Lecture 3

Organic Pharm. Chemistry for Pharmacy Students

By

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- Prodrugs and Drug Delivery Systems
- Drug Discovery:
  1. Drug design and development
  2. Drug Design: optimizing target interaction
  3. Drug Design: Optimizing access to the target

Prodrugs and Drug Delivery Systems

Drug Latentiation : pharmacological modification of an active drug (as to delay or prolong its action) that produces a compound which reverts (يرجع) to the original active compound when subjected to biological processes after administration.

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

A prodrug can be defined as a drug substance that is inactive in the intended pharmacological actions and is must to be converted into the pharmacologically active agent by metabolic or physico-chemical transformation.

Prodrugs can exist naturally such as many phytochemicals/botanical constituents and endogenous substances, or they can result from synthetic or semisynthetic processes – produced intentionally as part of a rational drug design or unintentionally during drug development.

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- **Examples** of prodrugs that exist naturally or were produced unintentionally during drug development include aspirin, parathion, codeine, heroin, L-dopa, and various antiviral nucleosides.
- **Examples** of products resulting from pharmaceutical processes as part of strategically targeted drug design include sulfasalazine, oseltamivir, various nonsteroidal anti-inflammatory drugs (ketoprofen, diclofenac), statins (lovastatin, simastatin), ACE inhibitors (captopril, lisinopril) and penicillin-related agents (bacampicillin, sarmoxicillin).

- **The need to design and produce a prodrug is often related to issues such as**
- (1) bioavailability, such as poor aqueous solubility (*e.g.*, corticosteroids),
- (2) poor absorption/permeability (*e.g.*, ampicillin),
- (3) high first pass extraction (*e.g.*, propranolol),
- (4) instability (*e.g.*, short half-life, such as dopamine),
- (5) poor site specificity (*i.e.*, that the site of action of an active drug is rather nonspecific such as anticancer agents),
- (6) incomplete absorption (epinephrine),
- (7) unfavorable organoleptic properties (chloramphenicol),
- (8) pharmaceutical formulation difficulties, and
- (9) other adverse effects or toxicities.

- **Current Classifications of Prodrugs**
- There are potentially many methods of classifying prodrugs. These could include those:
- (1) based on therapeutic categories; for example, anticancer prodrugs (i), antiviral prodrugs (ii), antibacterial prodrugs (iii), nonsteroidal anti-inflammatory prodrugs(iv), cardiovascular prodrugs (v), etc.;
- (2) based on the categories of chemical linkages or moiety/carriers that attach to the active drug; for example, esteric prodrugs (vi), glycosidic prodrugs (vii), bipartite prodrugs (viii), tripartite prodrugs ix), and antibody-, gene-, virus-directed enzyme prodrugs (x); or
- (3) based on functional categories using strategic approaches to circumvent deficiencies inherent to the active drug; for example, prodrugs for improving site specificity (xi), prodrugs to bypass high first-pass metabolism (xii), prodrugs for improving absorption (xiii) , and prodrugs for reducing adverse effects (xiv).

- The primary **goal** in pharmaceutical design of a prodrug has been to circumvent some disadvantageous pharmacodynamic or pharmacokinetic property of the active drug; *e.g.*, to increase bioavailability or to reduce adverse effects.
- based on their cellular sites of conversion into the final active drug form:
- **Type I** being those that are converted intracellularly (*e.g.*, anti-viral nucleoside analogs, lipid-lowering statins,),
- **Type II** being those that are converted extracellularly, especially in digestive fluids or the systemic circulation (*e.g.*, etoposide phosphate, valganciclovir, fosamprenavir, antibody-, gene- or virus-directed enzyme prodrugs [ADEP/GDEP/VDEP] for chemotherapy or immunotherapy).

