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: physical & chemical properties
3. Drug Design: clinical studies according to FDA rules.(phase I, phase II, Phase III)
4. Drug Design : formulation studies.
5. Launching the drug

Prodrugs and Drug Delivery Systems

Drug Latentiation :

The **prodrug** concept was first proposed by Albert in 1958.This included both compounds that are **designed** to undergo a transformation to yield an active substance and those that were **discovered by serendipity** to do so.

These two situations were distinguished by Harper, who in 1959 introduced the term **drug latentiation** to refer to drugs that were specifically designed to require bioactivation.

Prodrug –

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

Prodrugs and drugs are opposite

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

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

Ideal Requirements of Prodrugs

An ideal prodrug must meet the following requirements:

1. The prodrug is inactive or less active than the parent compound.
2. The linkage between the drug and the carrier must be cleaved in vivo.
3. The carrier molecule released in vivo must be non-toxic.
4. The metabolic fragments of carrier molecule, apart from the drug should be non toxic.

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

The Applications of Prodrugs:

The various applications of prodrug approach are:

1. Improved physicochemical properties (e.g., better solubility in the intended formulation).
2. Enhanced delivery characteristics and/or therapeutic value of the drug.
3. To improve drug penetration through biological membranes.
4. To increase site specificity of the drug.
5. To improve the drug's stability.
6. To increase duration of pharmacological activity.
7. To decrease the drug's toxicity and adverse effects.
8. To improve patient acceptance.

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.

Prodrugs can exist

A- naturally

- such as many phytochemicals/botanical constituents and endogenous substances, or

B- they can result from synthetic or semisynthetic processes

- – produced intentionally as part of a rational drug design
- -or unintentionally during drug development.

- **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, simvastatin), ACE inhibitors (captopril, lisinopril) and penicillin-related agents (bacampicillin, sarmoxicillin).

Classifications of Prodrugs

- There are potentially many methods of classifying prodrugs. These could include those:

(**1) based on therapeutic categories**; for example,

i. anticancer prodrugs ,

Ii. antiviral prodrugs ,

Iii. antibacterial prodrugs ,

iv. nonsteroidal anti-inflammatory prodrugs,

v.cardiovascular prodrugs , etc.;

(**2) <u>based on the categories of chemical linkages</u>** or moiety/carriers that attach to the active drug; for example,

Vi. esteric prodrugs ,

Vii. glycosidic prodrugs ,

viii. bipartite prodrugs ,

Ix. tripartite prodrugs , and

X. antibody-, gene-, virus-directed enzyme prodrugs ; or

(3) based on functional categories using strategic approaches to circumvent deficiencies inherent to the active drug; for example,

Xi. prodrugs for improving site specificity ,

xii. prodrugs to bypass high first-pass metabolism

xiii. prodrugs for improving absorption , and

xiv. prodrugs for reducing adverse effects .

- 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**.

(4) - 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.

- **Type I:**
- **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.

Table 1
Classification of Prodrugs.

Prodrug Types	Site of Conversion	Subtypes	Tissue Location of Conversion	Examples
Type I	Intracellular	A	Therapeutic Target Tissues/Cells	Type IA: Acyclovir L-Dopa 6-Mercaptopurine
		B	Metabolic Tissues (liver, GI mucosal cell, lung, etc.)	Type IB: Captopril Phenacetin Primidone Suldinac
Type II	Extracellular	A	GI Fluids	Type IIA: Lisdexamfetamine Loperamide oxide Oxyphenisatin Sulfasalazine
		B	Systemic Circulation and Other Extracellular Fluid Compartments	Type IIB: Acetylsalicylate Bacampicillin Chloramphenicol succinate
		C	Therapeutic Target Tissues/Cells	Type IIC: ADEPs GDEPs VDEPs

- 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 **prodrug** is capable of overcoming one or more of **the barriers to drug delivery** more efficiently than the parent drug.
- Some of **the potential barriers** related to the

(a) pharmaceutical phase and

(b) pharmacokinetic phase, respectively.

The pharmaceutical phase comprises:

i. Incorporation of a potential drug entity into a convenient drug delivery system or a dosage form.

ii. Release of the active drug from the formulation.

Whereas **the pharmacokinetic phase** embraces the absorption, distribution, metabolism, and excretion of the drug.

THE PHARMACEUTICAL PHASE Barrriers

- There are two barriers identified in the development phase of commercially usable drug products , which are:
- **A. Aesthetic properties** such as odour, taste (in case of paediatric use or when intended for oral administration), pain upon injection, gastrointestinal (GI) irritability of the new molecule
- B**. Drug formulation problems** such as stability profile, undesirable physicochemical properties like solubility, polarity, partition coefficient and pKa values due to which prevent its incorporation into a specific drug delivery system.

THE PHARMACOKINETIC PHASE

- This phase can be considered as the phase involving absorption, distribution, metabolism and excretion of the drug.
- The pharmacokinetic studies 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.

- **What are the principal barriers which identified in the pharmacokinetic phase?!**
- 1. Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood brain barrier.
- 2. Incomplete systemic delivery of an agent due to pre-systemic metabolism in the gastrointestinal lumen mucosal cells and liver.
- 3. Toxicity problems associated with local irritation or distribution into tissue other than the desired target organ.
- 4. Poor site specificity of the drug.

- **HOW CAN WE USE PRODRUGS TO OVERCOME THE PHARMACEUTICAL BARRIERS ?!**

1- Masking taste or odour :

The undesirable taste arises due to adequate solubility and interaction of drug with taste receptors.

- **So, what we have to do?!!**
- **The answer** is: We can overcome this problem by lowering the solubility of drug or prodrug in saliva.

- **Example 1 : “ The undesirable test”** Chloramphenicol which produces a bitter taste when given as the parent drug.
- The hydrophobic palmitate ester does not dissolve to any appreciable extent in the mouth, so there is little chance for interaction with taste receptors.

Example 2 : “The malodour”

Odour is another aesthetic concern for some drugs, that are often volatile liquid or solids with significant vapour pressure that makes them difficult to formulate.

