Lecture 4

Organic Pharm. Chemistry for Pharmacy Students

By

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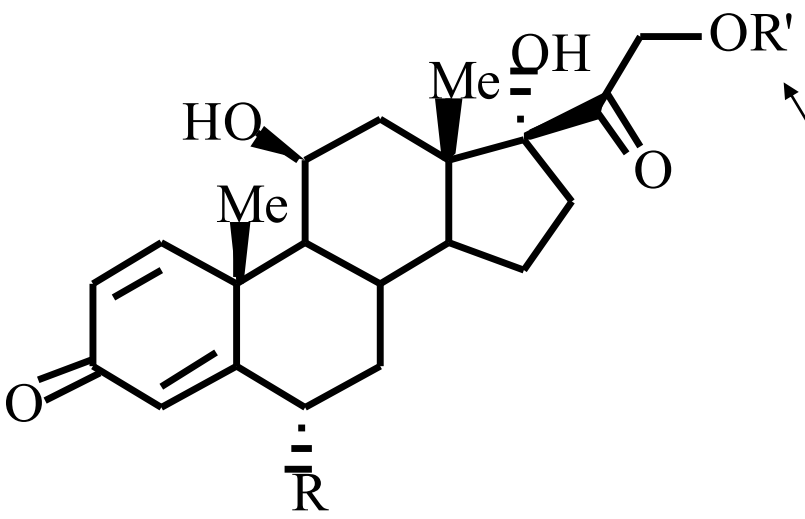
Examples of Carrier-Linked Bipartate Prodrugs

1. Prodrug for Increased Water Solubility



$R' = C(=O)CH_2CH_2CO_2Na$

Prodrug forms

$R' = PO_3Na_2$

for aqueous injection or opthalmic use

prednisolone (R = R' = H)
methylprednisolone (R = CH_3, R' = H) poor water solubility

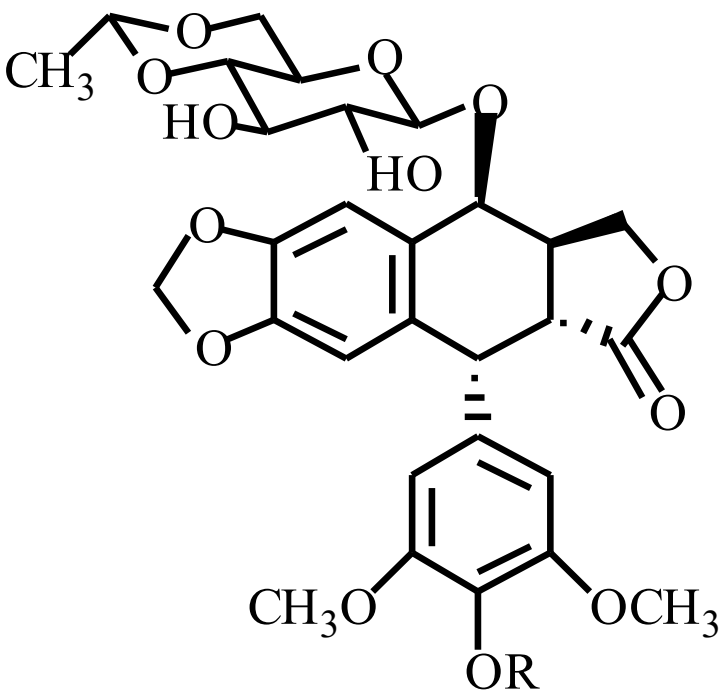
8.11

corticosteroid

Choice of water solubilizing group: The ester must be stable enough in water for a shelf life of > 2 years (13 year half-life), but must be hydrolyzed in vivo with a half-life < 10 minutes).

