Faculty of Pharmacy
Organic pharmaceutical chemistry IV
Fifth year

Lect 2

Types of Prodrugs

by

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Types of prodrug

Various prodrugs for compounds containing different functional groups are given below

Prodrug

- ***1. Esters***

Prodrug

- ***2. Prodrug for Amides, Imides and Other Acidic Compounds***

Prodrug

- ***3. Prodrugs for Amines***

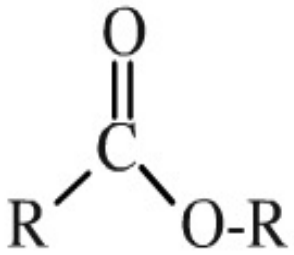
Prodrug

- ***4. Prodrugs with Carbonyl Group***

Types of prodrug

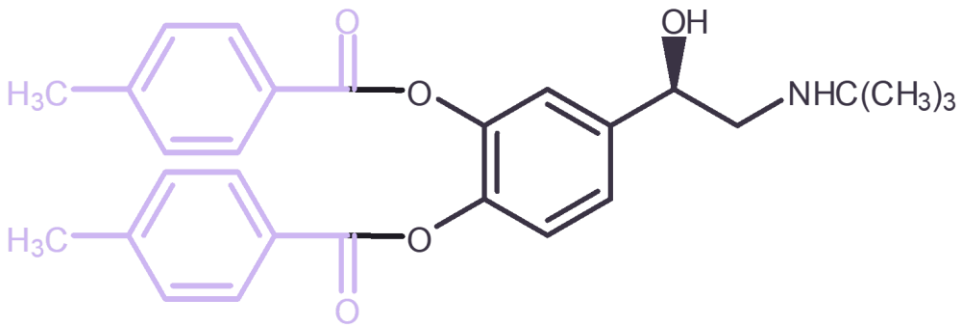
1- Esters

Ester derivatives are suitable prodrug for therapeutic agents containing carboxyl and hydroxyl functional groups.



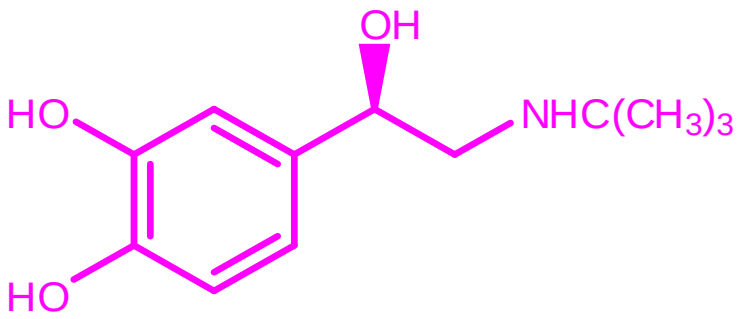
Chemical reactivity of esters is readily predictable on the basis of the steric and electronic properties of the substitutes in both the acyl and alcohol molecules

hydrophilic properties and charge of ester may play a major role in enzyme hydrolysis