How can we use organic chemistry to sort out this problem?

A classic example is the volatile mercaptans used as tuberculostatic agents for the treatment of leprosy. The ethyl mercaptan has a boiling point of 25ºC and a strong disagreeable odour.

On the other hand, diethyl dithio isophthalate, a prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless.

2- Minimizing Pain at Site of Injection

Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs.

So, it is the problem of poor aqueous solubility of drugs!! **What we have to do**?!

Example: Intramuscular injection of antibiotic like clindamycin and anticonvulsant drug like phenytoin was found painful due to poor aqueous solubility and could be overcome by making phosphate ester prodrugs respectively and maintaining the formulations at pH 12

3- Alteration of Drug Solubility

The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use.

For example, chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively.

On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration.

Administration of a drug parenterally may cause pain at the site of injection, especially if the drug begins to precipitate out of solution and damage the surrounding tissue.

- This situation can be remedied by preparing a drug with increased solubility in the administered solvent.
- Since chloramphenicol has low water solubility, the succinate ester was prepared to increase the water solubility of the agent and facilitate parenteral administration.
- The succinate ester itself is inactive as an antibacterial agent, so it must be converted to chloramphenicol for this agent to be effective. This occurs in the plasma to give the active drug and succinate. The ester hydrolysis reaction can be catalysed by esterases present in large amounts in the plasma.

4- Enhancement of Chemical Stability

Chemical stability is a most extreme necessary parameter for every therapeutic agent to bring out its pharmacological activity for a longer duration.

A shelf life of at least 2 years is desirable except for vaccines, cytotoxic agents and other life saving drugs.

Although chemical unstability can be solved to a greater extent by appropriate formulations, its failure necessitates the use of prodrug approach.

How this work?!

The prodrug approach is based on the modification of the functional group responsible for the instability or by changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable.

- **Example:** This approach was successfully used to inhibit the auto aminolysis, which occur due to capability of NH2 group of side chain to attach β–lactam ring of other molecule,
- In ampicillin molecule in concentrated solution it generates polymeric species of ampicillin.
- By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin „ties up‟ the amine group and thus inhibits auto aminolysis.

- The other advantage of this modification is it decreases the basicity of the α-amino group and reduces protonation in the small intestine so that the agent is more lipophilic.
- In this manner, the absorption of the drug from the small intestine is increased after oral dosing, and chemical hydrolysis after absorption regenerates ampicillin.

Utility of Prodrugs

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

   (drug) (prodrug)

   (eg.methyl-predniselon→ succenate ester)

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

   (eg.Ampicillin → ethyl 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 (يضيف) something that directs the drug to a particular site , often tried to limit the toxicity of anticancer drugs.
- oxyphenisatin (R = H) (administer rectally)
- prodrug R = Acetyl (administer orally)

Utility of Prodrugs (cont'd)

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

eg . propanolol (R = R' = H) → prodrug R' = O CCH_2 CH_2 COOH

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

haloperidol (R = H) → haloperidol decanoate

($R = CO(CH_2)_8CH_3$)

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

dipivefrin (R = Me_3 CCO) → epinephrine (R = H)

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

Clindomycin (R = H) → Clindomycin phosphate (R = PO_3 H_2)

Chloramphenicol → Chloramphenicol pulmitate

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

Formaldehyde → methenamine

Types of Prodrugs –(Continue…

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 يرجع 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.

Prodrug Derivative Types

-Small molecule Prodrug

has MW in 200-500 g/mole range called a low molecular weight prodrug

-**Macromolecule**

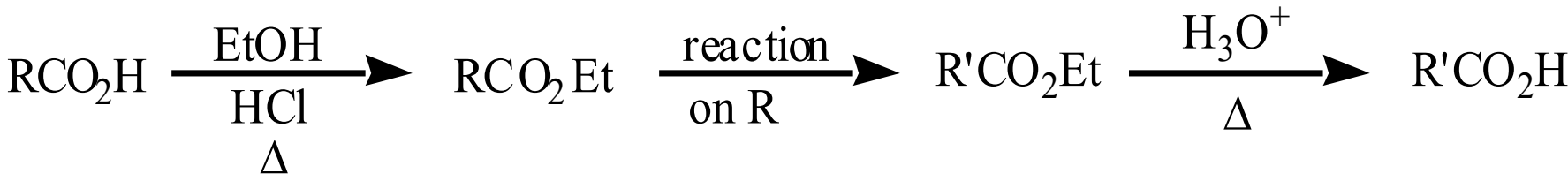
conjugate drug reversibly to biomolecule

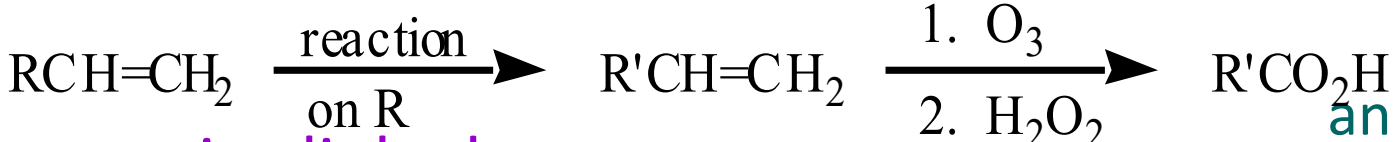
antibody

hormone

polymer

Protecting Group Analogy for the Concept of Prodrugs

A. 

B. 

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.

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.