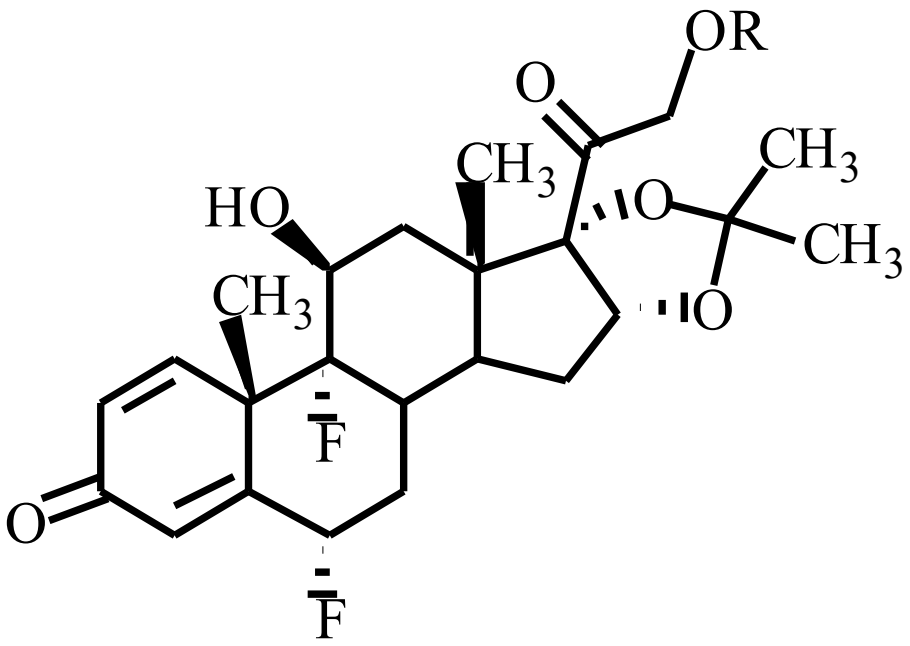
Therefore, in vivo/in vitro lability ratio about 10^6.

To avoid formulation of etoposide with detergent, PEG, and EtOH (used to increase water solubility), it has been converted to the phosphate prodrug.



etoposide (R = H)
etoposide phosphate (R = PO_3H_2)
8.12

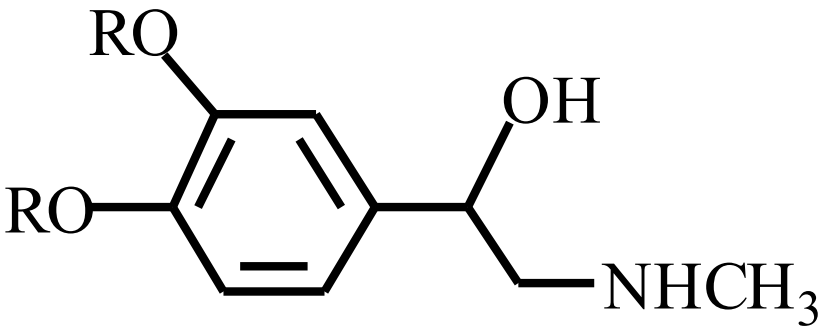
2. Prodrug for Improved Absorption Through Skin



fluocinolone acetonide (R = H)
fluocinonide (R = COCH$_3$)
8.14

corticosteroids - inflammation, allergic, pruritic skin conditions

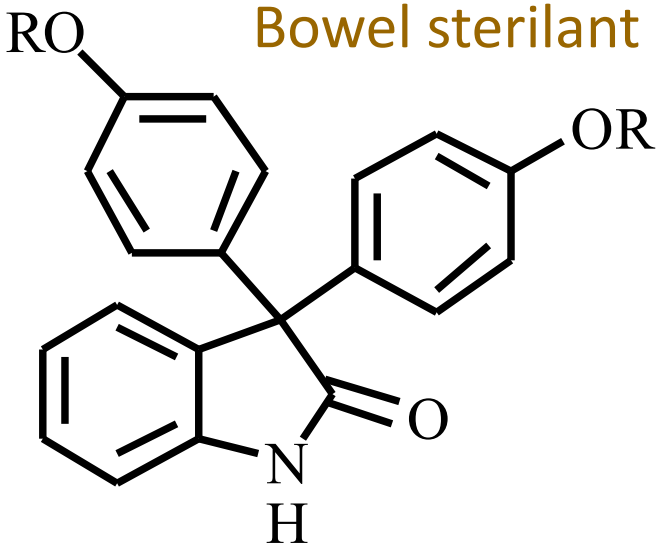
Better absorption into cornea for the treatment of glaucoma