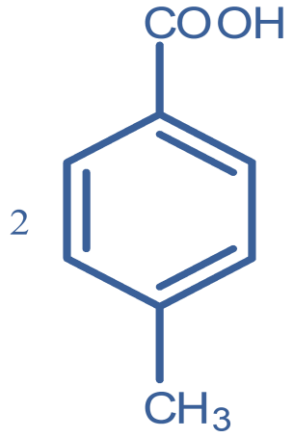


Bitolterol

Esterase



Colterol **β-blocker**



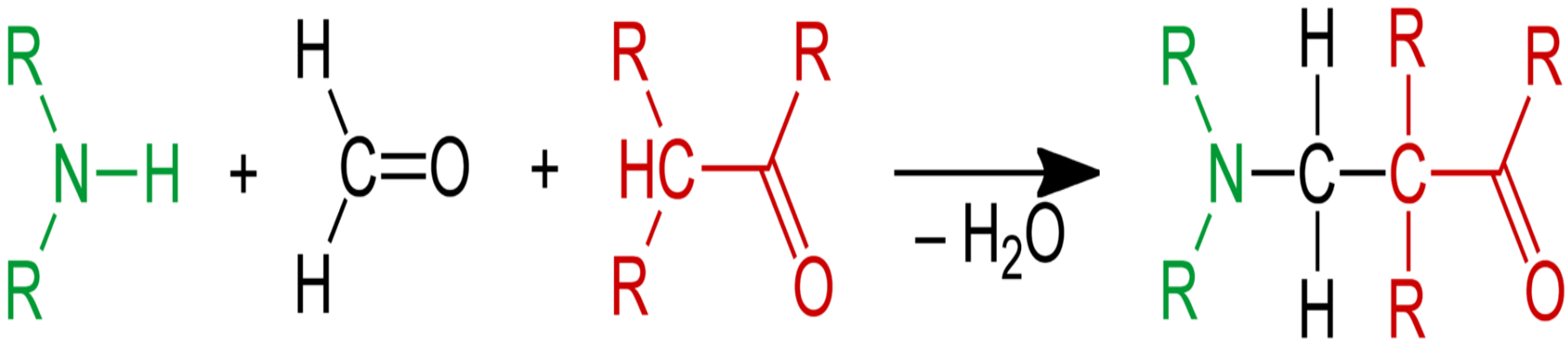
p-Toluic Acid

Types of prodrug

2- Prodrug for Amides, Imides and Other Acidic Compounds

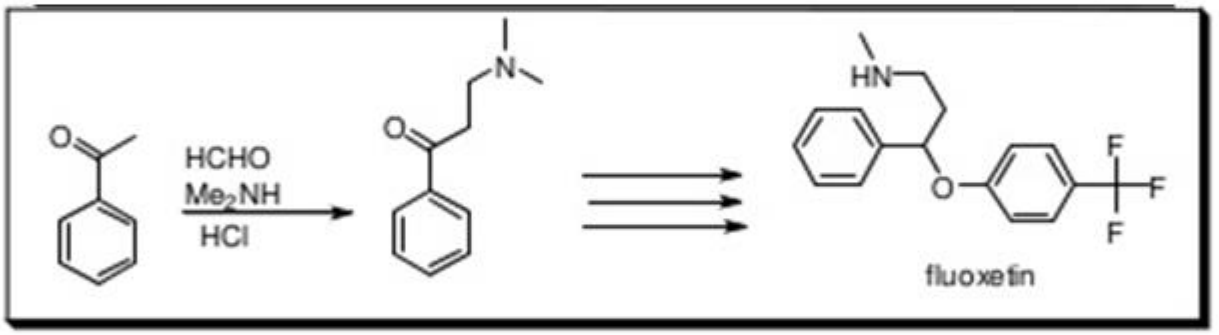
Mannich Bases and Acyloxy Derivatives	*N–Mannich bases can function as a prodrug candidate for compounds such as amides, imides and urea derivatives*
	Similarly, N-α-acyloxy alkylation of various amides, imides and N–heterocyclic amines also were adopted as a common approach to obtain prodrugs.
	The derivatives showed good stability in aqueous solution in vitro, they are in general rapidly cleaved in vivo by virtue of enzyme mediated hydrolysis

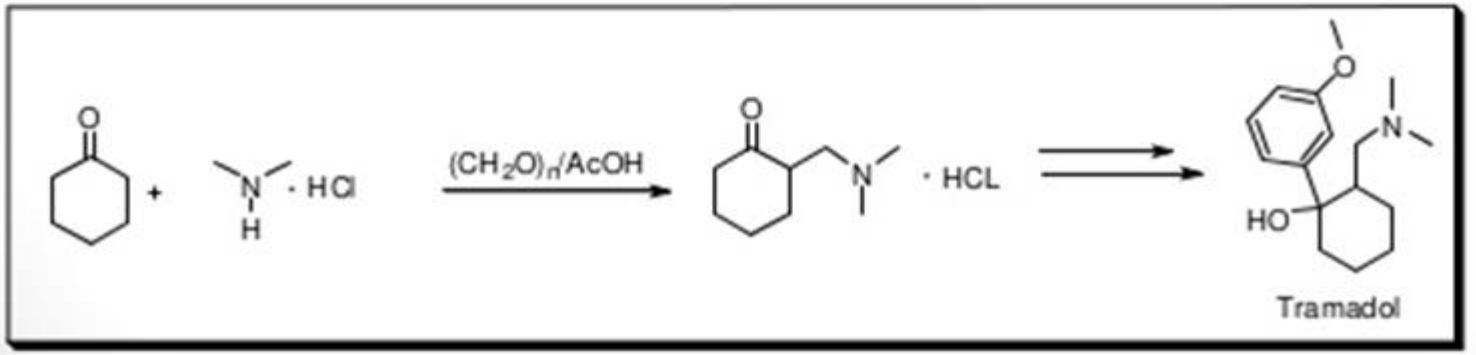
- The Mannich reaction is a three-component organic reaction that involves the amino alkylation of an acidic proton next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia.
- The final product is a β-amino-carbonyl compound also known as a Mannich base.