Ideal Drug Carriers

Properties of 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

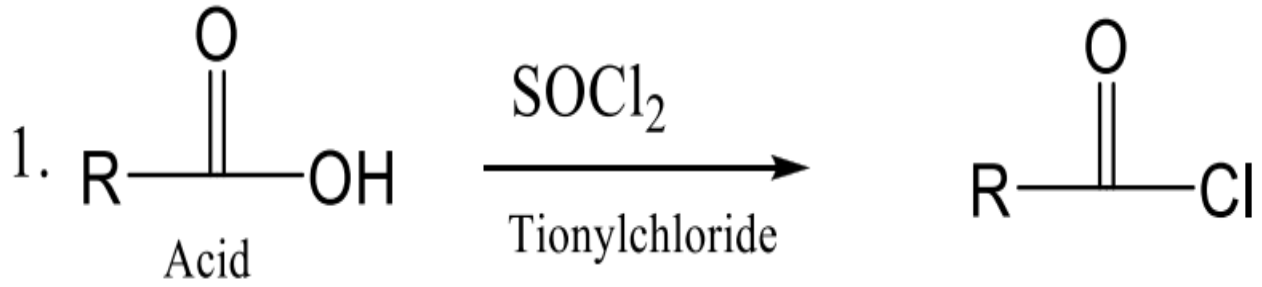
Carrier Linkages for Various Functional Groups

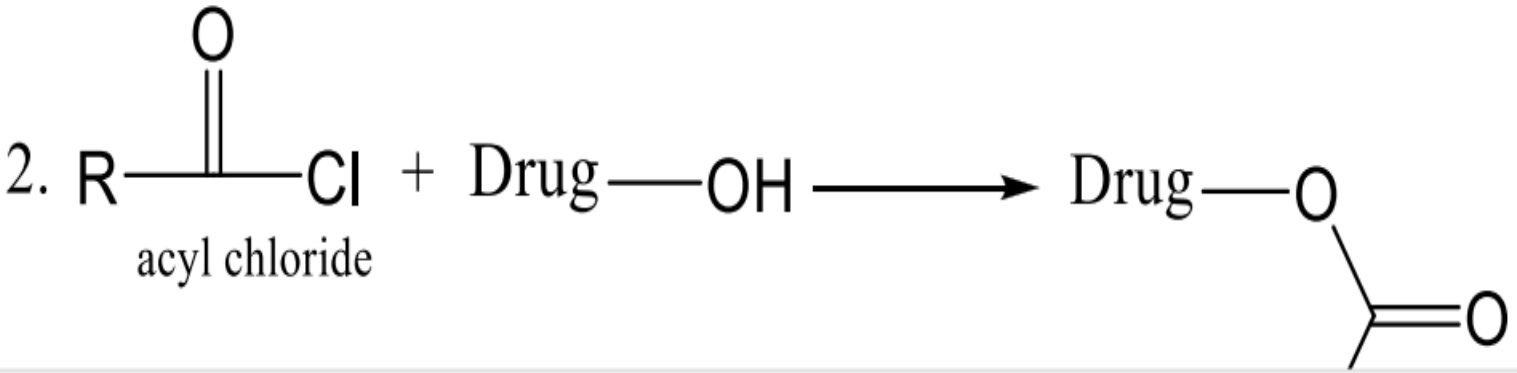
Alcohols, Carboxylic Acids, and Related Groups

Most common prodrug form is an ester : Why 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