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

The cornea has significant esterase activity

3.Prodrug for Site Specificity



Bowel sterilant

oxyphenisatin (R = H) (administer rectally)

8.16

prodrug R = Ac (administer orally)

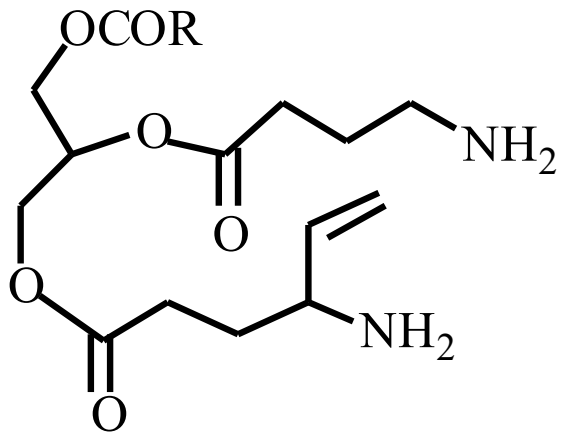
hydrolyzed in intestines

3. Prodrug for Site Specificity (cont….)

The blood-brain barrier prevents hydrophilic molecules from entering the brain, unless actively transported. The anticonvulsant drug **vigabatrin** crosses poorly.

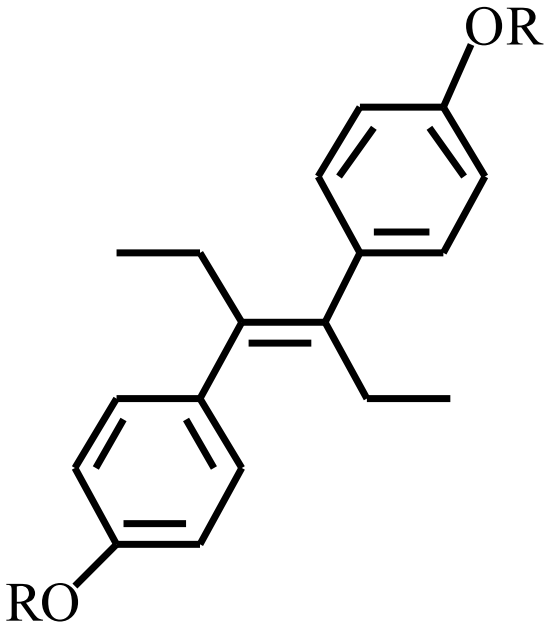
A glyceryl lipid (**8.17**, R = **linolenoyl**) containing one GABA ester and one vigabatrin ester was 300 times more potent in vivo than vigabatrin.

GABA : gama amino butyric acid
NH2-CH2-CH2-CH2-COOH



8.17

Site Specificity Using Enzymes at the Site of Action



diethylstilbestrol diphosphate (R = $PO_3^{=}$)

diethylstilbestrol (R = H)

8.18

Phosphatase should release the drug selectively in tumor cells.

This approach has not been successful because the prodrugs are too polar, enzyme selectivity is not sufficient, or tumor cell perfusion rate is poor.

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 incorporated

Criteria for Success with Enzyme-Prodrug Therapies

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

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 low cytotoxicity and the drug high cytotoxicity

6. The activated drug should be highly diffusable to kill neighboring nonexpressing 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

