

Lec1: Basic concept of prodrugs

Module objectives:

1. To give the students knowledge and experience in prodrugs and hormones as part of their medicinal and pharmaceutical field.
2. It includes classification, synthesis, biotransformation and/or formulation of certain drugs to improve their action as well as to avoid some side effect.

➤ *Why to study Organic Pharmaceutical Chemistry?*

About this module: *Topics to be covered.*

1. "Basic concept of prodrugs; Covalent bonds (cleavable); Prodrugs of functional groups; Types of prodrugs."
2. "Chemical delivery systems; Polymeric prodrugs; Types and structure of polymers; Cross-linking reagents."
3. "Drug targeting."
4. "Project."
5. "Combinatorial chemistry; Peptides and other linear structures; Drug like molecules; Support and linker; Solution-phase combinatorial chemistry."
6. "Detection, purification and analgesics; Encoding combinatorial libraries; High-throughput screening; Virtual screening; Chemical diversity and library design."

Basic concept of prodrugs:

- The term prodrug was introduced by Albert who used “prodrug” or “proagent” to refer to a pharmacologically inactive compound that is transformed by the mammalian system into an active substance by either chemical or metabolic means.

Basic concept of prodrugs:

- Another term drug latention, which implies a time lag element or component, was coined by Harper.

Basic concept of prodrugs:

- Later, the concept of prodrug and latentiated drug for solving various problems was attempted and the definition of drug latentiation was extended to include non-enzymatic regeneration of parent compounds.

Basic concept of prodrugs:

- The prodrug approach has emerged as a tool in overcoming various obstacles to drug formulation and targeting such as:
 1. *Chemical instability.*
 2. *Poor aqueous solubility.*
 3. *Inadequate brain penetration.*
 4. *Insufficient oral absorption.*
 5. *Local irritation.*
 6. *Toxicity.*

Basic concept of prodrugs:

- It is justified by the fact that once the barrier to the use of parent compound has been overcome, these temporary forms can be converted to the free parent compound that can exert its pharmacological activity.

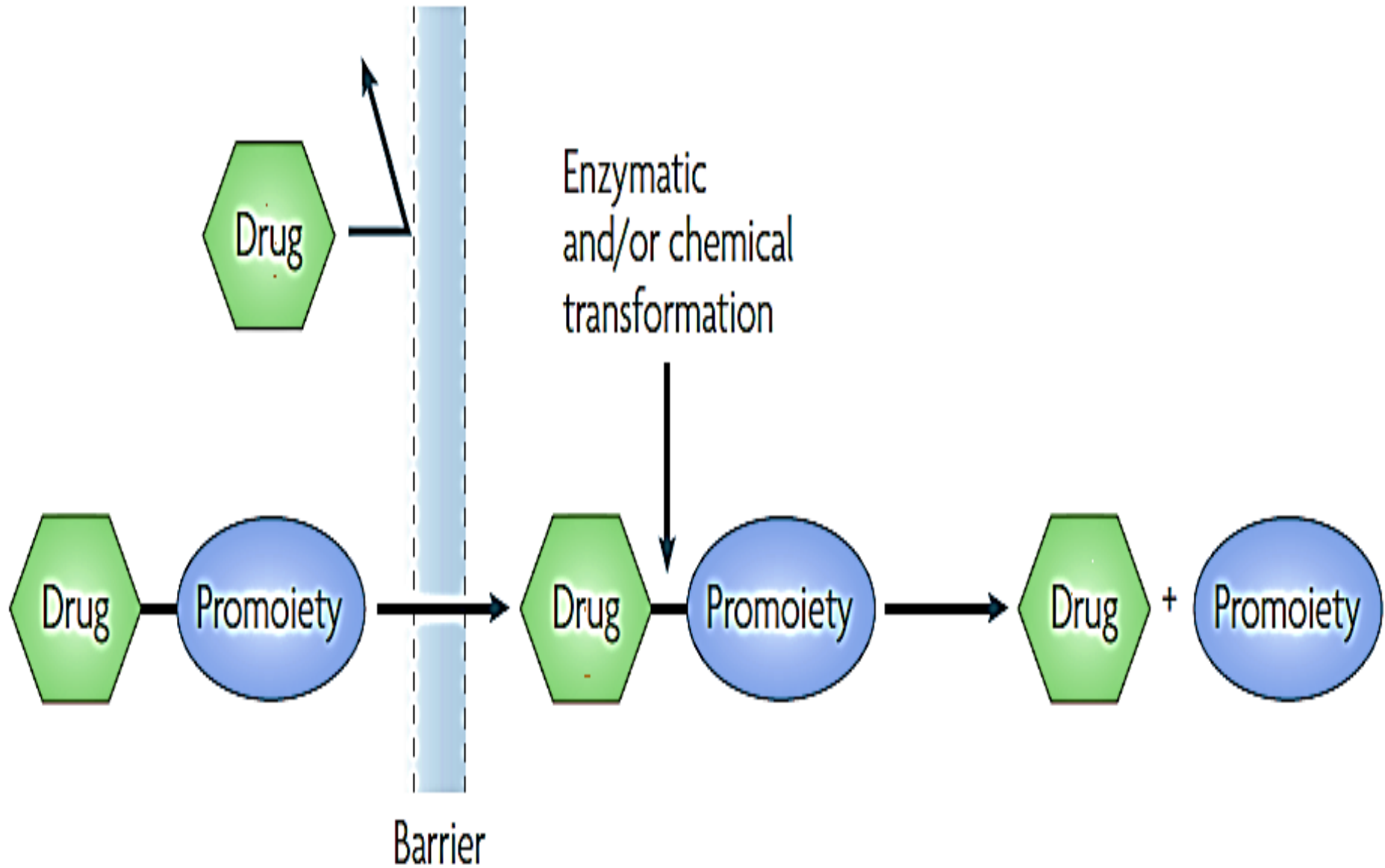
Definition

- A *prodrug* is thus defined as a biologically inactive derivative of a parent drug molecule that usually requires a chemical or enzymatic transformation (activation) within the body to release the active drug, and possess improved delivery properties over the parent molecule.