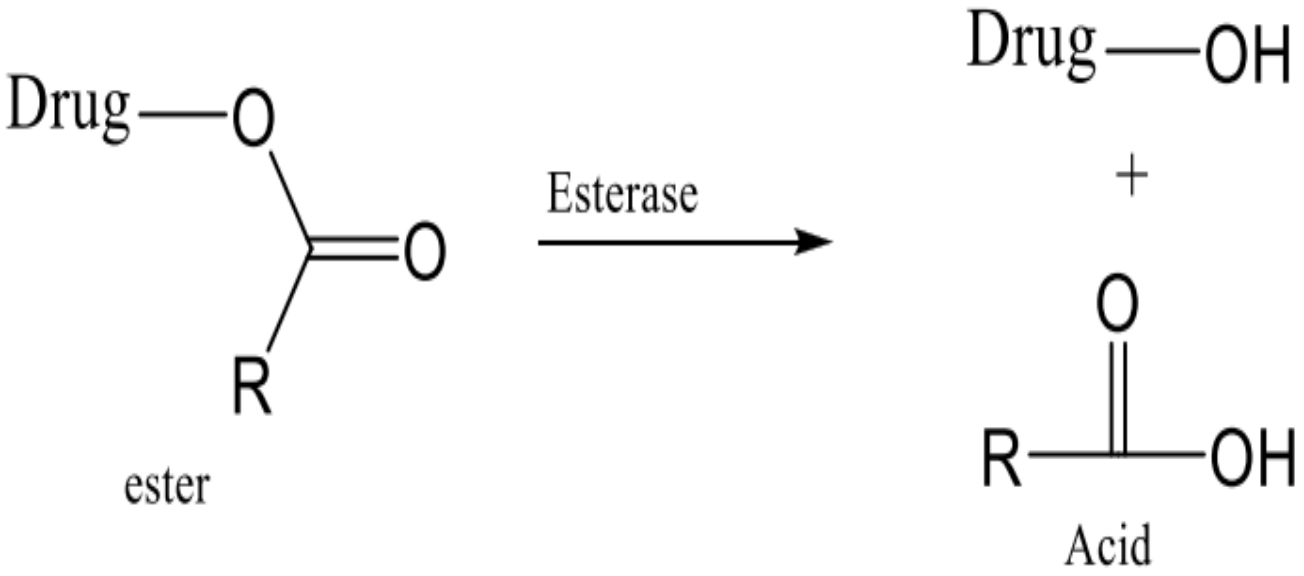
Synthesis of ester





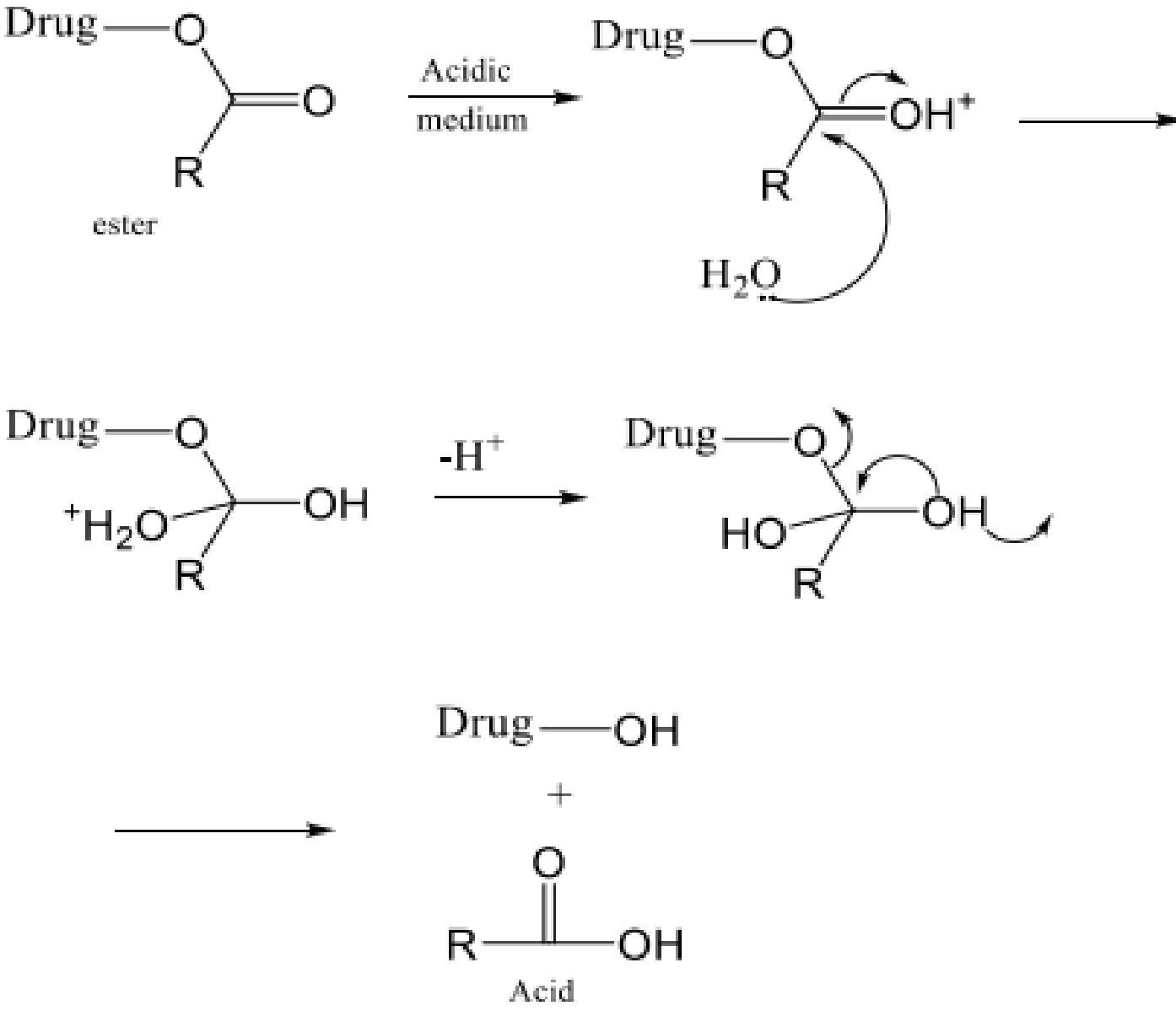
Ester hydrolysis

Enzymatic hydrolysis

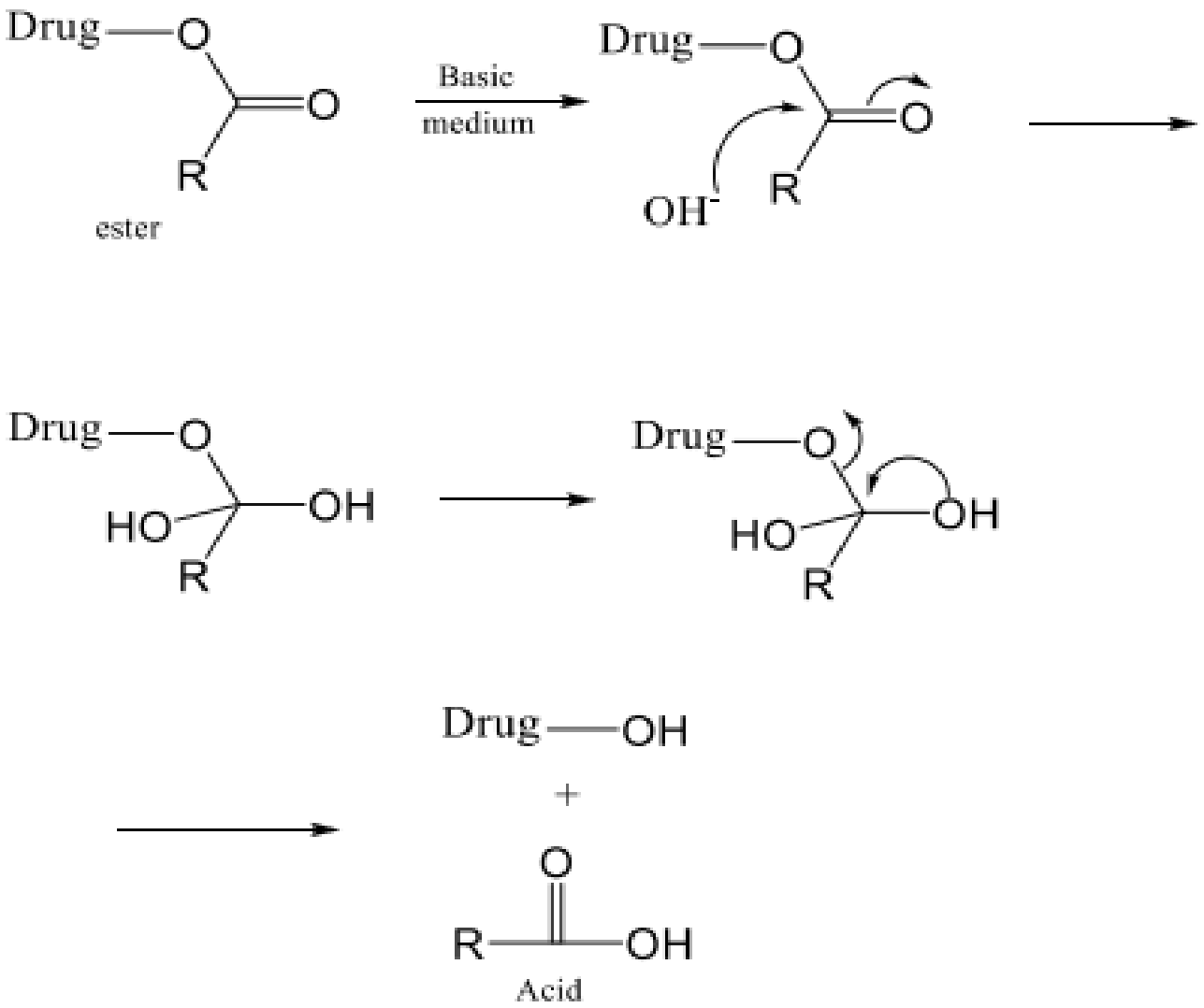


Chemical hydrolysis

Acidic hydrolysis

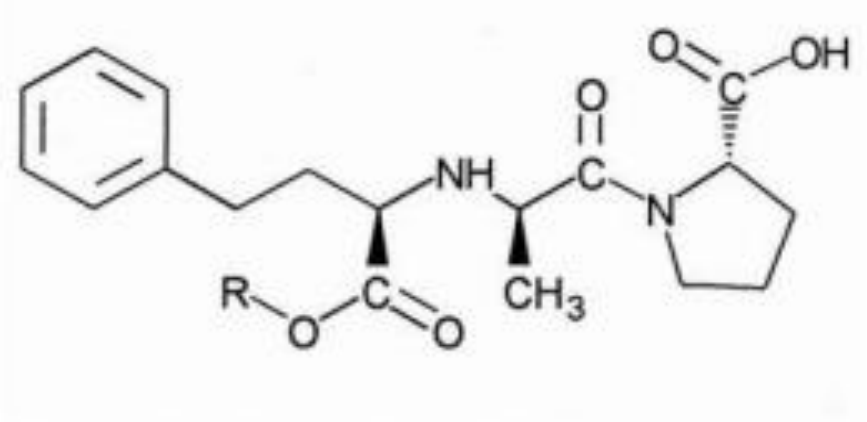


Basic hydrolysis



Carboxylic Acid-Containing Groups

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

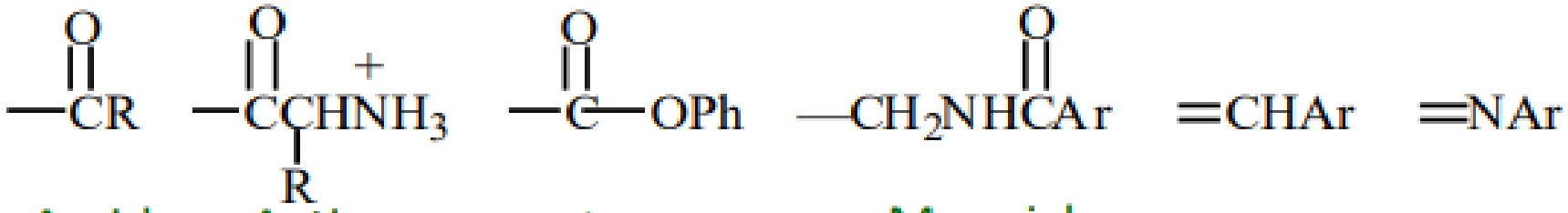


Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