Mechanism of the Mannich Reaction

Applications





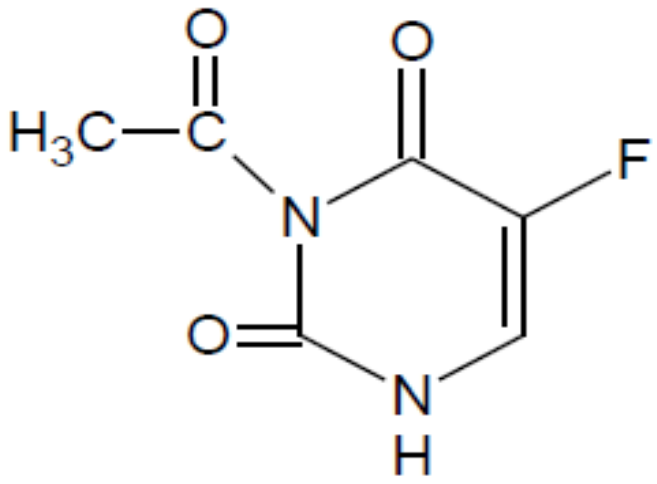
N–Acyl Derivatives

Plasma enzyme catalyzed hydrolysis Of the N–acyl derivatives

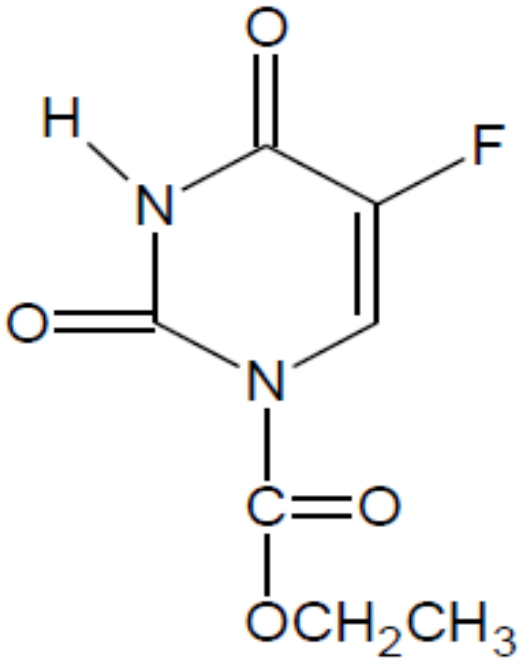
makes N–acylation of amide or imide fruitful in some cases such as N– acetyl–5–fluorouracil and N-ethoxy carbonyl–5-fluorouracil

Improved physicochemical properties and easy bioconversion of N–acyl derivative of 5–fluorouracil enhances the oral and rectal absorption of the parent drug

N–Acyl Derivatives



N_3-acetyl-5-fluorouracil



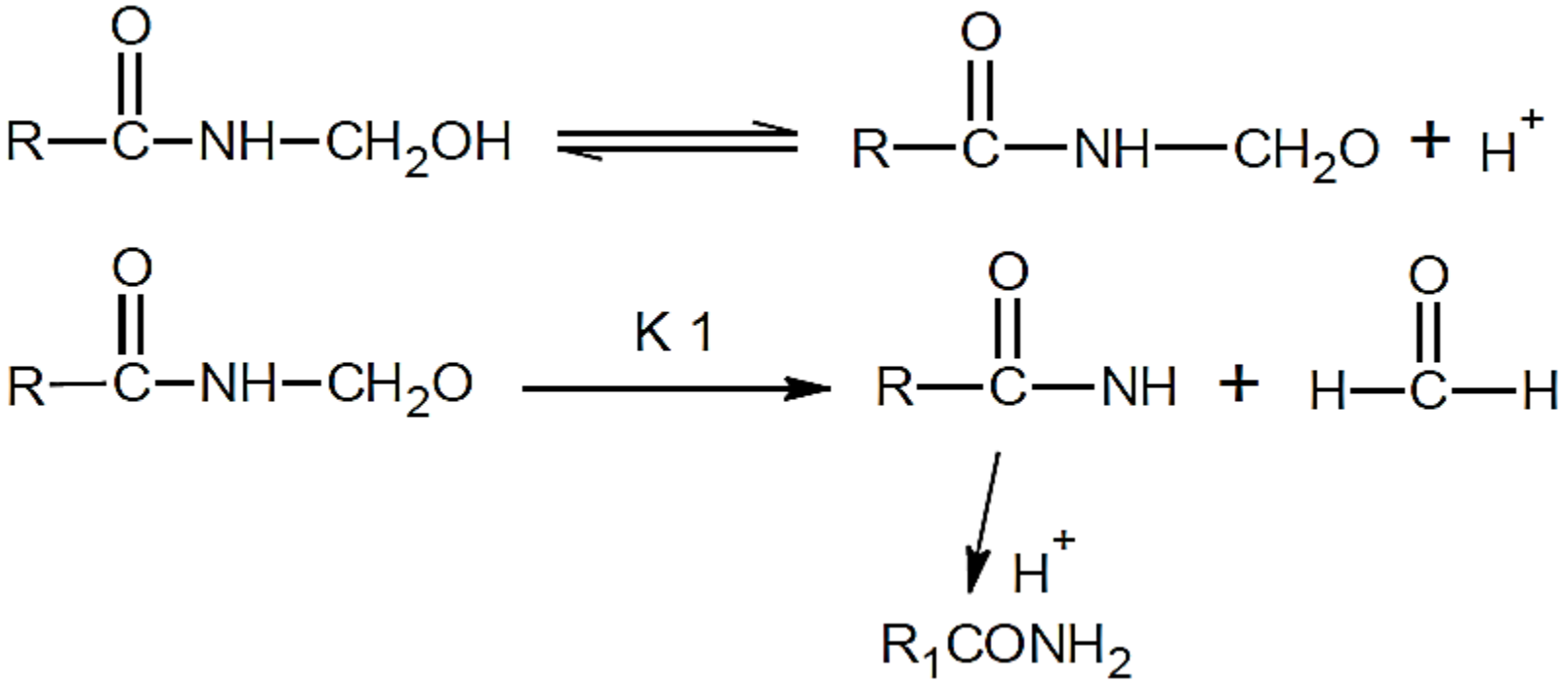
N_1-ethoxycarbonyl-5-fluorouracil

N–Hydroxy Methyl Derivatives

The N–hydroxyl methyl derivatives of amides or imide type compounds are more water soluble than the parent compounds.