- Both types can be further categorized into Subtypes, *i.e.*, Type IA, IB and Type IIA, IIB, and IIC based on whether or not the intracellular converting location is also the site of therapeutic action, or the conversion occurs in the gastrointestinal (GI) fluids or systemic circulation.
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- **Type IA** prodrugs include many antimicrobial and chemotherapy agents (*e.g.*, 5-flurouracil).
- **Type IB** agents rely on metabolic enzymes, especially in hepatic cells, to convert the prodrugs intracellularly to active drugs.
- **Type II :**
- **(Type IIA**) :prodrugs are converted extracelluarly, either in the milieu(بيئة.. وسط) of GI fluids within the systemic circulation and/or other
- **(Type IIB):** extracellular fluid compartments
- **(Type IIC**), or near therapeutic target tissues/cells relying on common enzymes such as esterases and phosphatases or target directed enzymes.

- This new classification system of prodrugs can help in the understanding of a drug product's pharmacokinetics, safety and efficacy.
- It provides a more systematic approach to categorizing a prodrug based on the biological site of conversion.

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

Prodrugs and soft drugs are opposite:

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

A pro-soft drug would require metabolism to convert it to a soft drug

The pharmacokinetic studies :

considered as the phase involving absorption, distribution, metabolism and excretion of the drug.

This phase can provide valuable information regarding the in vivo properties of a **drug's limitation** such as poor absorption, too rapid elimination and pre systemic metabolism.

If these properties can be related back to the physicochemical and dosage form properties of the system, then corrections will require prodrug interventions (تدخل).

How Can We Use The Prodrug Approach To Overcome Pharmacokinetic Barriers ?!

(when we use prodrugs)

- Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood brain barrier.
- Incomplete systemic delivery of an agent due to pre-systemic metabolism in the gastrointestinal lumen mucosal cells and liver.
- Toxicity problems associated with local irritation or distribution into tissue other than the desired target organ.
- Poor site specificity of the drug.

Utility of Prodrugs

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

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

3. **Site Specificity** - to target a particular organ or tissue if a high concentration of certain enzymes is at a particular site or append (يضيف) something that directs the drug to a particular site---often tried to limit the toxicity of anticancer drugs.

Utility of Prodrugs (cont'd)

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

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

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

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

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

Types of Prodrugs

Drug Latentiation - rational prodrug design

Latentiation : pharmacological modification of an active drug (as to delay or prolong its action) that produces a compound which reverts to the original active compound when subjected to biological processes after administration.

1.Carrier-linked prodrug

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

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

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

C. **mutual** - two, usually synergistic, drugs attached to each other

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 COOH, to afford the active form.

Protecting Group Analogy for the Concept of Prodrugs

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

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

carrier-linked

The ester group can be used to modify properties of the drug

analogous to bioprecursor

Keep in mind that a prodrug whose design is based on rat metabolism may not be effective in humans.

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.

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 non immunogenic
6. Are easily prepared and inexpensive
7. Are stable in the dosage form

Carrier Linkages for Various Functional Groups

Alcohols, Carboxylic Acids, and Related Groups

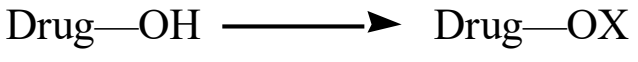
Most common prodrug form is an ester

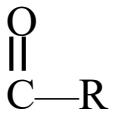
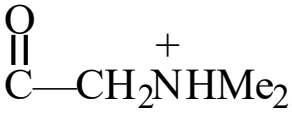
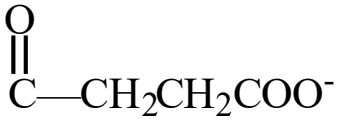
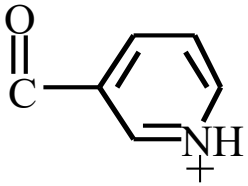
- esterases are ubiquitous (واسع الانتشار)
- can prepare esters with any degree of hydrophilicity or lipophilicity
- ester stability can be controlled by appropriate electronic and steric manipulations

Prodrugs for Alcohol-Containing Drugs

Table 8.1

Ester analogs as prodrugs can affect lipophilicity or hydrophilicity



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)

To accelerate hydrolysis rate:

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

The strongest EWGs are groups with pi bonds to electronegative atoms:

Nitro groups (-NO_2)
Aldehydes (-CHO)
Ketones (-C=OR)
Cyano groups (-CN)
Carboxylic acid (-COOH)
Esters (-COOR)

attach an electron-donating group if an acid hydolysis mechanism is important.