Definition

- These attractive features render the prodrugs a well-recognized strategy to improve drug targeting.
- The drug targeting improvement is employed to enhance the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the usefulness of a potential drug.

Prodrug Concept



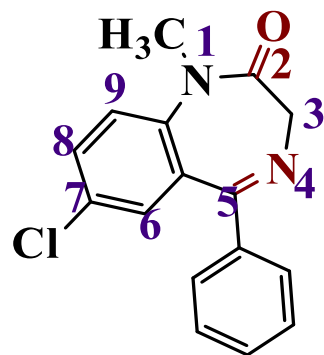
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What is the difference between “prodrug” and the “codrug”?

Explain briefly and give an example on each.

drugs → Pharmacological active cpds **Transformed** → active metabolites
(one or more)

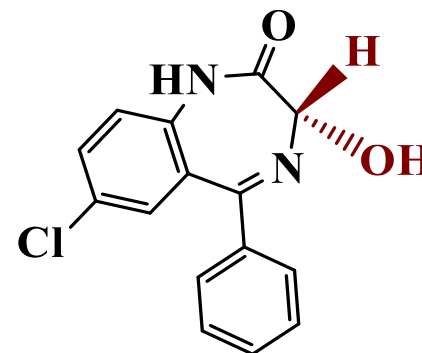
Example:-



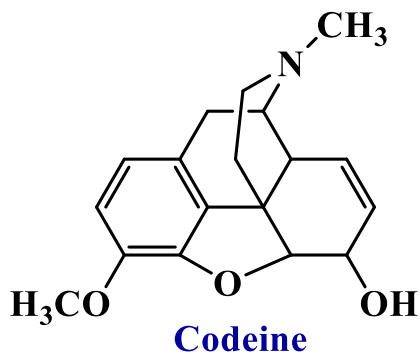
Diazepam (Valium)
Active

P-450(MFO)

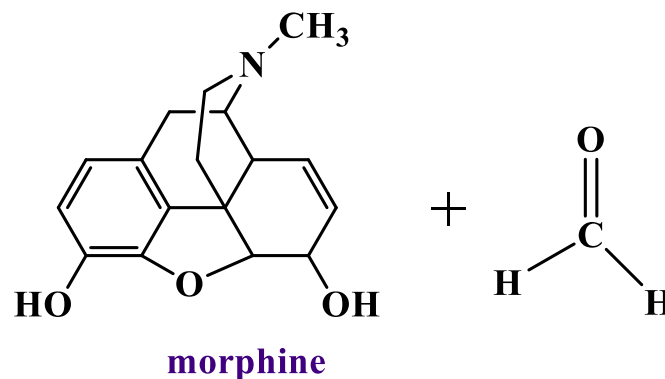
N-demethylation



Oxazepam
more active



Codeine



morphine

Non-prodrugs

It is also important to distinguish prodrugs from soft and hard drugs.

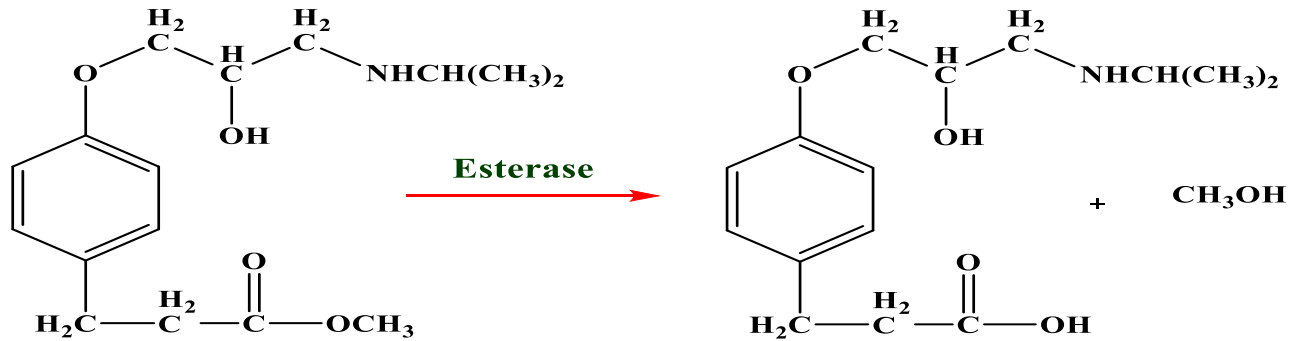
Hard drugs:- are compounds that are designed to contain the structural characteristics necessary for pharmacological activity but in a form that is not susceptible to metabolic or chemical transformation.



- 1- Increased efficiency by avoiding metabolism.
- 2- No toxic metabolites are formed.
- 3- **HOWEVER**, less readily eliminated due to lack of metabolism.

Soft drugs: - “biologically active compounds (drugs) characterized by a predictable and fast in vivo metabolism to inactive and non-toxic moieties, after they have achieved their therapeutic role” (such as short acting β -blocker agent, esmolol), Thus soft drugs are considered to be the opposite of prodrugs.

Soft drugs: -



Esmolol

Antihypertensive and cardiac arrhythmias

half-life 9 min → short DOA → rapid hydrolysis by esterase

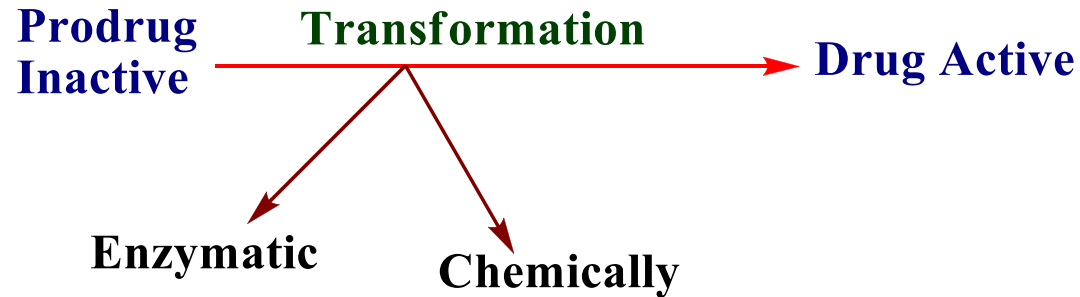
weak β -blockers and not exhibit clinically significant effects

administered by continuous IV infusion for control ventricular rate in patient with atrial flutter, atrial fibrillation, or sinus tachycardia