By replacing a proton bind to nitrogen atom by a hydroxyl methyl group

Intra or intermolecular hydrogen bonding in such molecules may cause a decrease in melting point and increase in water solubility



The mechanism for the decomposition of N-hydroxyl methyl derivatives

Prodrugs for Amines

Prodrugs of amines are generally designed by making their amide

N–(acyloxy alkoxy carbonyl) derivatives and oxazolidine

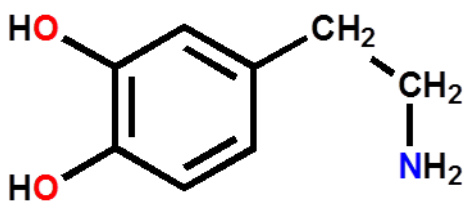
N–(Acyloxy alkoxy carbonyl) Derivatives and Amide Derivatives

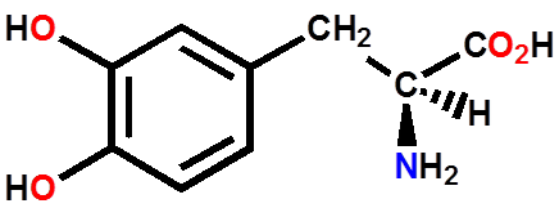
The utility of the N–(acyloxy alkoxy carbonyl) derivative is limited due to the resistance to undergo enzymatic cleave in vivo.

However, certain activated amides are chemically labile and also certain amides formed with amino acids may undergo enzymatic cleavage

For example the γ-glutamyl derivatives of dopamine, L-Dopa and sulfamethoxazole are rapidly hydrolyzed by γ-glutamyl transpeptidase in vivo.

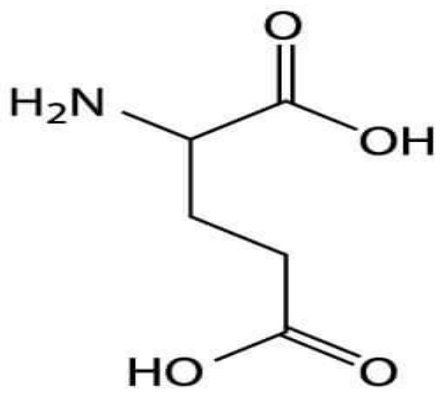
Similarly N–glycyl derivative, midodrin and N–1–isoleucine derivative of dopamine are the enzymatically labile amide prodrugs