Examples of good electron donating groups are groups with lone pairs to donate, such as The **oxygen anion**, -O.

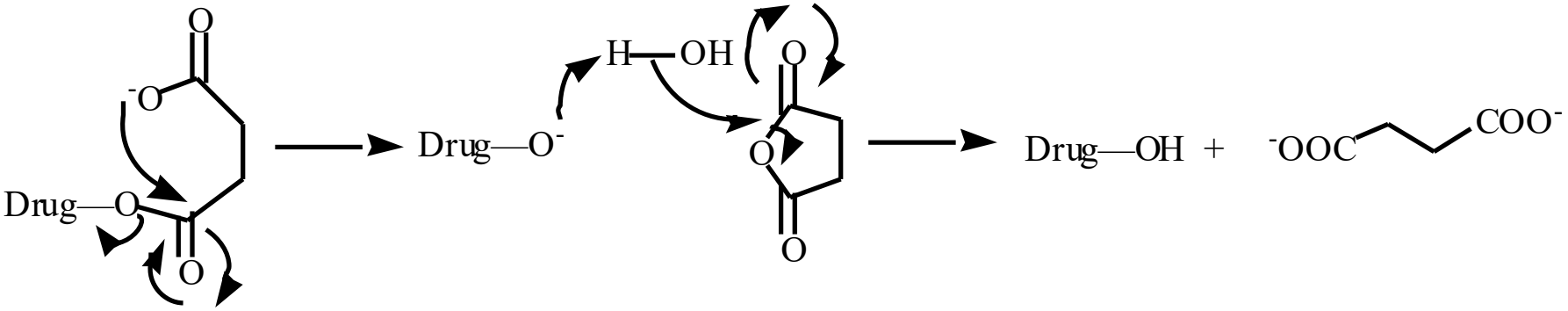
To slow down hydrolysis rate:

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

Another Approach to Accelerate Hydrolysis

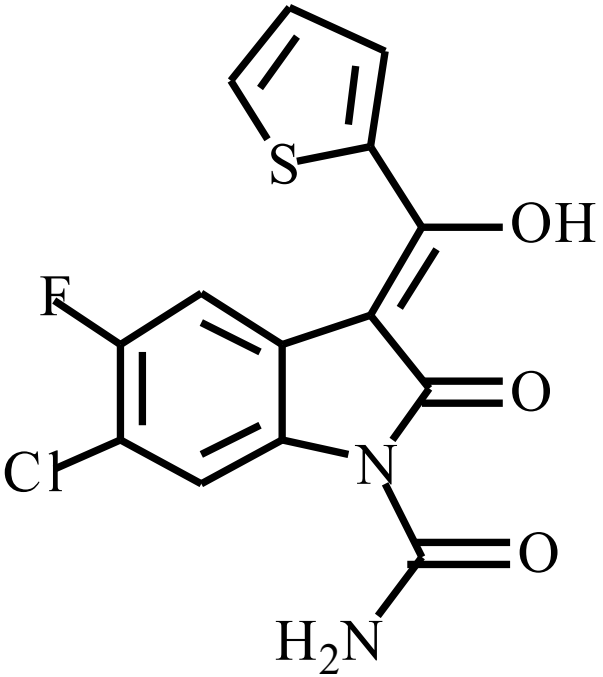
Intramolecular hydrolysis of succinate esters