Soft drug $\xrightarrow{\text{Transformation}}$ Inactive cpd
Active

Prodrug $\xrightarrow{\text{Transformation}}$ Drug Active
Inactive

There are two mechanism for the conversion of prodrug to an active drug:-



1- Metabolizing enzyme within the body

- **More common**
- **Chemically stable**
- **Degradation occurs in the body (in vivo)**
- **Enzymatic dependent**
- **Patient dependent**

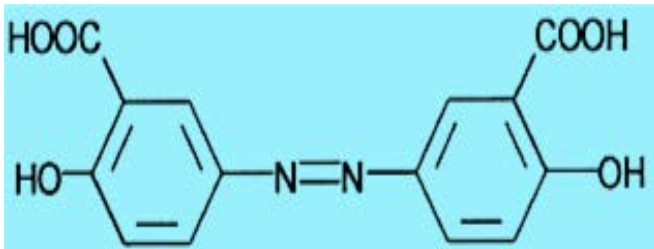
**2- Chemically method
hydrolysis, decarboxylation**

- **Less common**
- **Chemically unstable**
- **Degradation occurs out side the body (in vitro)**
- **Not enzymatic dependent**
- **Not patient dependent**

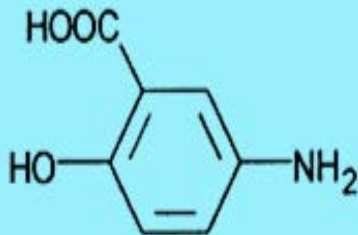
Covalent bonds (cleavable):

- Olsalazine and chloramphenicol palmitate are examples of prodrugs that are cleaved to smaller compounds, one of which is the active drug.

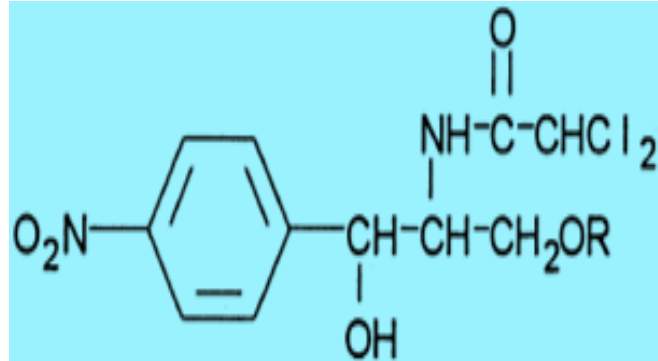
Covalent bonds (cleavable):



Olsalazine



Mesalamine



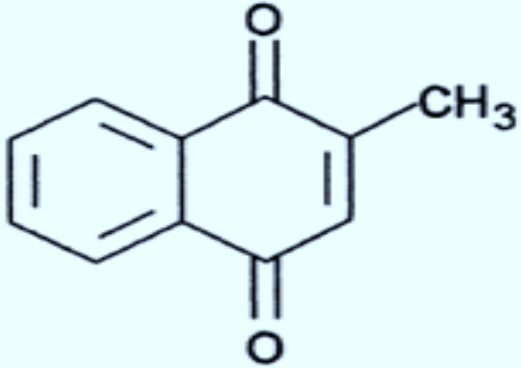
Chloramphenicol: R = H

Chloramphenicol Palmitate: R = CO(CH₂)₁₄CH₃

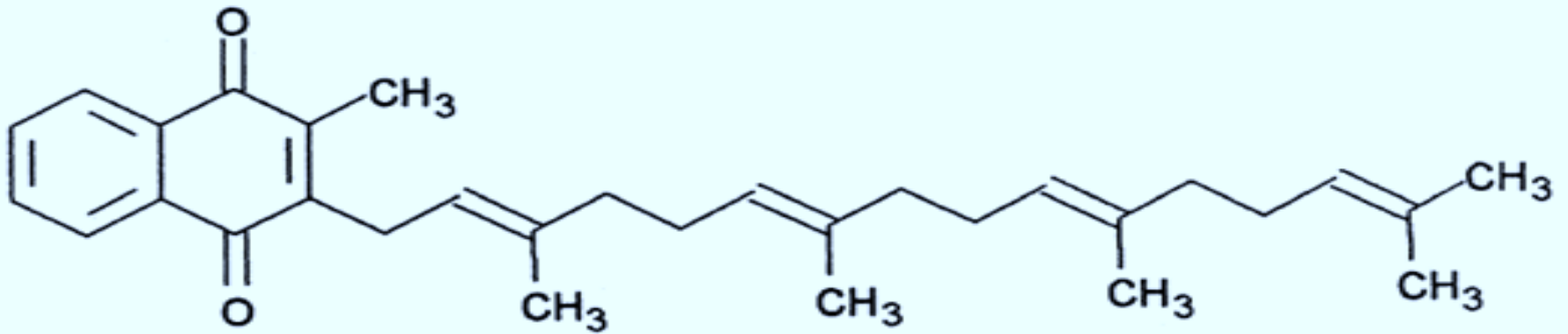
Covalent bonds (cleavable):

- Others are metabolic precursors that is converted to the active form.
- An example of this type of prodrug is menadione, a simple naphthoquinone that is converted in the liver to phytonadione (vitamin K)

Metabolic precursors



Menadione



Phytonadione (Vitamin K)