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

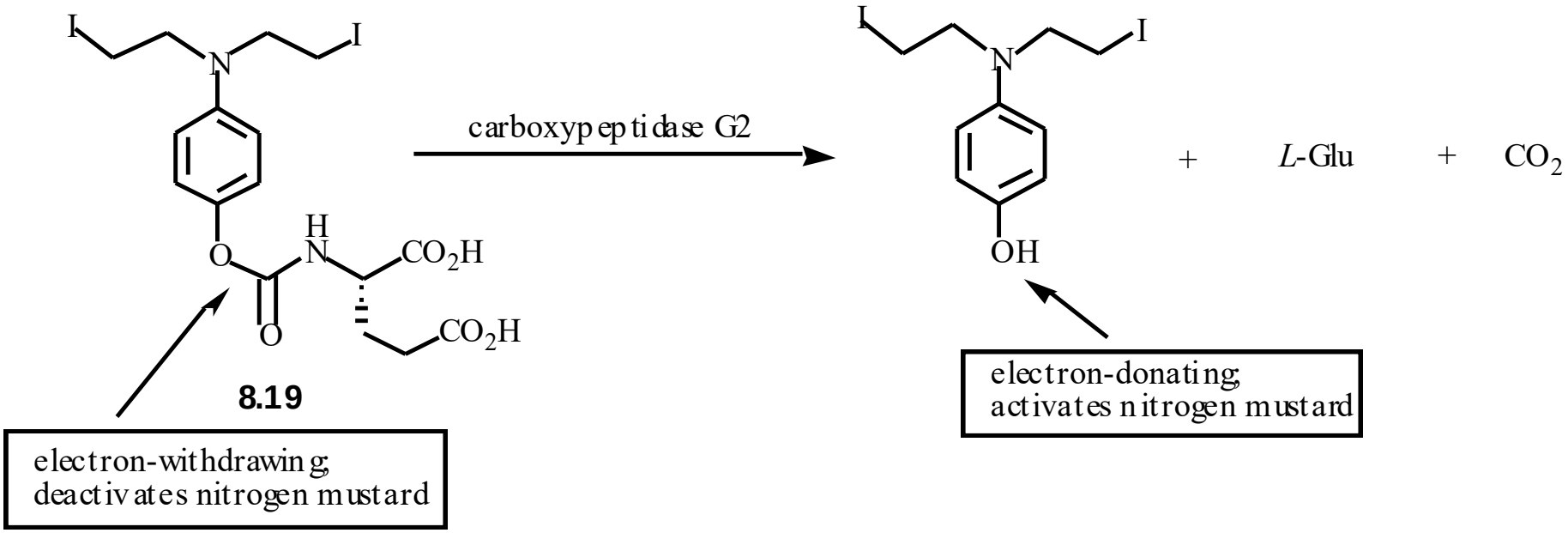
Advantages:

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 leakback of the active drug

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



Humanization of antibodies minimizes immunogenicity. Note the prodrug-activating enzyme is a bacterial enzyme.

