Lec 1 5th stage

Organic Pharmaceutical Chemistry IV

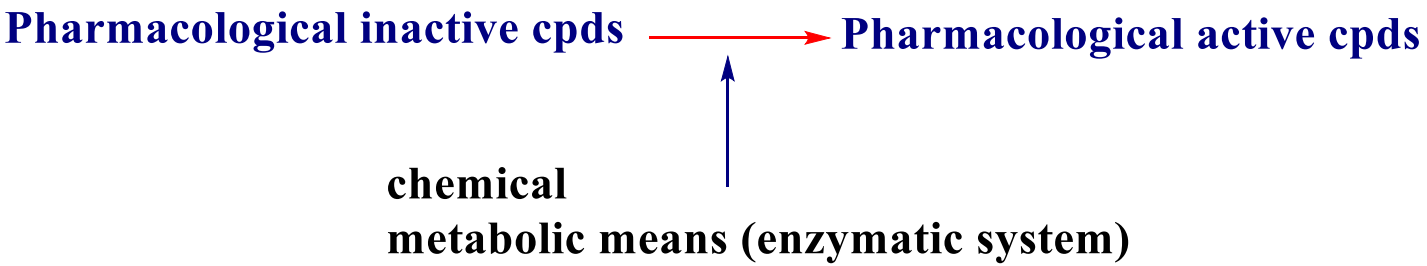
2018-2019

Prodrug and drug latentiation

Prodrug and drug latentiation

The concept of **"prodrug"** was first introduced by Adrian Albert in 1958 to describe compounds that undergo biotransformation prior to eliciting their pharmacological effect.

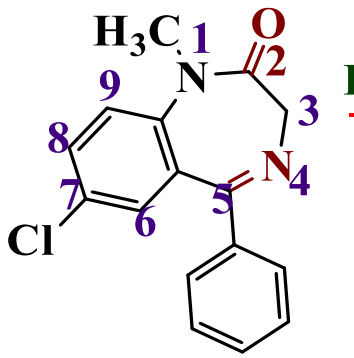
Prodrug:- defined as pharmacologically inactive cpd that is transformed by the mammalian system into an active substance by either chemical or metabolic means (enzymatic system).



However, prodrugs should not be confused with drugs which are intrinsically active, yet are transformed into one or more active metabolites. In this case, two or more active agents will contribute to the observed clinical response in proportions that depend on differences in pharmacological activities.

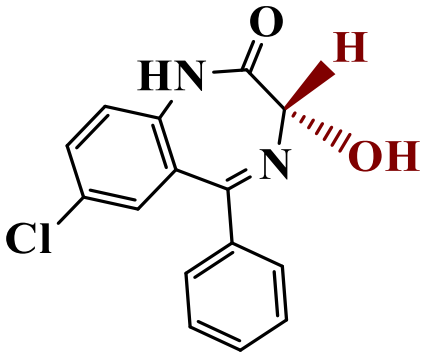
drugs→Pharmacological active cpds —Transformed→ active metabolites (one or more)