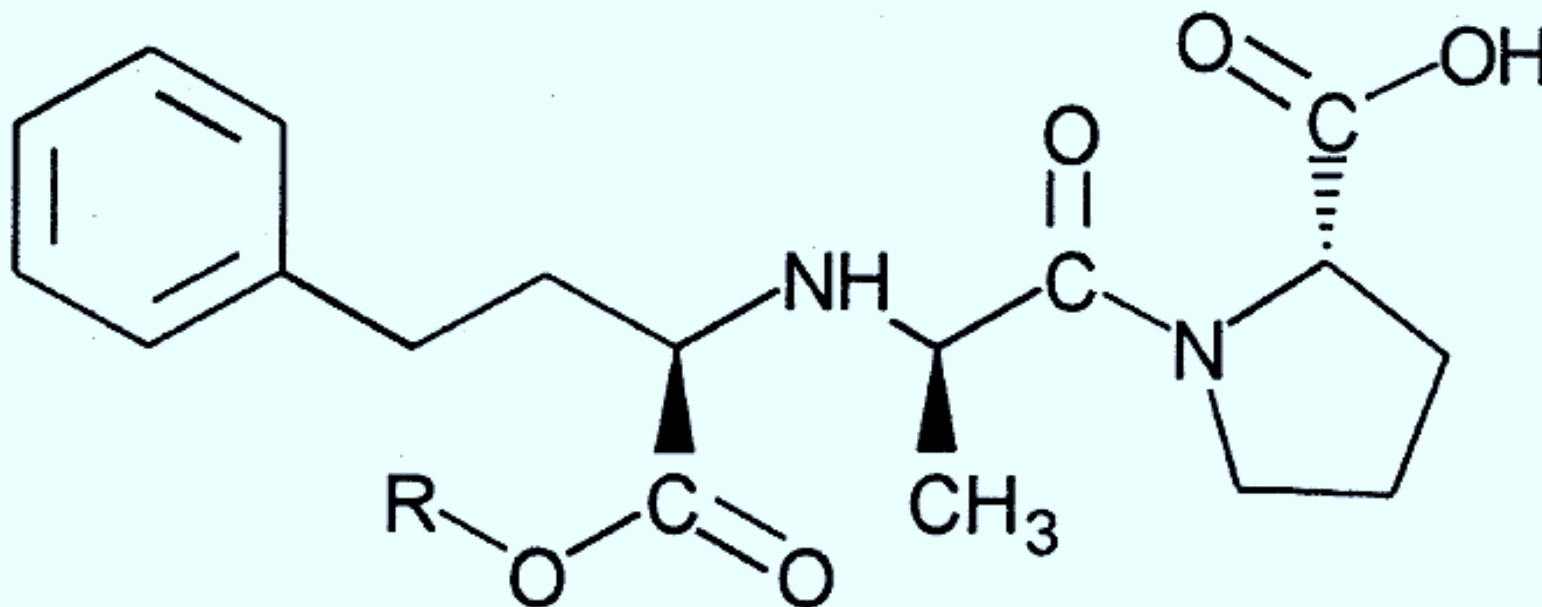
Prodrugs of functional groups:

- Occasionally, the prodrug approach is used to enhance the absorption of a drug that is poorly absorbed from the gastrointestinal tract.

Prodrugs of functional groups:

- Enalapril is the ethyl ester of enalaprilic acid, an active inhibitor of angiotensin-converting enzyme (ACE).
- The ester prodrug is much more readily absorbed orally than the pharmacologically active carboxylic acid.

Prodrugs of functional groups:



Enalapril: $R = C_2H_5$

Enalaprilic Acid: $R = H$

Bio reversible derivatives for various functional groups

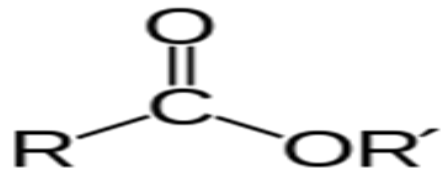
- Various types of functional groups are present in different therapeutic agents.
- These functional groups react with other functional groups of nontoxic promoiety to form prodrugs.

Types of prodrugs:

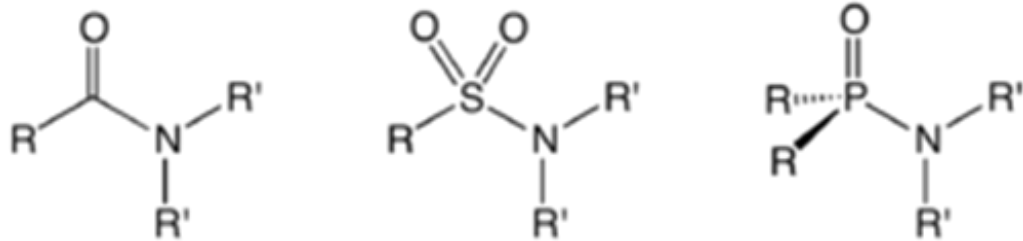
- Various prodrugs for compounds containing different functional groups are listed below:

1. *Esters.*
2. *Prodrug for Amides, Imides and Other Acidic Compounds.*
3. *Prodrugs for Amines, and.*
4. *Prodrugs with Carbonyl Groups.*

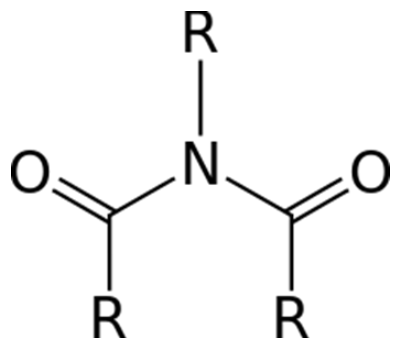
• Esters:



• Amides:



• Imides:



• Amines:

Primary amine	Secondary amine	Tertiary amine
$\begin{array}{c} \text{H} \\ \vdots \\ \text{N} \\ / \quad \backslash \\ \text{R}^1 \quad \text{H} \end{array}$	$\begin{array}{c} \text{H} \\ \vdots \\ \text{N} \\ / \quad \backslash \\ \text{R}^1 \quad \text{R}^2 \end{array}$	$\begin{array}{c} \text{R}^3 \\ \vdots \\ \text{N} \\ / \quad \backslash \\ \text{R}^1 \quad \text{R}^2 \end{array}$

Advantages of prodrug

1) Overcome drug problems such as

- A) Alleviation pain at the site of injection.
- B) Elimination of unpleasant taste, this is so important for children, when we not have more or other choices.
- C) Decrease metabolic inactivation.
- D) Increase chemical stability.
- E) Prolong or decrease the duration of action. according to the need, mostly the main purpose that is need is prolong the duration of action. Specially for drug for chronic use (specially multiple and long use) such as antibiotic.
- F) Decrease toxicity of drug.
- G) Increase absorption of drug.
- H) Poor site specificity: - Site- directed delivery system (drug targeting) to get effective concentration in a certain tissue. Targeting of drug mean the controlling on its distribution, this lead to decrease the coast ,get large concentration in certain organ, better effect, less S/E, this is so important specially in case of anticancer drug to decrease toxicity.