Scheme 8.2

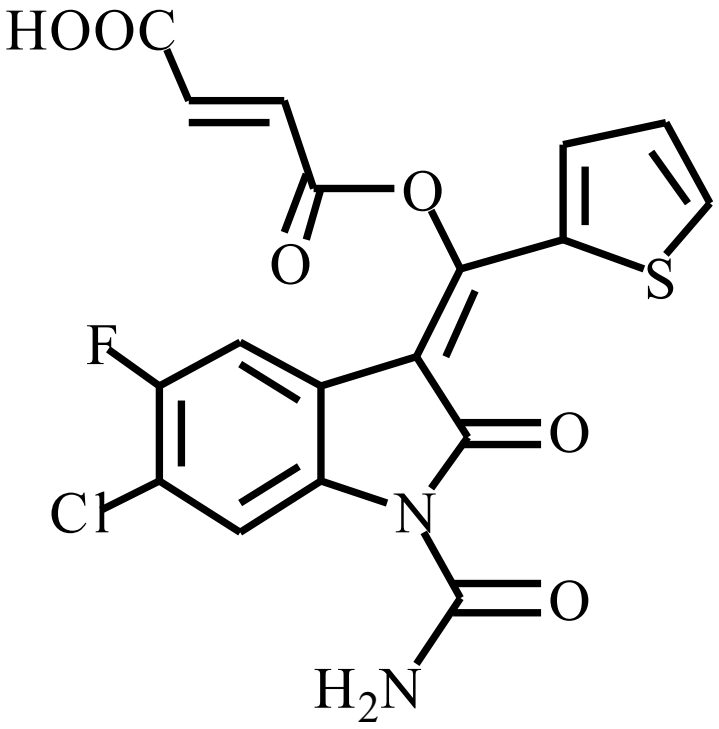


Also, acetals or ketals can be made for rapid hydrolysis in the acidic medium of the GI tract.

Enolic hydroxyl groups can be esterified as well.



oxindole
8.1
antirheumatic agent

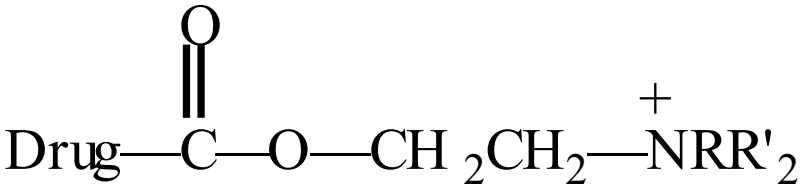


8.2

Carboxylic Acid-Containing Groups

Esterify as with alcohols

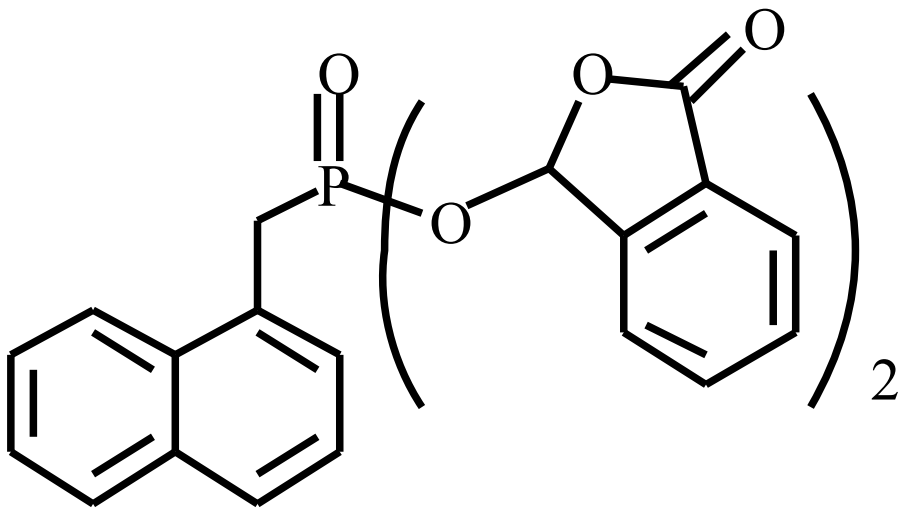
Maintaining Water Solubility of Carboxylate Prodrugs