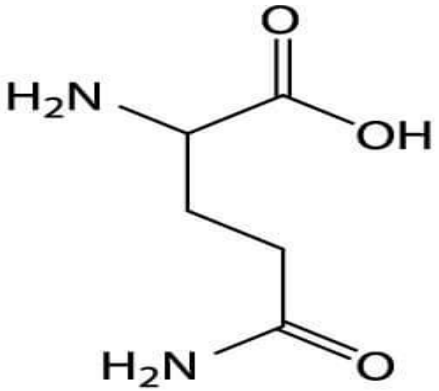


Dopamine

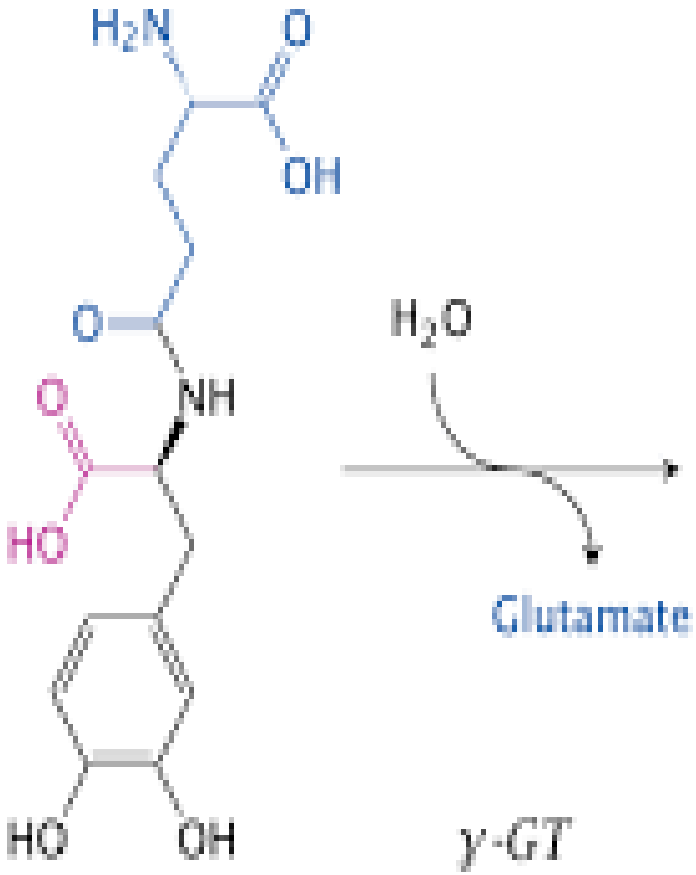
Levodopa

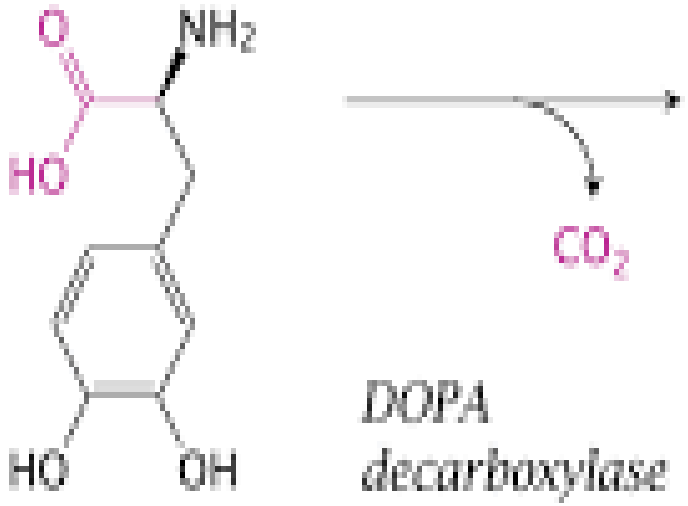


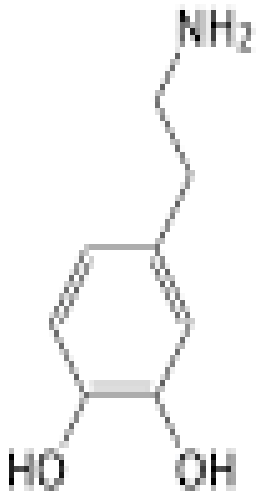
Glutamic acid

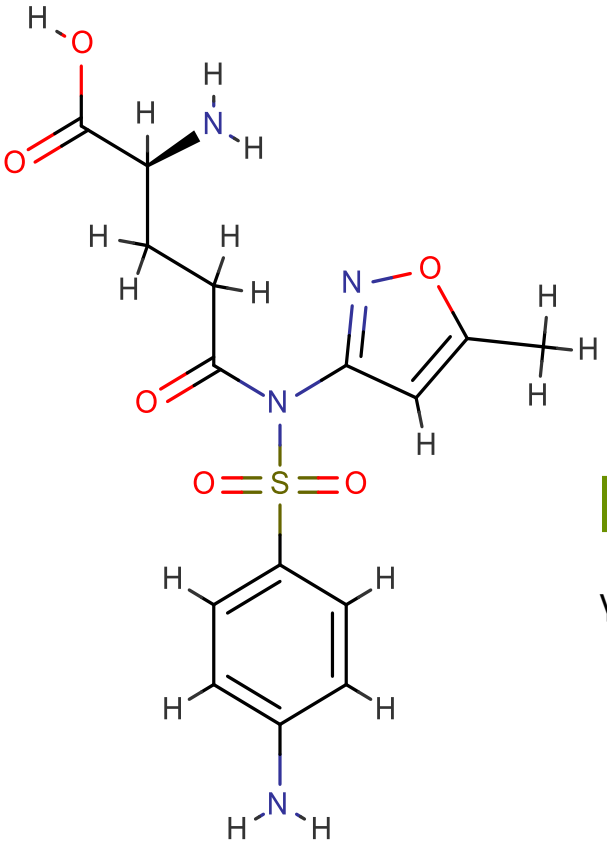


Glutamine

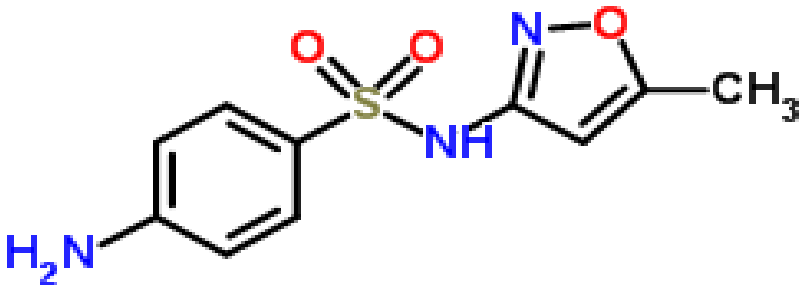








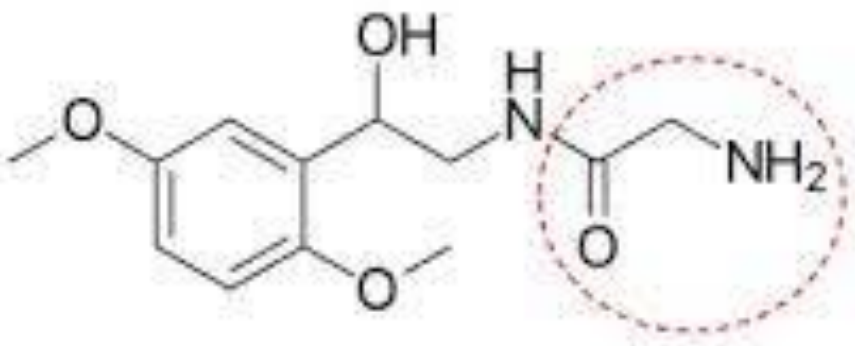
γ-glutamyl transpeptidase



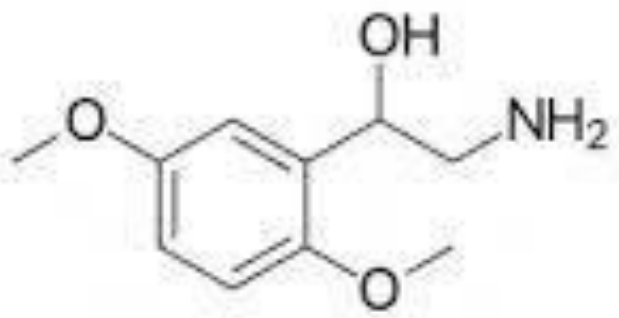
γ-glutamyl sulfamethoxazole

sulfamethoxazole

Midodrine is a prodrug which undergoes enzymatic hydrolysis to the selective alpha 1-adrenoceptor agonist desglymidodrine after oral administration.