2) To overcome cost and time problems. (And this is the advantage of prodrug over drug derivatives).

So for such drug, the problem is detected and depends on it the prodrug is design.

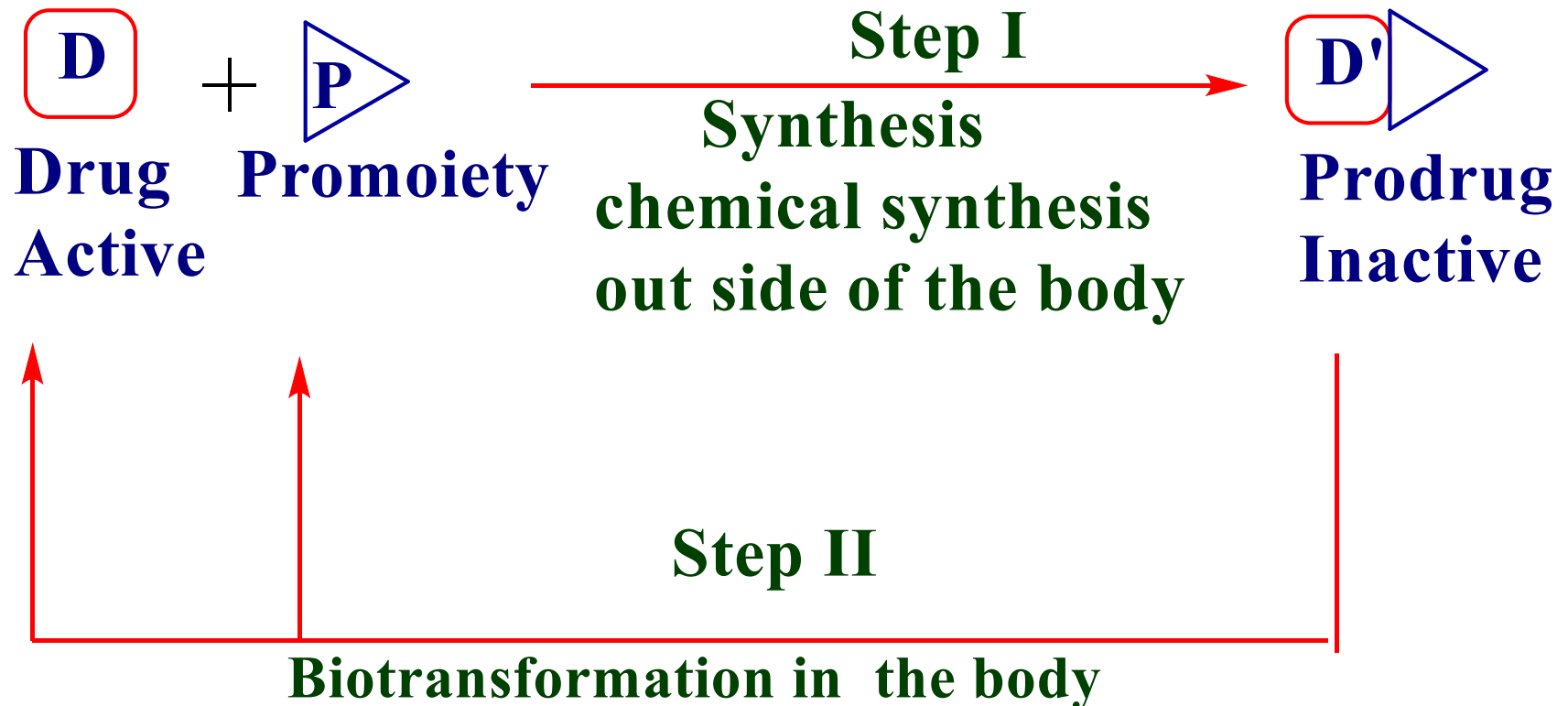
Properties of ideal prodrug

- 1- Pharmacological Inertness**
- 2- Rapid transformation, chemically or enzymatically,
into the active form at the target site**
- 3- Non-toxic metabolic fragments followed by their
rapid elimination**

Types of prodrugs

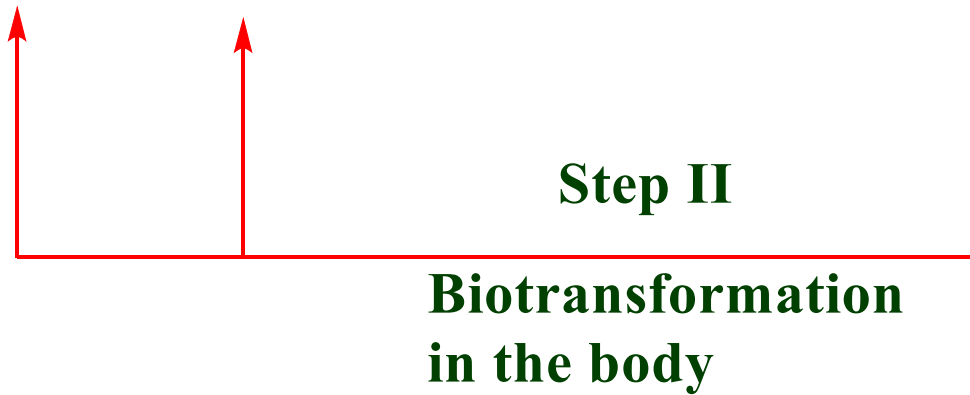
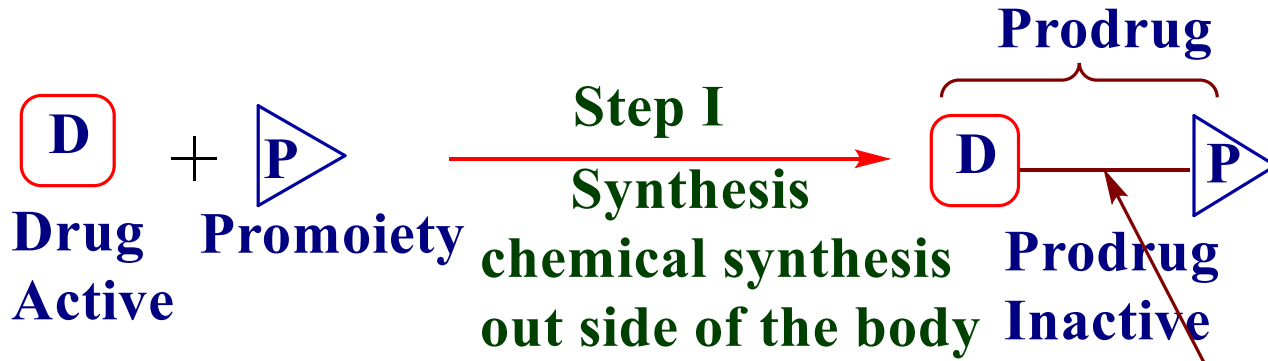
There are four major classes of prodrugs, namely:-