Amine Prodrugs

X



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

Amides are commonly not used because of stability

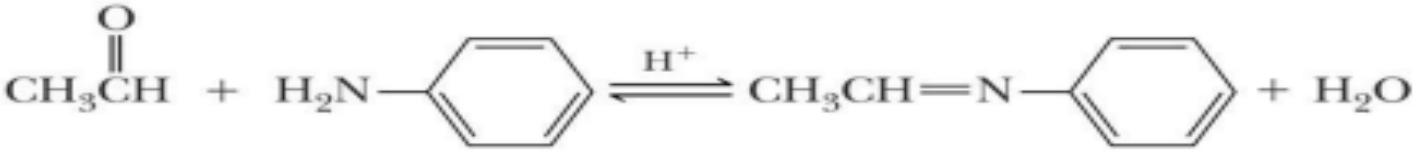
Activated amides (low basicity amines or amino acids) are effective

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

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), $RN{=}CR_2$.

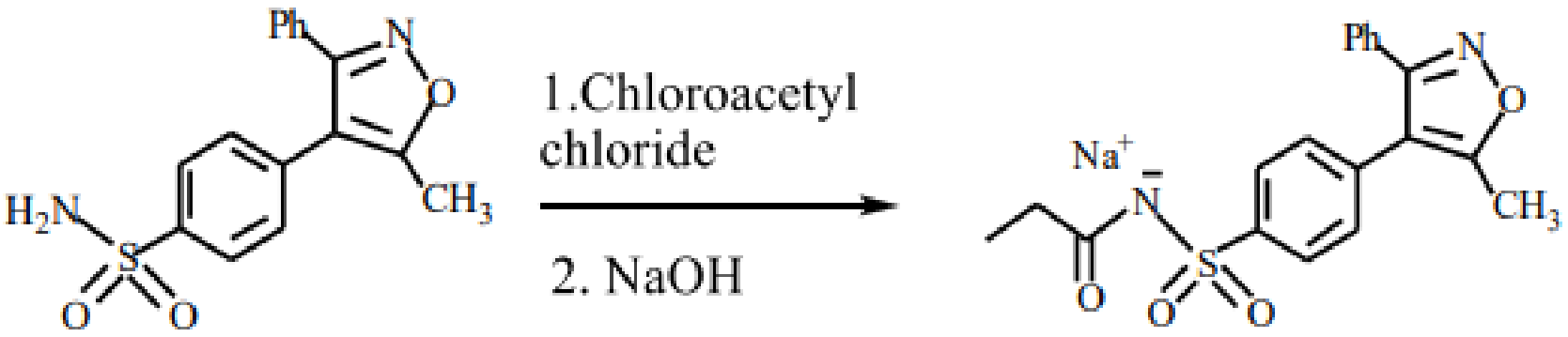


Acetaldehyde Aniline An imine (a Schiff base)