8.3

Can vary pK_a by appropriate choice of R and R′

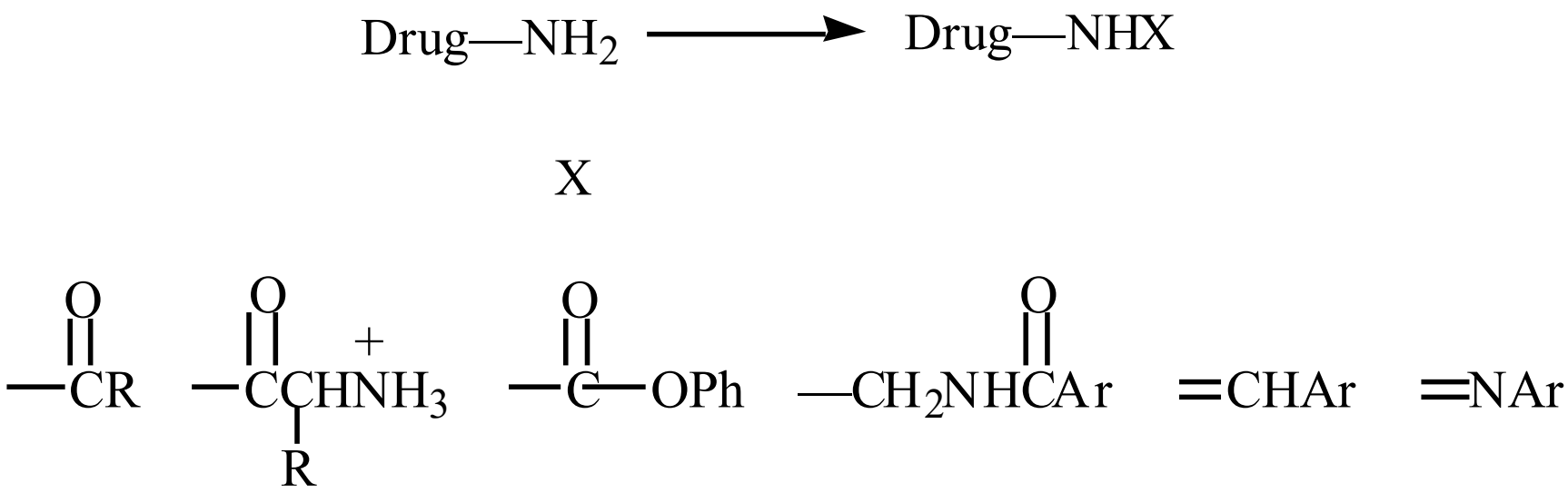
Prodrugs for Phosphate- or Phosphonate-Containing Drugs



8.4

Amine Prodrugs

Table 8.2

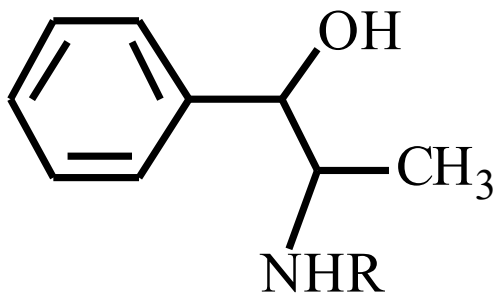


Amides are commonly not used because of stability

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 = $CH_2NHCOAr$)