1) **Carrier –linked prodrugs:** A compound that contains an active drug linked to a carrier group (also known as a promoiety), that is removed enzymatically.



- 1) **Bioprecursor prodrugs:** which do not contain a promoiety but rather contain a latent functionality that is metabolically or chemically transformed to the active drug molecule.
- 1) **Macromolecular prodrugs:** where the carrier is a macromolecule such as a PEG(polyethyleneglycol).
- 1) **Drug-antibody conjugates:** where the carrier is an antibody raised against tumor cells.

Carrier-linked prodrugs:- Drug is linked to promoiety and bond must be covalent bond and must be liable in vivo to hydrolysis by either enzyme or change in the pH.



Covalent bond liable in vivo to hydrolysis by enzyme or change pH

The promoiety who is not necessary for activity but may impart some desirable property to the drug such as increase lipid or water solubility or site directed delivery.

The promoiety could be small or polymer (so called polymeric prodrug), that mean the carrier either small or large to give the purpose. Small molecule may be amino acid (single) which is L-type or simple aliphatic acid such as succinic acid or aromatic acid such as benzoic acid. The amino acid or acid could be used to increases the hydrophilicity and water solubility. While branched aliphatic, long chain or aromatic acid could used to increases the hydrophobicity.

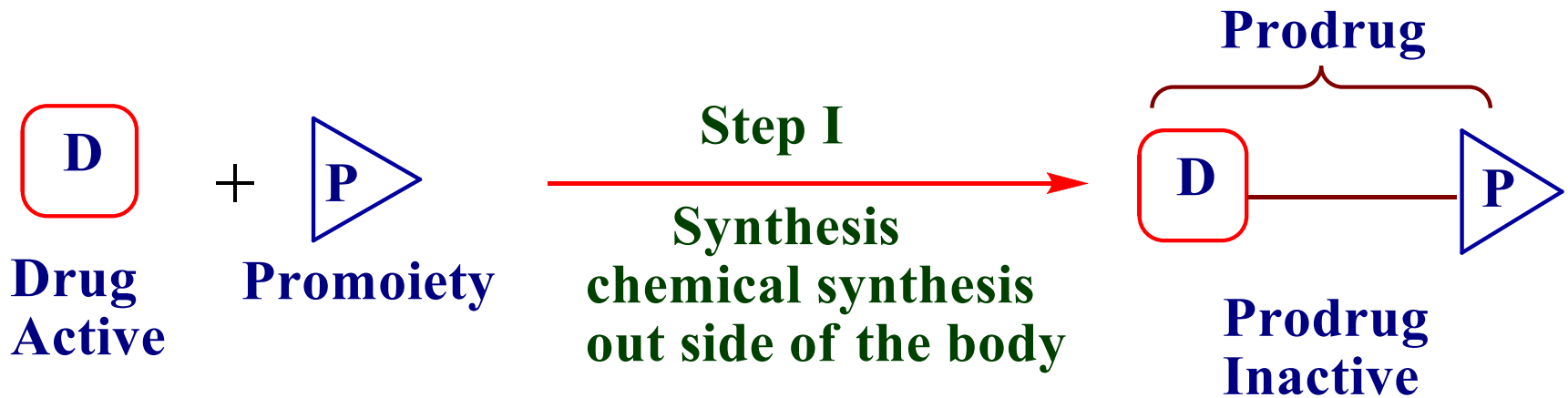
The polymer mainly uses which is either natural or synthetic, the natural polymer such as carbohydrate (Dextran), protein or poly peptide or poly amino acid, while there is limited synthetic polymer use for medical use.

Criteria of promoiety :-

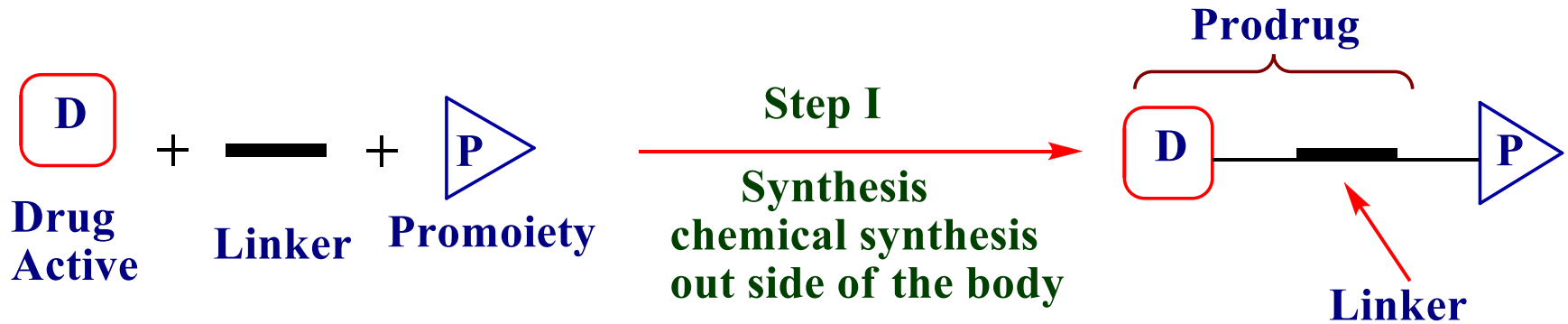
- 1) Should contain functional group that can interact chemically with the drug.**
- 2) Must solve drug problem**
- 3) Must be safe**
- 4) Not toxic**
- 5) Biodegradable**
- 6) Excretable**
- 7) Not accumulate(moderate MW)**