Primary amine

Prodrugs of Sulfonamides

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

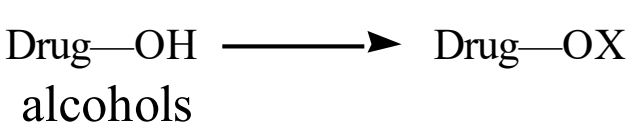


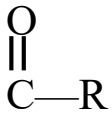
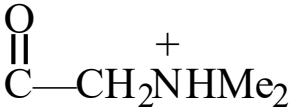
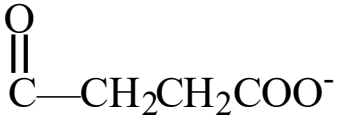
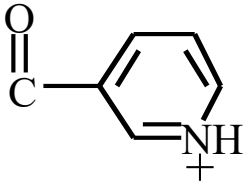
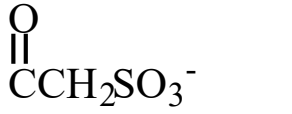
valdecoxib
8.9

parecoxib sodium
8.10

Prodrugs for Alcohol-Containing Drugs

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)

A. To accelerate hydrolysis rate:

i. 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)

ii. 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.

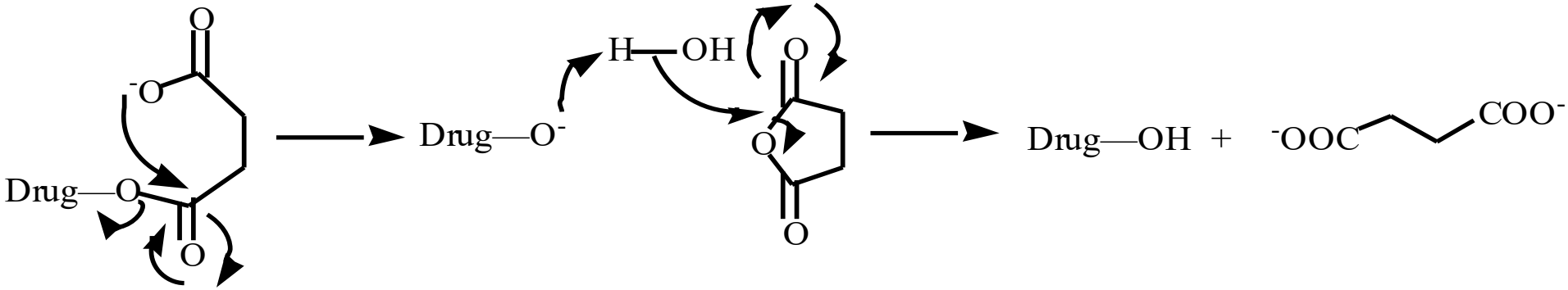
B. To slow down hydrolysis rate:

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

Another Approach to Accelerate Hydrolysis

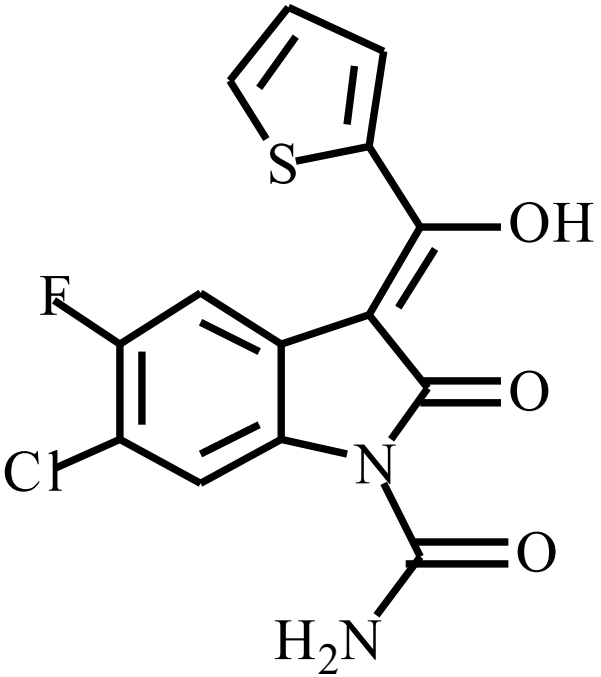
Intramolecular **hydrolysis of succinate esters**

Scheme 8.2



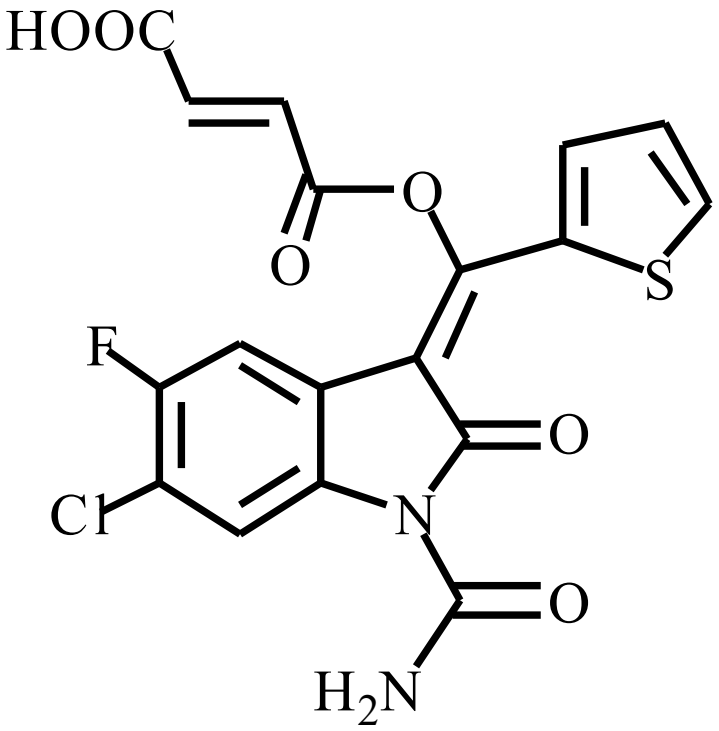
Also, acetals or ketals can be made for rapid hydrolysis in the acidic medium of the GI tract.