Midodrine
(prodrug)



Desglymidodrine
(active metabolite)

Midodrin:
Midodrine is an alpha-adrenergic agonist used to treat orthostatic hypotension.

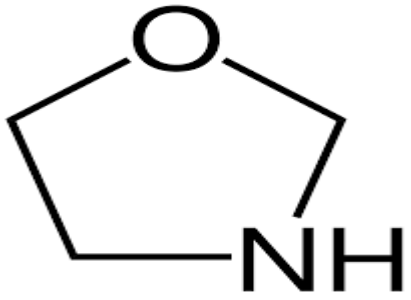
Oxazolidines

Oxazolidines are cyclic condensation products of β-amino alcohols and aldehydes or ketones, and they undergo a complete hydrolysis in aqueous solution.

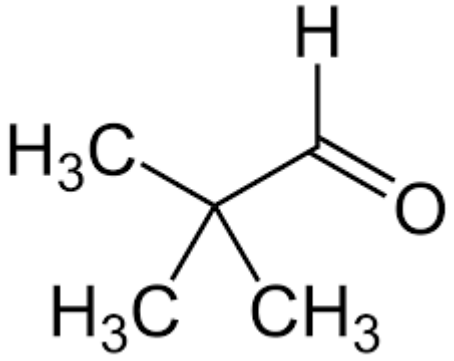
Alteration in carbonyl moiety controls the rate of formation of given β-amino alcohol.

Oxazolidines are weaker bases (PKa 6–7) than parent β-amino alcohols and found as more lipophilic than the parent compound at physiological pH.

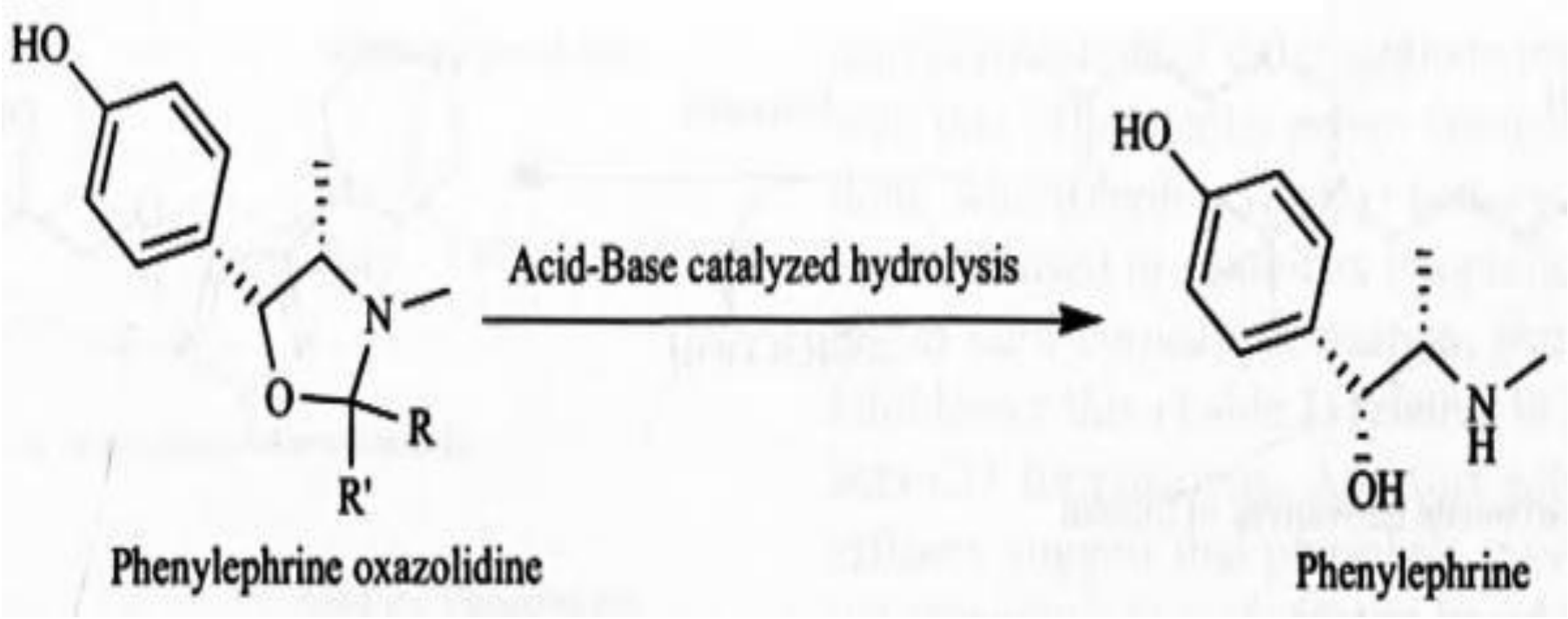
For example the oxazolidine prodrug of phenylephrine prepared from pivaldehyde has penetrated the cornea much more easily than the parent drug as a result of increased lipophilicity