Carrier linked prodrug can be further subdivided into:-

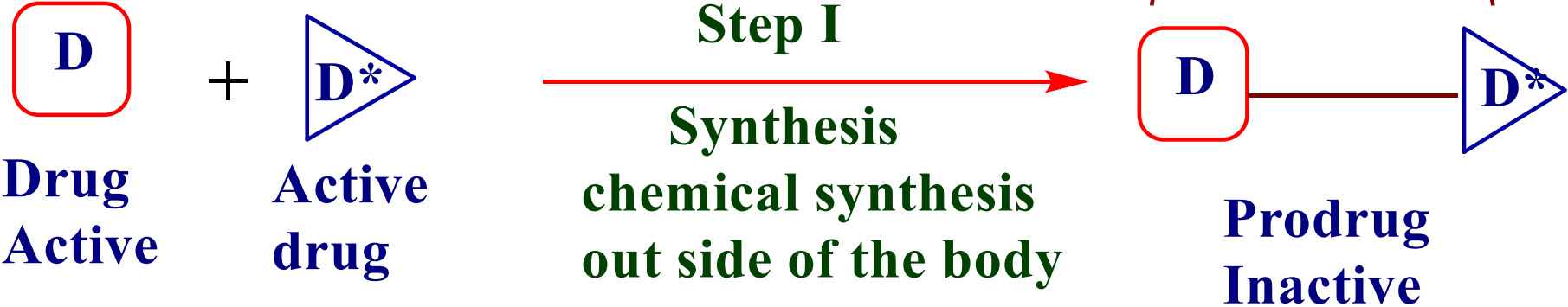
1- Bipartate:- composed of one carrier (group) attached to the drug.



2- Tripartate:- carrier group is attached via linker to drug. •



3- Mutual prodrug:- two drugs linked together. •



Chemical classification of carrier linked prodrug

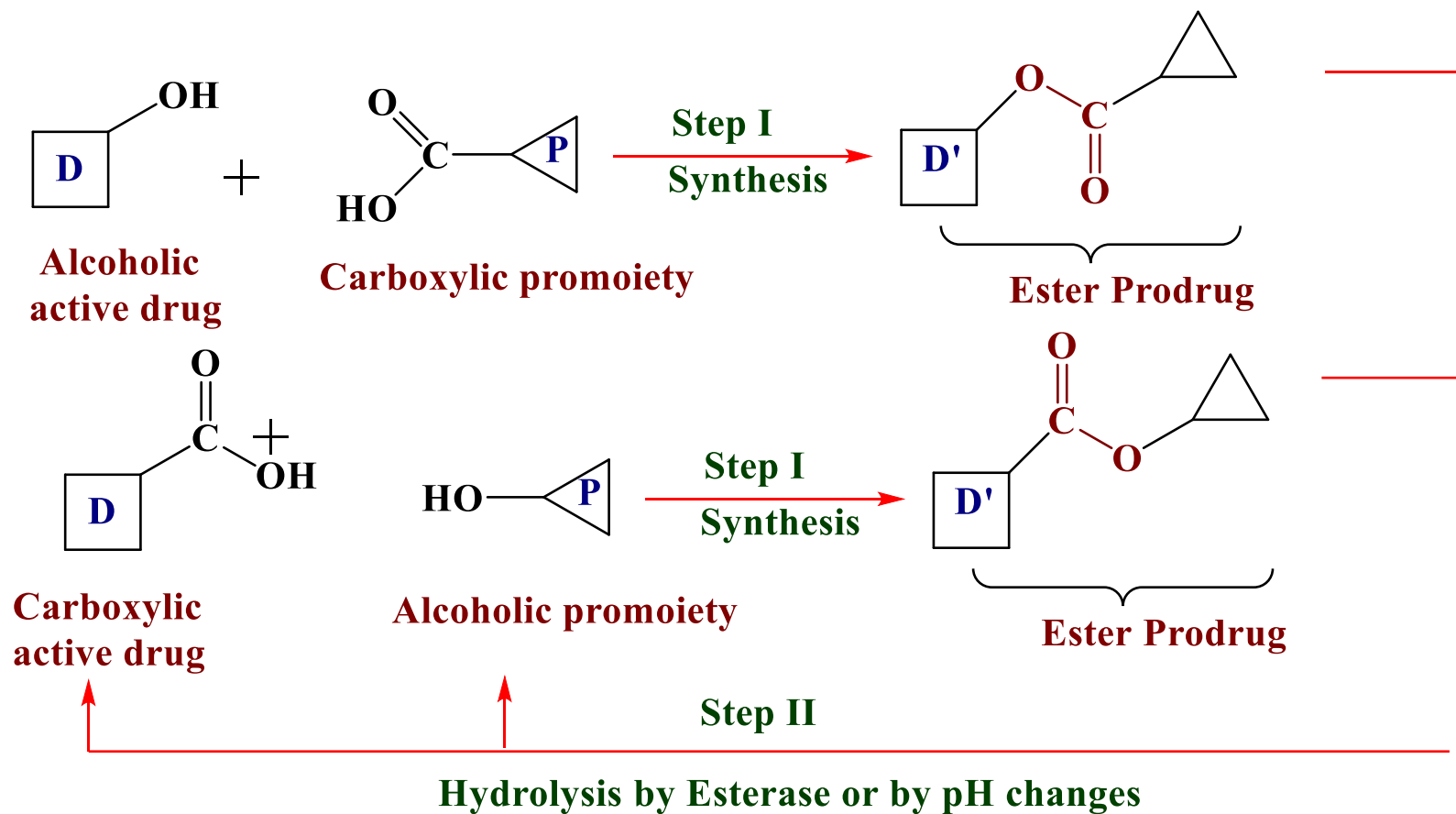
The chemical nature of carrier linked prodrugs that can be prepared depend on the two factors:-

- 1) Chemical nature of the original drug (type of functional group)
- 2) Type of a problem in the original drug to be solved.