Example:-

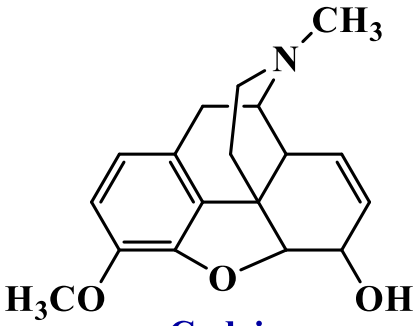


Diazepam (Valium)
Active

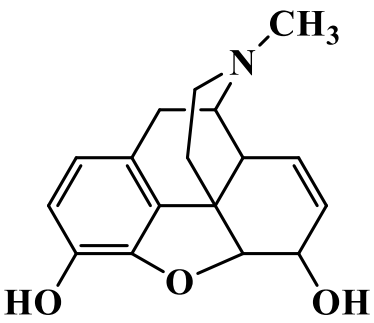
P-450(MFO) → N-demethylation →



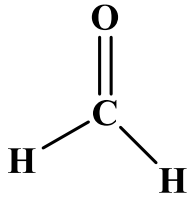
Oxazepam
more active

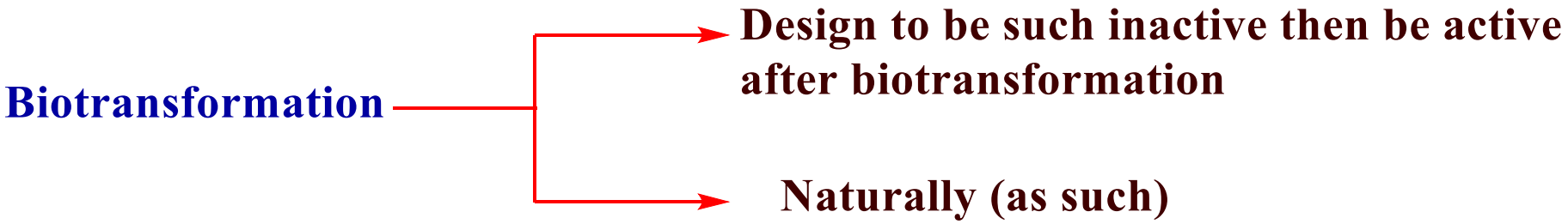


Codeine →



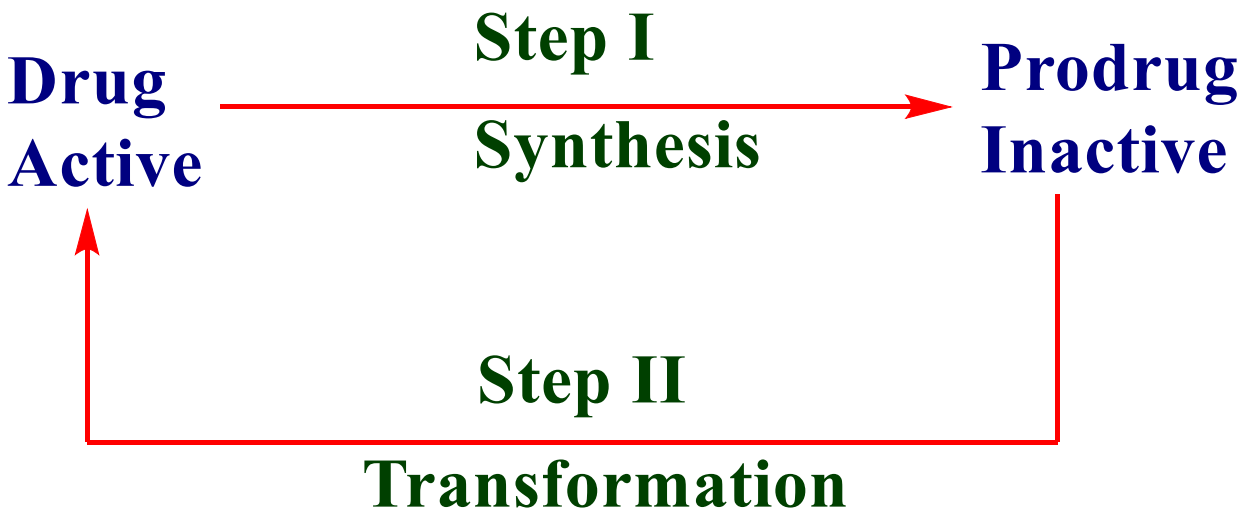
morphine +





These two situations were distinguished by Harper, who in 1959 introduces the term **drug latentiation** (included later).

Drug latentiation(Harper):- The process of purposely designing and synthesizing a molecule that specifically requires bioactivation to a pharmacologically active substance.



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.

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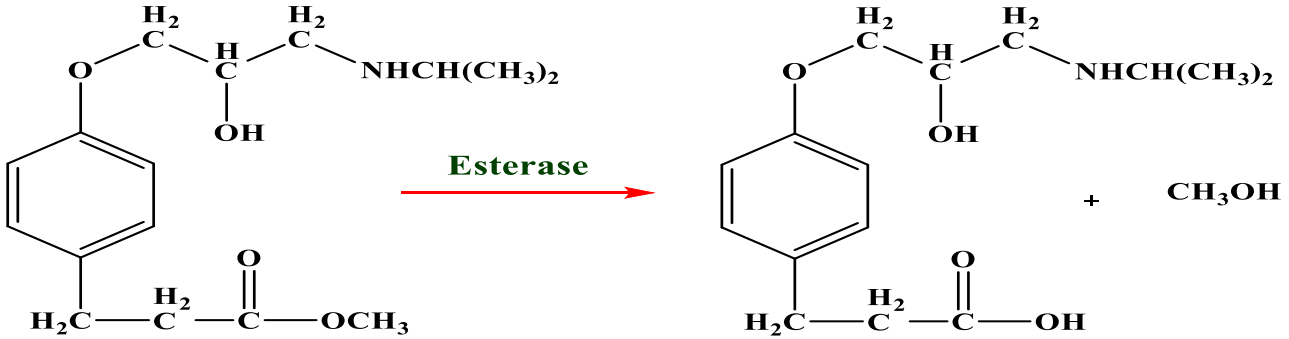
Soft drugs: - “biologically active compounds (drugs) characterized by a predictable and fast
in vivo metabolism to inactive and non-toxic moieties, after they have achieved their therapeutic role”(such as short acting β-blocker agent, esmolol),Thus soft drugs are considered to be the opposite of prodrugs.