Enolic hydroxyl groups can be **esterified as well.(succinate ester)**



oxindole
8.1

antirheumatic agent

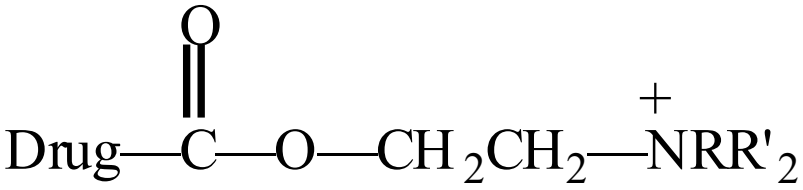


8.2

Carboxylic Acid-Containing Groups

Esterify as with alcohols

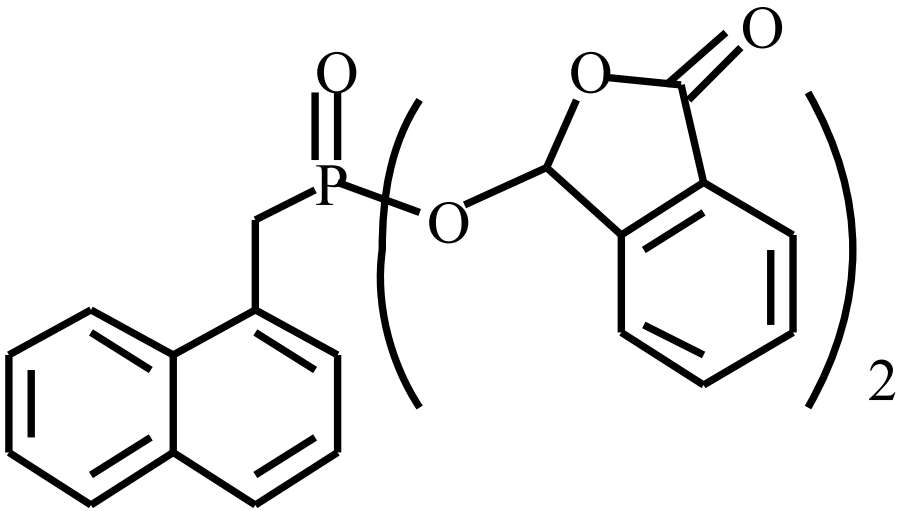
Maintaining Water Solubility of Carboxylate Prodrugs



8.3

Can vary pK_a by appropriate choice of R and R′

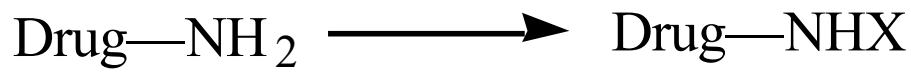
Prodrugs for **Phosphat**e- or Phosphonate-Containing Drugs



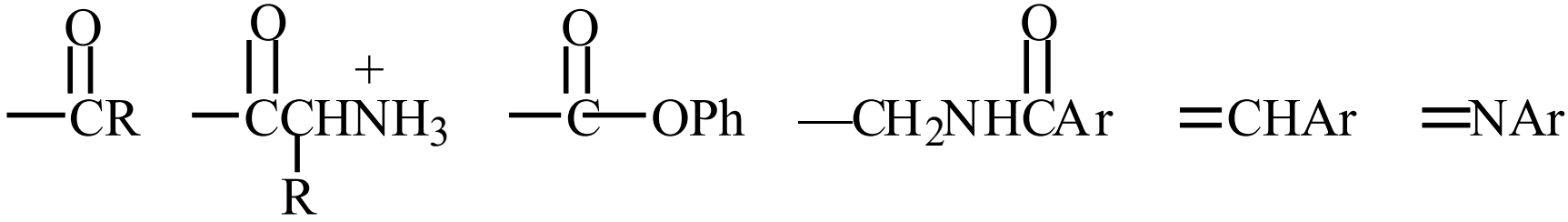
8.4

Amine Prodrugs

Table 8.2



X

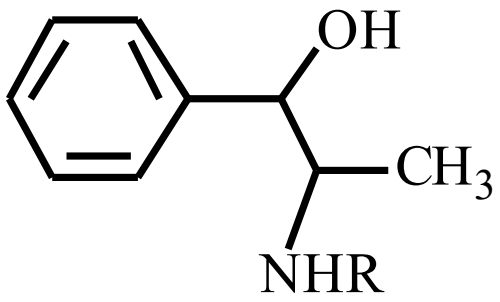


Amides are commonly not used because of stability

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 = $CH_2NHCOAr$)

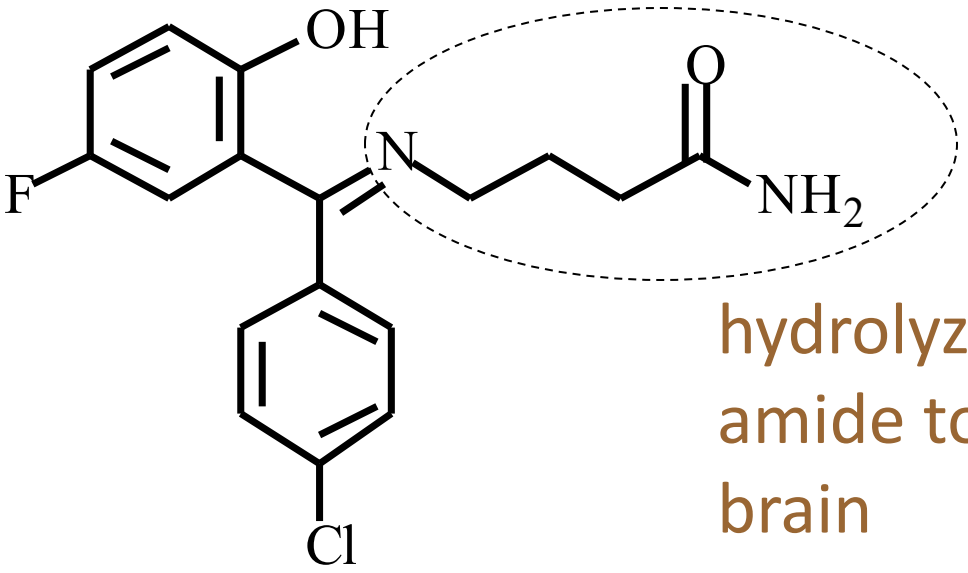
N-Mannich base (R = $CH_2NHCOPh$) has a log $D_{7.4}$ two units greater than the parent compound.