The carrier linked prodrugs are classified according to the chemical structure or nature of the prodrug.

Ester pro drug:

If the molecule contains either an alcohol or carboxylic acid functionality an ester prodrug may be easily synthesized.

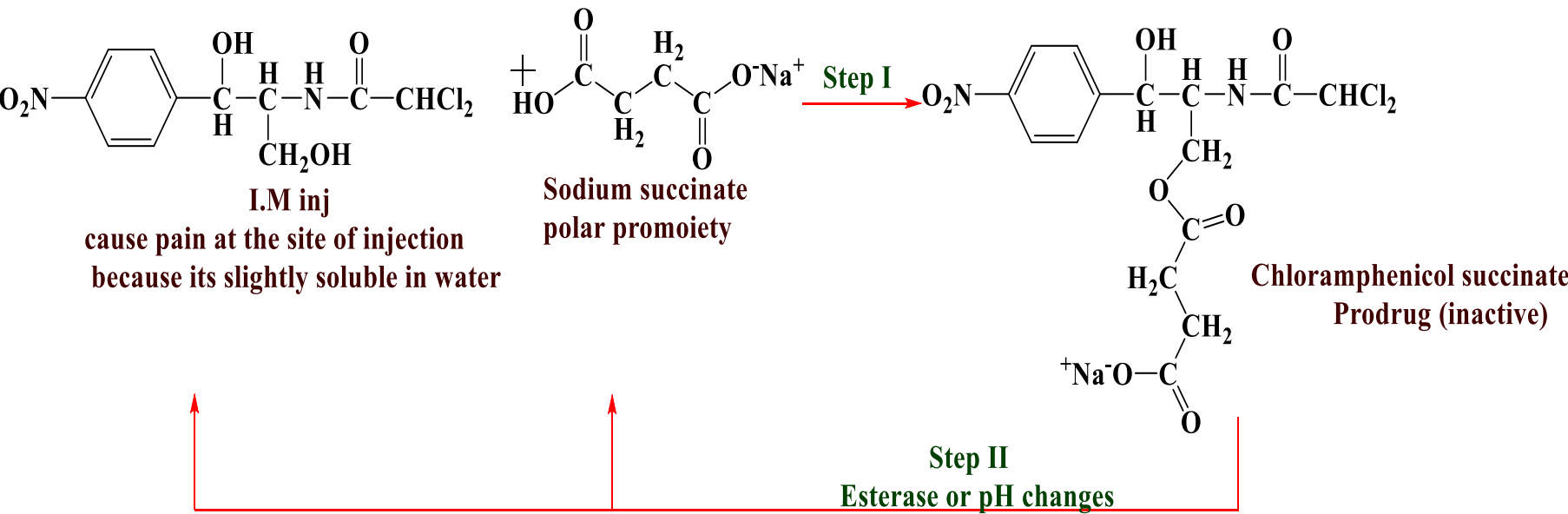


The ester prodrug is the most common type of prodrug because:-

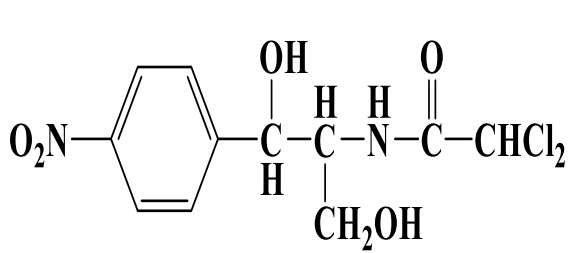
1. The ease of formation the ester prodrug.
2. The ester prodrug can be hydrolyzed easily to give the active drug.
3. Hydrolysis is take place by esterase enzyme.
4. Esterase enzyme present in must tissue that are capable of hydrolyzing a wide variety of ester linkages.
5. Chemical hydrolysis of the ester function may also occur to some extent.

Examples:-

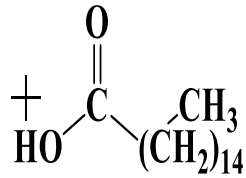
Chloramphenicol(antibiotic)



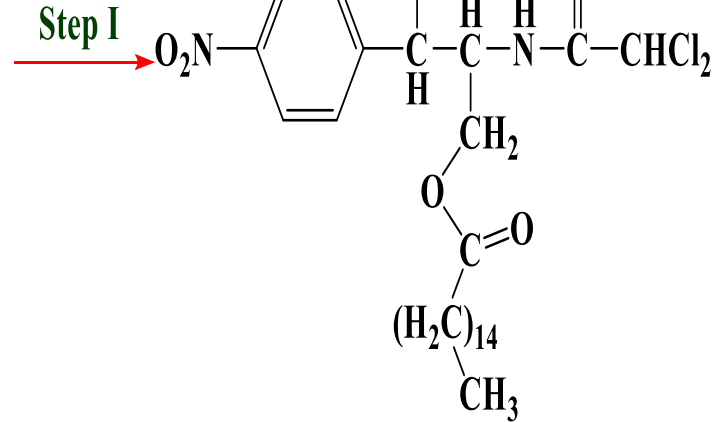
Chloramphenicol when given parentally by IM inj. it is painful ,since it ppt. at site of injection because of its low water solubility, so when polar functional group like succinate was added lead to increase water solubility and reduce pain.



Oral administration
cause bitter taste
because water solubility 2.5mg/ml



Palmitic acid
Non polar moiety



Chloramphenicol palmitate
ester prodrug
water solubility 1.05mg/ml
it can formulated as suspension that
pass over the taste receptor on the tongue

Step II
Esterase or pH changes