Soft drugs: -



Esmolol

Antihypertensive and cardiac arrythemias

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

weak β-blockers and not exhibit clinically

significant effects

administered by continous IV infusion for control ventricular rate

in patient with atrial flutter , atrial fibrillation, or sinus tachycardia

Soft drug
Active

Transformation →

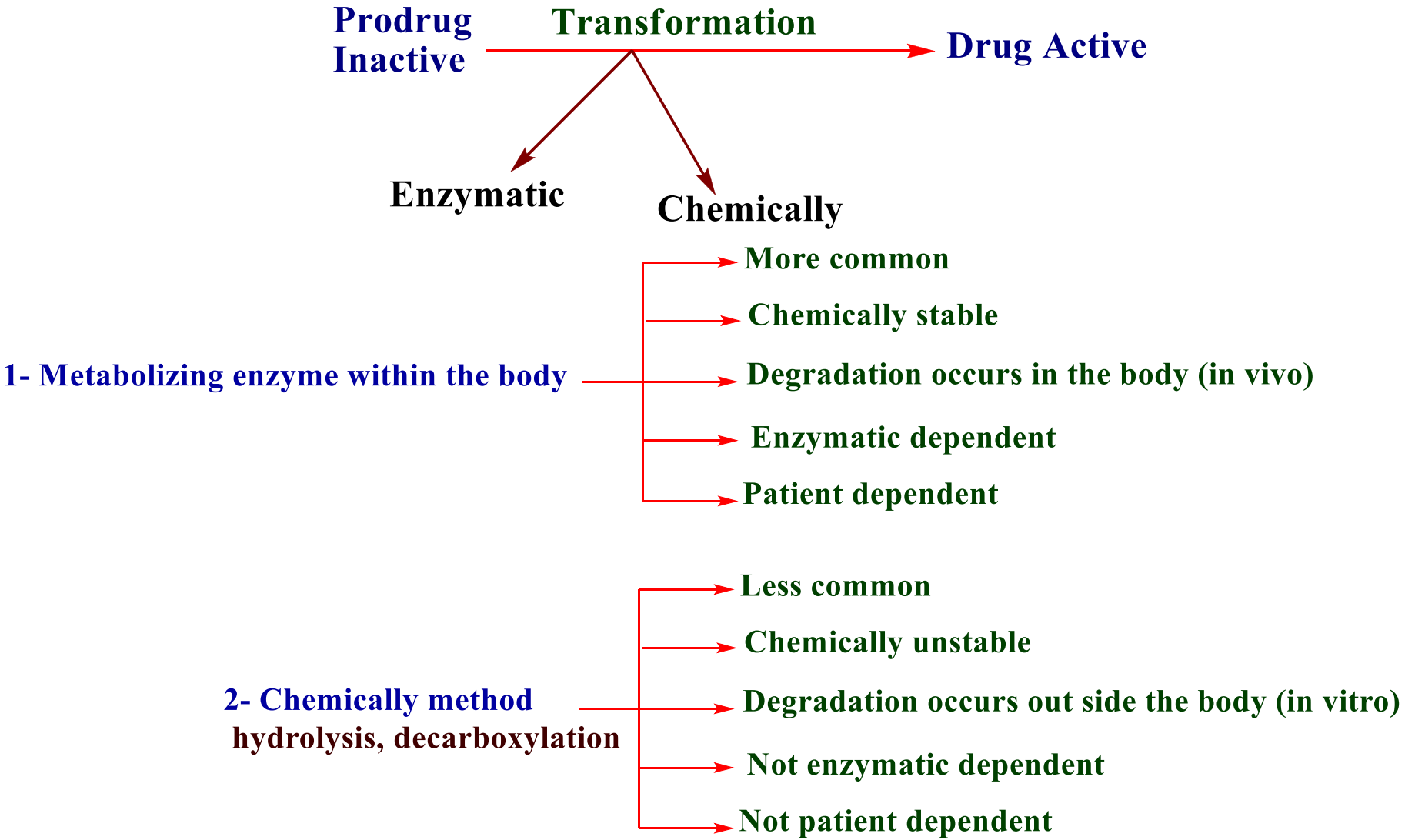