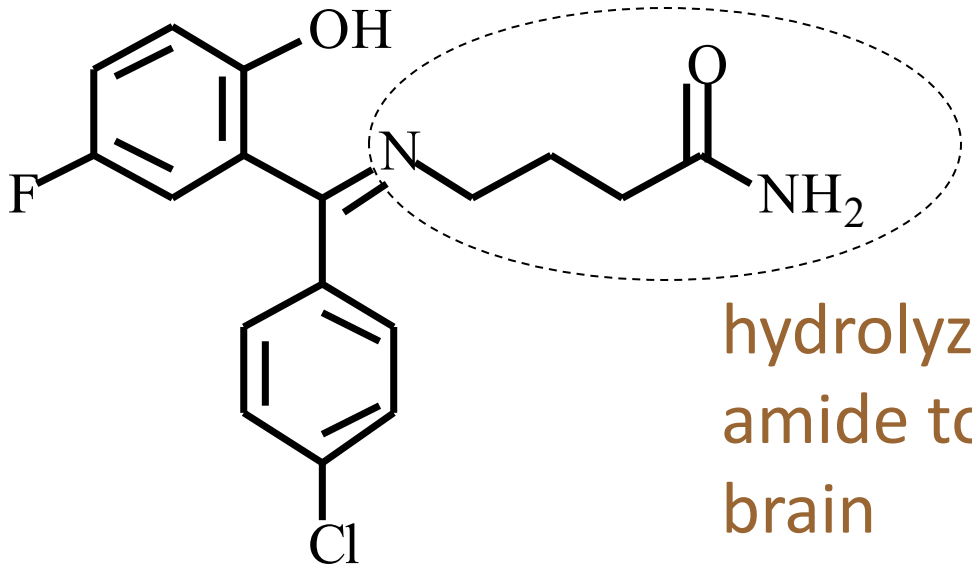
N-Mannich base (R = $CH_2NHCOPh$) has a log $D_{7.4}$ two units greater than the parent compound.



