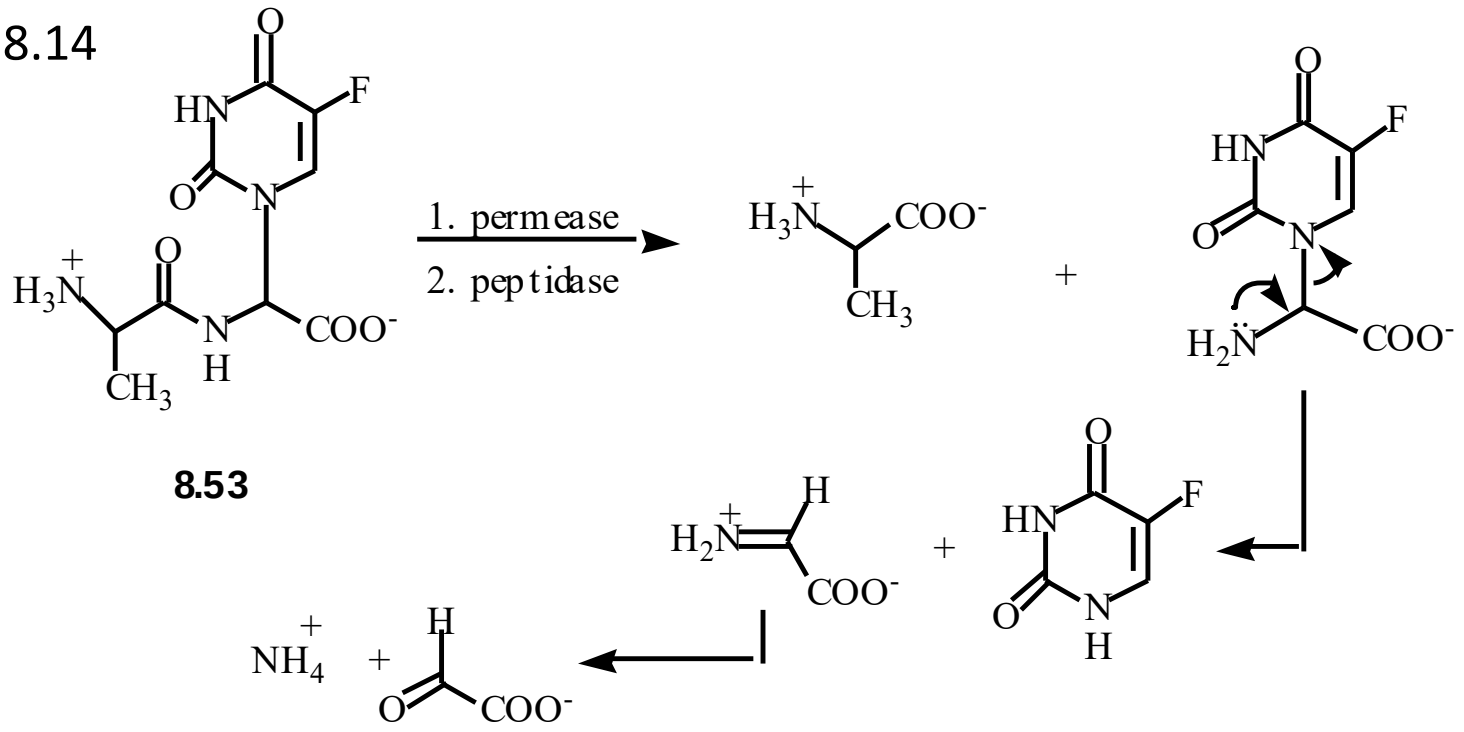
Scheme 8.13

High concentrations of β-lactams delivered into brain.

Tripartate Prodrug for Delivery of Antibacterials

Permeases are bacterial transport proteins for uptake of peptides.

Scheme 8.14



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