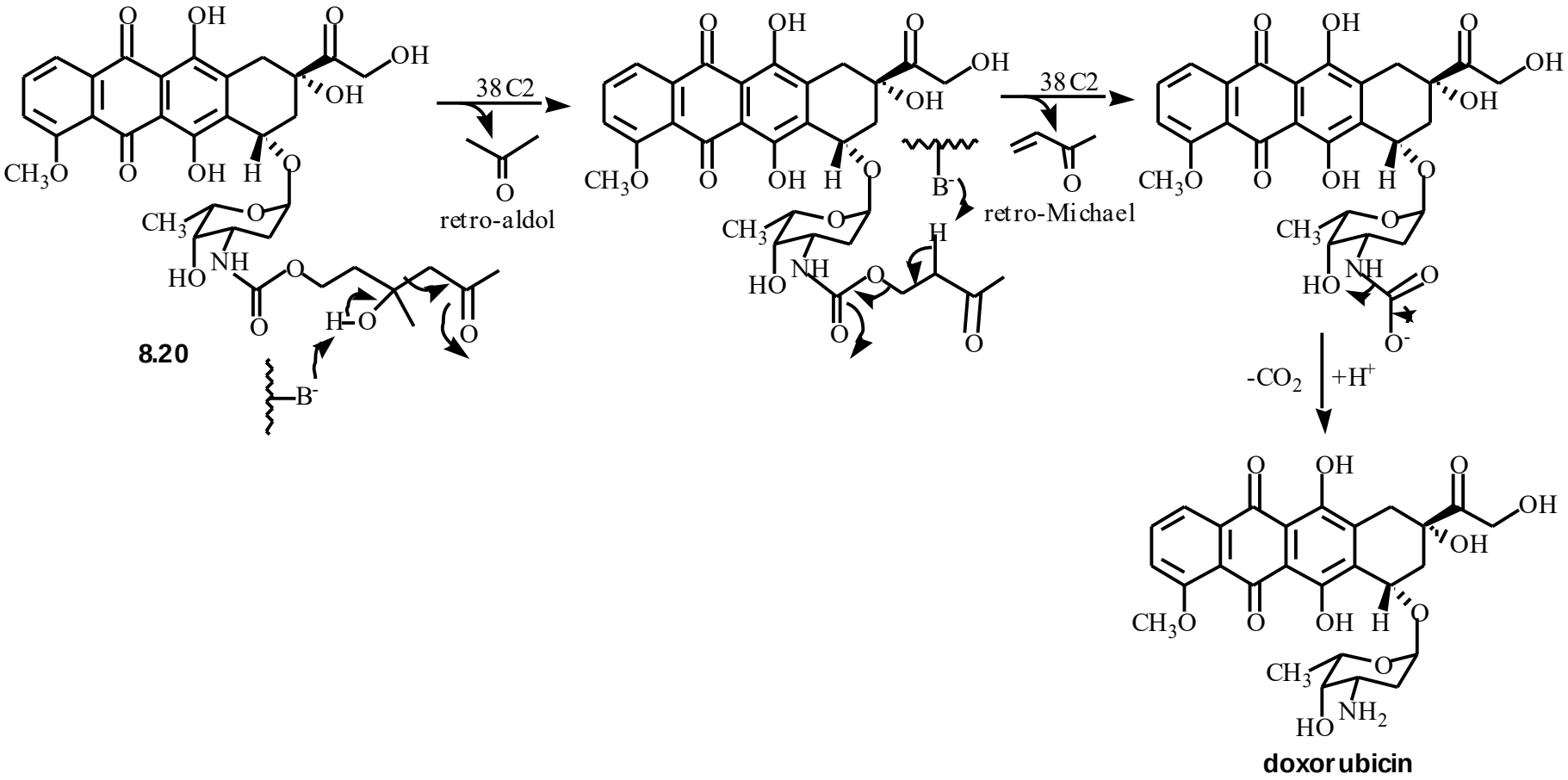
Antibody-Directed Abzyme Prodrug Therapy (ADAPT)

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.