phenylpropanolamine hydrochloride (R = H·HCl)
8.5

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

Imine (Schiff base) prodrug

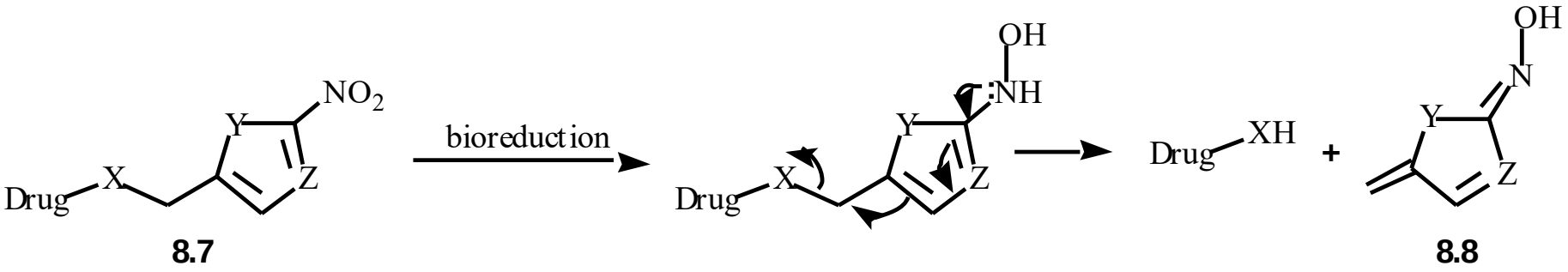


hydrolyze imine and amide to GABA inside brain

progabide
8.6
anticonvulsant

A Reductive Carrier-Linked Prodrug Approach

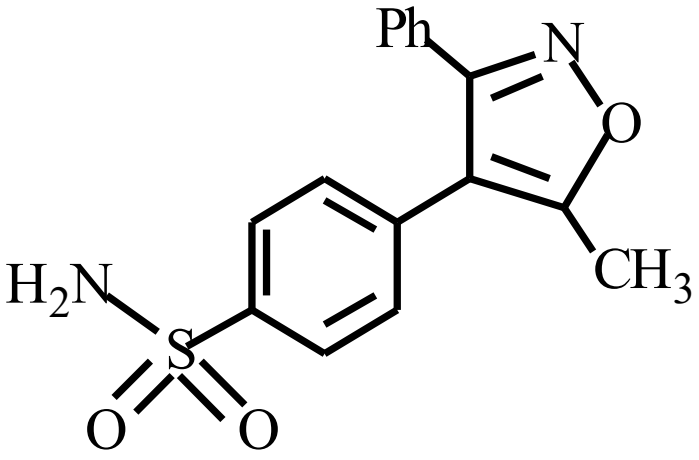
Scheme 8.3



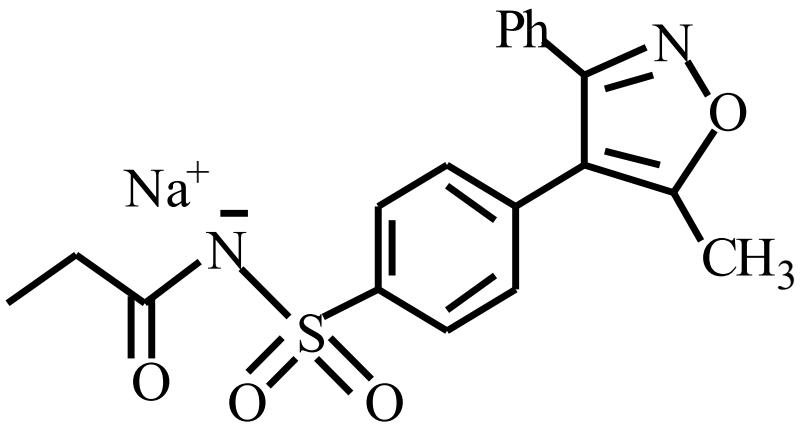
8.7 **8.8**

Prodrugs of Sulfonamides

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



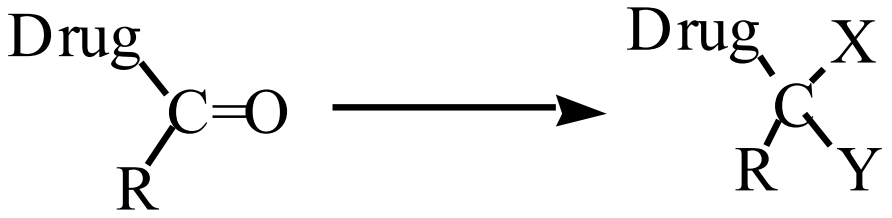
valdecoxib
8.9

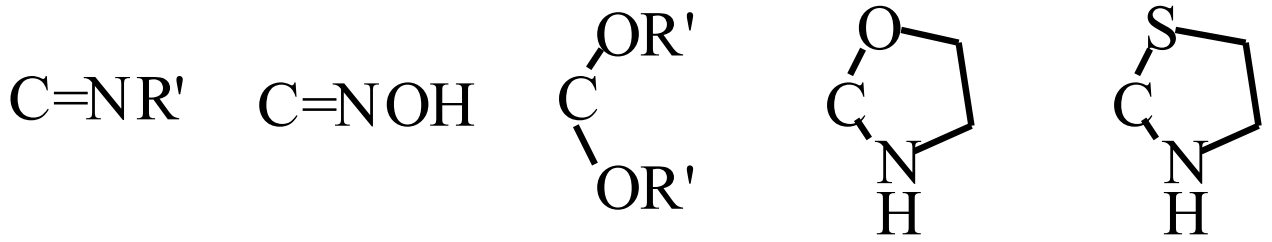


parecoxib sodium
8.10

Prodrug Analogs of Carbonyl Compounds

Table 8.3





imines oximes ketals

- **Questions :**

1.Define each of the followings : Prodrug , Drug Latetiation, Carrier-linked prodrugs,

2. What are the factors or limitations necessitate the uses of prodruds?

3. What are the utility of prodrugs ?

4. What are the different types of prodrugs ?

5. What are the properties of ideal drug-carier ?