Oxazolidine



pivaldehyde



Oxazolidine prodrug of phenylephrine

Prodrugs with Carbonyl Groups

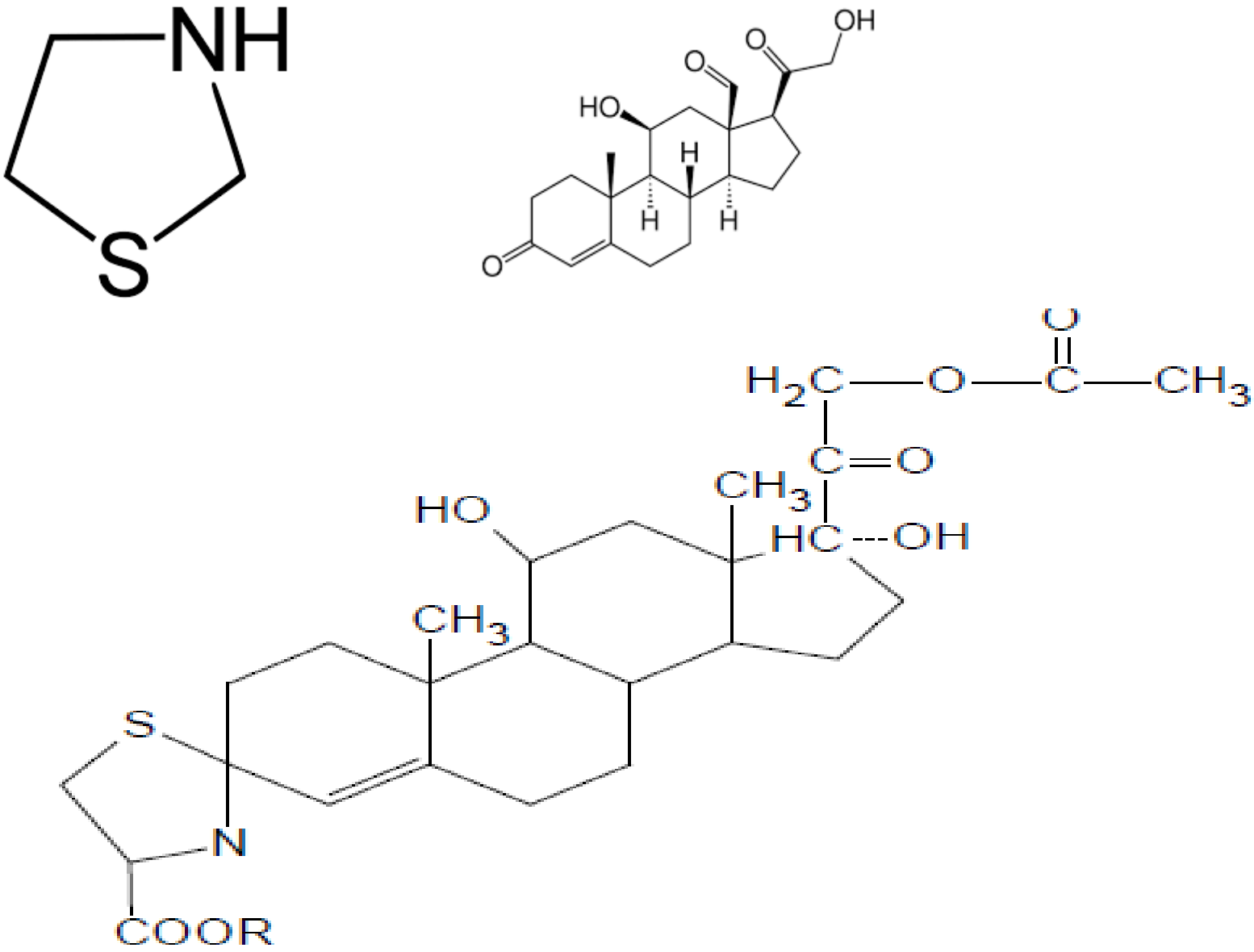
Weakly basic character of carbonyl containing drugs may be advantageous as the transformation of such drugs into oxazolidine

introduces a readily ionizable moiety, which allows the preparation of derivatives with increased aqueous solubilities at acidic pH.

Thiazolidines

Thiazolidine has been applied as prodrug derivative for various steroids containing a 3-carbonyl group to improve their topical anti inflammatory activity.

Thiazolidine derivatives of hydrocortisone and hydrocortisone 21-acetate prepared with cysteine esters to related β-aminothiols, have been shown to be readily converted to the parent corticosteroids at conditions similar to those prevailing in the skin, thus meeting the requirement for a prodrug



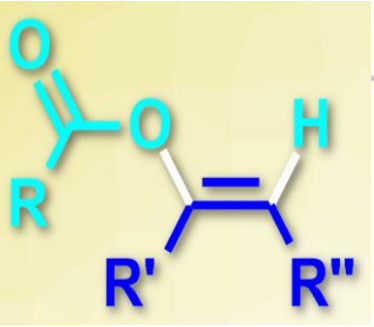
Thiazolidine prodrug of steroids

Enol Esters

Enol form, of keto–enol equilibrium under proper conditions can be trapped by alkylation or acylation.