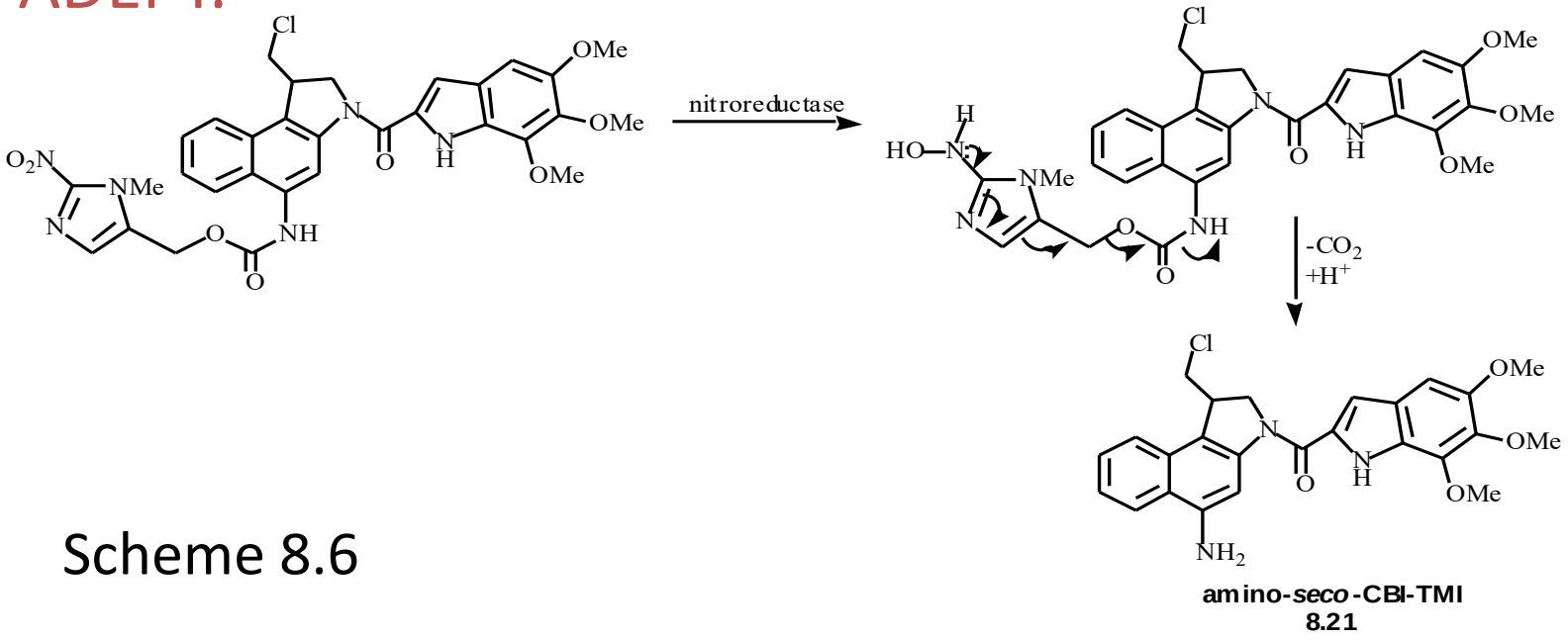
Abzyme 38C2 Activation of a Doxorubicin Prodrug



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.



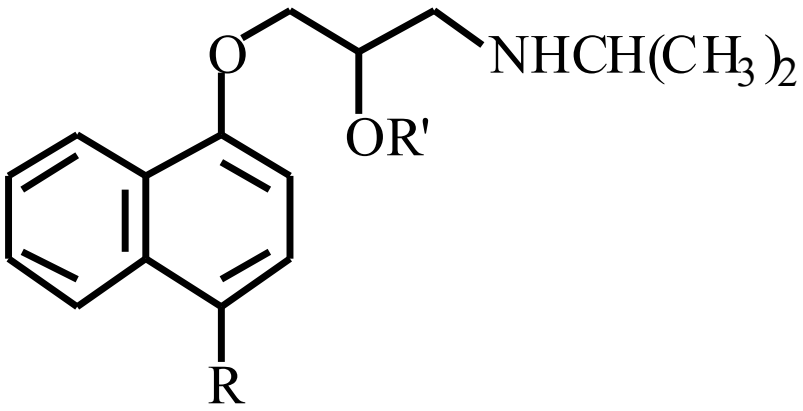
Scheme 8.6

amino-*seco*-CBI-TMI
8.21

4.Prodrug for Stability

protection from first-pass effect

Oral administration has lower bioavailability than i.v. injection.



propanolol (R = R' = H)
8.22

antihypertension

prodrug R' = $\overset{O}{\overset{\|}{C}}CH_2CH_2COOH$

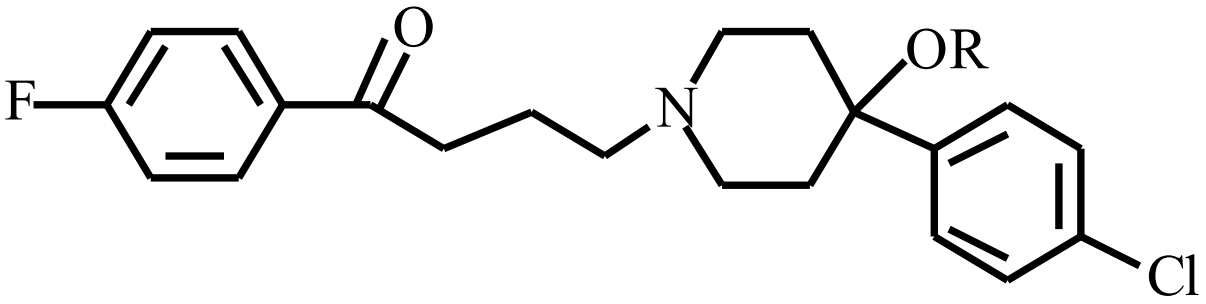
plasma levels 8 times that with propanolol