phenylpropanolamine hydrochloride (R = H HCl)
8.5

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

Imine (Schiff base) prodrug

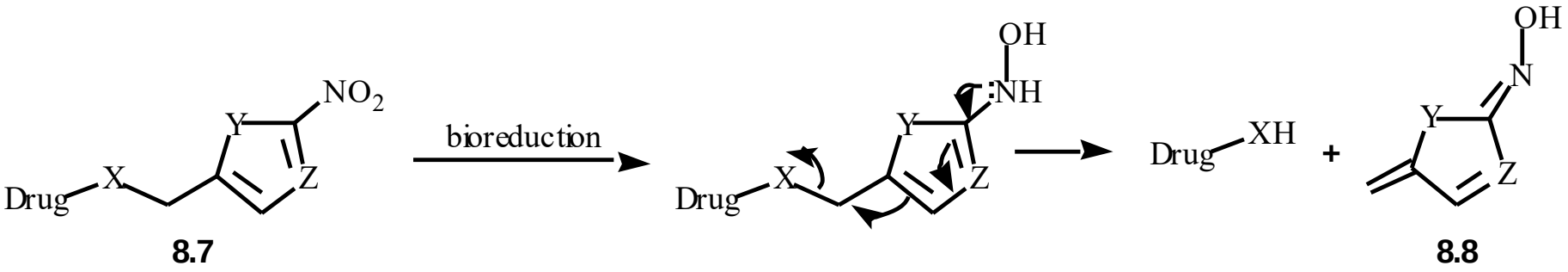


hydrolyze imine and amide to GABA inside brain

progabide
8.6
anticonvulsant

A Reductive Carrier-Linked Prodrug Approach

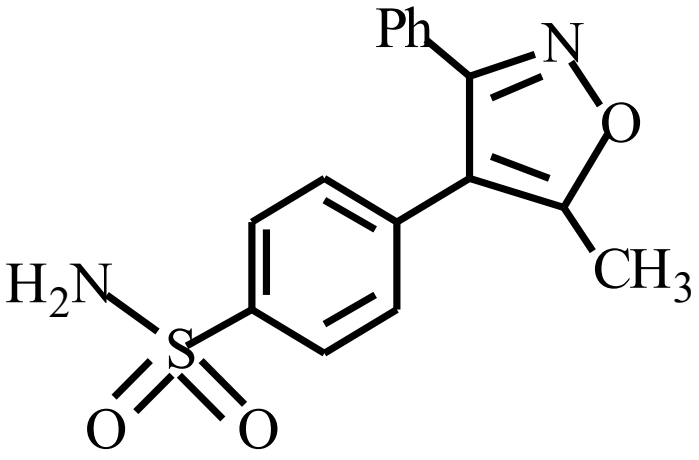
Scheme 8.3



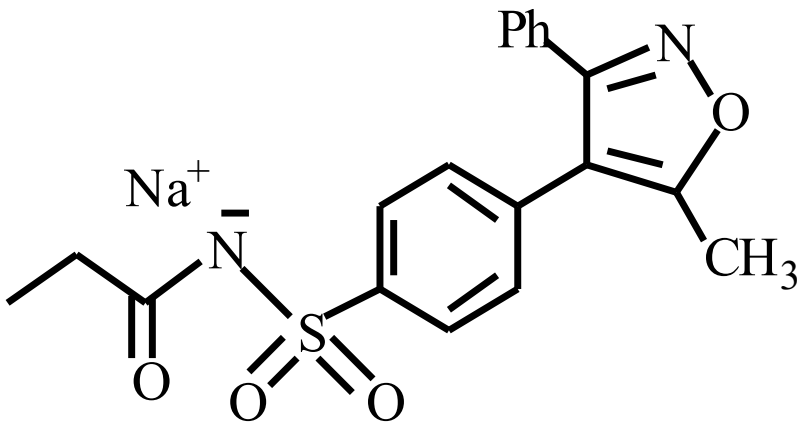
8.7 **8.8**

Prodrugs of Sulfonamides

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



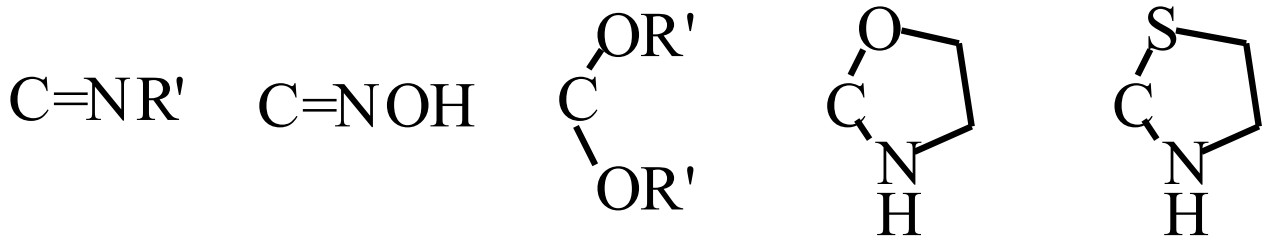
valdecoxib
8.9



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 ?