Enol Esters

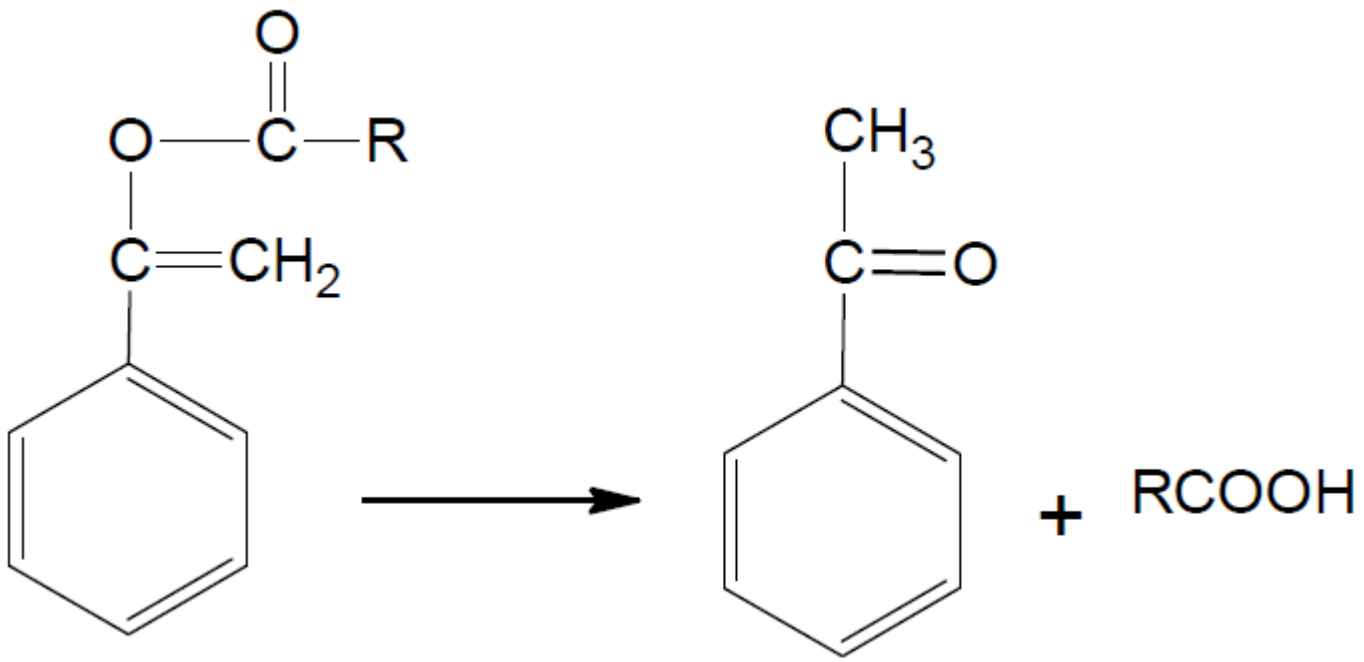
Such enol esters and ethers may readily undergo hydrolysis with liberation of free enol, which then reverts to the keto form almost instantaneously.



In the presence of plasma or liver enzymes, the enol esters are readily hydrolyzed.

For example the chemical stability of enol ester of acetophen is similar to that of phenol ester with maximum stability at pH 3.3.

On contrary it is rapidly hydrolysable in plasma and liver enzymes



Enol ester of acetophen

Types of prodrugs

- Many therapeutic agents are manufactured and administered in prodrug forms.
- A new classification system for prodrugs is proposed to provide useful information about where in the body a prodrug is converted to the active drug.
- In this system, prodrugs are classified into Type I or Type II and the respective Subtypes IA, IB, IIA, IIB or IIC based on their sites of conversion in to the final active drug form.

Type I prodrugs

Conversion occurs intracellularly (e.g. antiviral nucleoside analogues, lipid -lowering statins).

Type IA prodrugs refers to those that are converted at the cellular targets of therapeutic actions

whereas Type IB prodrugs conversion occurs in the primary metabolic tissues such as liver, gut, or lung.

Type II prodrugs

Conversion occurs occurs extracellularly for examples in digestive systemic, circulation or other extracellular body fluids (e.g., etoposide phosphate, valganciclovir, fosamprenavir).

For Type IIA prodrugs, the conversion process takes place extracellularly in the milieu of gastrointestinal fluids.

For Type IIB, the conversion occurs in the systemic circulation and/or other systemic extracellular fluid compartments .

For Typ IIC, the conversion occurs near therapeutical target cells.

Mixed type of prodrugs

A prodrug may belong to multiple categories and be recognized as a Mixed -Type prodrug .

For example a prodrug maybe converted both in target cells and metabolic tissues such as liver (i .e., named as a Type IA/IB prodrug)

or one converted in both GI fluids and systemic circulations

(i .e., named as a Type IIA/IIB prodrug)

New 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 5-Flurouracil
		B	Metabolic Tissues (liver, GI mucosal cell, lung, etc.)	**Type IB:** Cabamazepine Captopril
Type II	Extracellular	A	GI Fluids	**Type IIA:** Lisdexamfetamine Loperamide oxide
		B	Systemic Circulation and Other Extracellular Fluid Compartments	**Type IIB:** Acetylsalicylate Chloramphenicol succinate
		C	Therapeutic Target Tissues/Cells	**Type IIC:** ADEPs GDEPs VDEPs

References:

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- http://shodhganga.inflibnet.ac.in/bitstream/10603/3457/10/10_chapter%201.pdf

- Kuei Meng Wu(2009). Anew Classification of Prodrugs: Regulatory Perspectives [online]. Pharmaceuticals,2(3),7781;doi:10.3390/ph2030077. Accessed from http://www.mdpi.com/1424-8247/2/3/77.

THANK YOU