5.Prodrugs for Slow and Prolonged Release

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

(Long-chain fatty acid esters hydrolyze slowly

Intramuscular injection is used also).



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

Sedative/tranquilizer/antipsychotic

prodrug **R' =** $C(CH_2)_8CH_3$ slow release

inject i.m.

Antipsychotic activity for about 1 month

6.Prodrugs to Minimize Toxicity

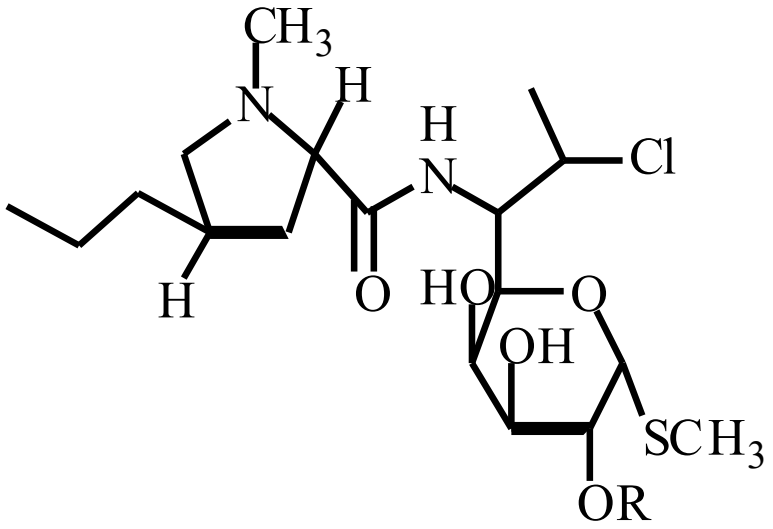
Many of the prodrugs just discussed also have lowered toxicity.

For example, **epinephrine** (for glaucoma) has ocular and systemic side effects not found in **dipivaloylepinephrine**.

7.Prodrug to Increase Patient Acceptance

The antibacterial drug clindamycin (**8.28**) is bitter and not well tolerated by children.

Clindamycin palmitate is not bitter.

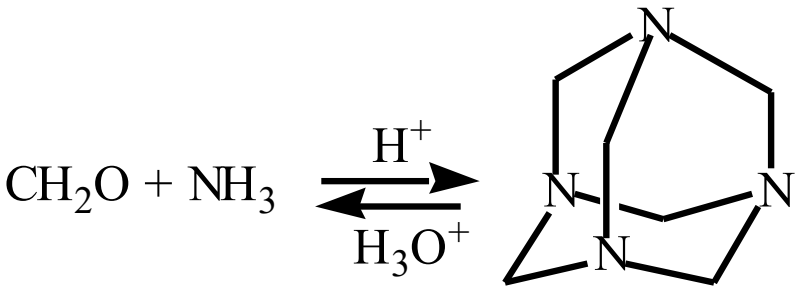


clindomycin (R = H)
clindomycin phosphate (R = PO_3H_2)
clindomycin palmitate (R = $O(CH_2)_{14}CH_3$)
8.28

Either not soluble in saliva or does not bind to the bitter taste receptor or both.

8.Prodrug to Eliminate Formulation Problems

Formaldehyde is a gas with a pungent odor that is used as a disinfectant. Too toxic for direct use.



methenamine
8.30

It is a stable solid that decomposes in aqueous acid.

The pH of urine in the bladder is about 4.8, so methenamine is used as a urinary tract antiseptic.

It has to be enteric coated to prevent hydrolysis in the stomach.