Inactive cpd

Prodrug
Inactive

Transformation →

Drug Active

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



Advantage s 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

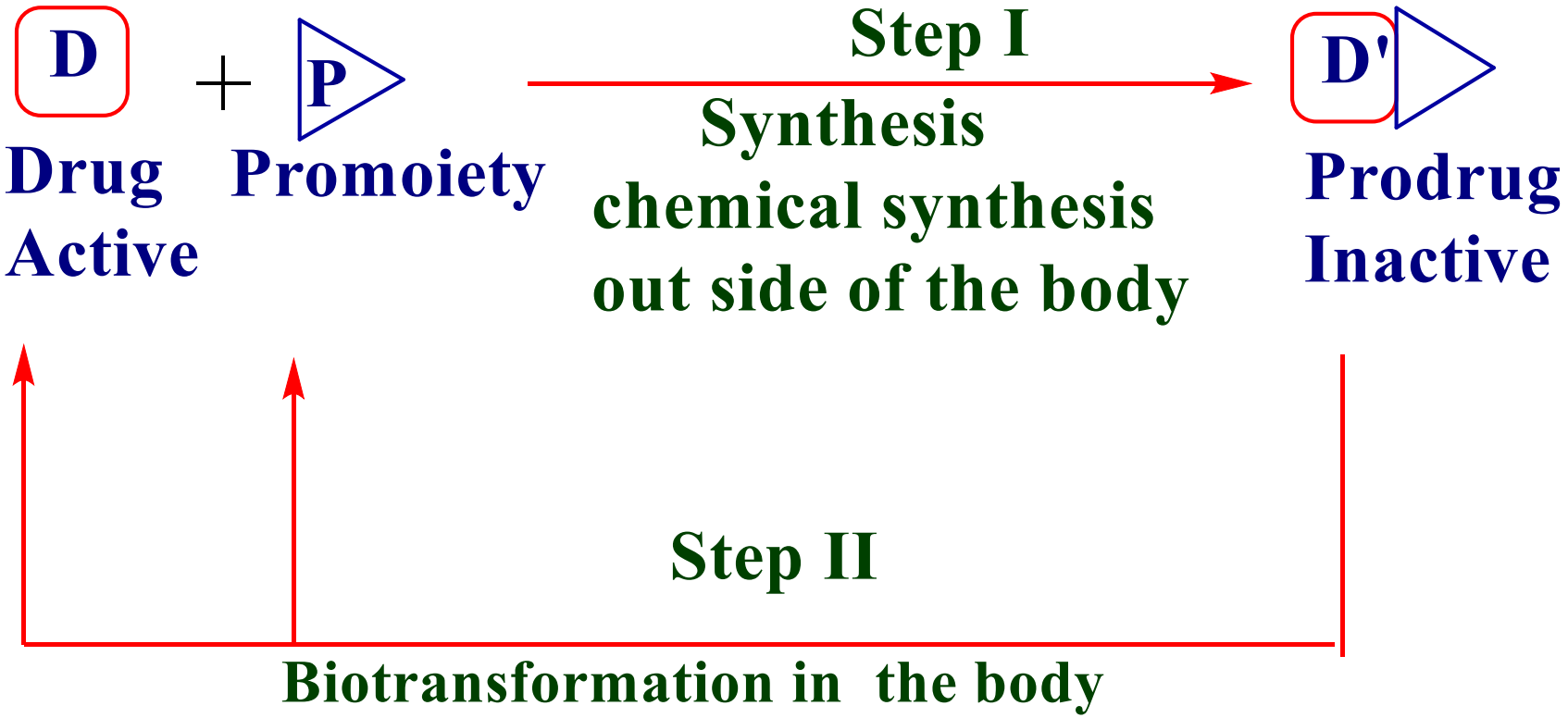
2- Rapid transformation, chemically or enzymatically, into the active form at the target site

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.

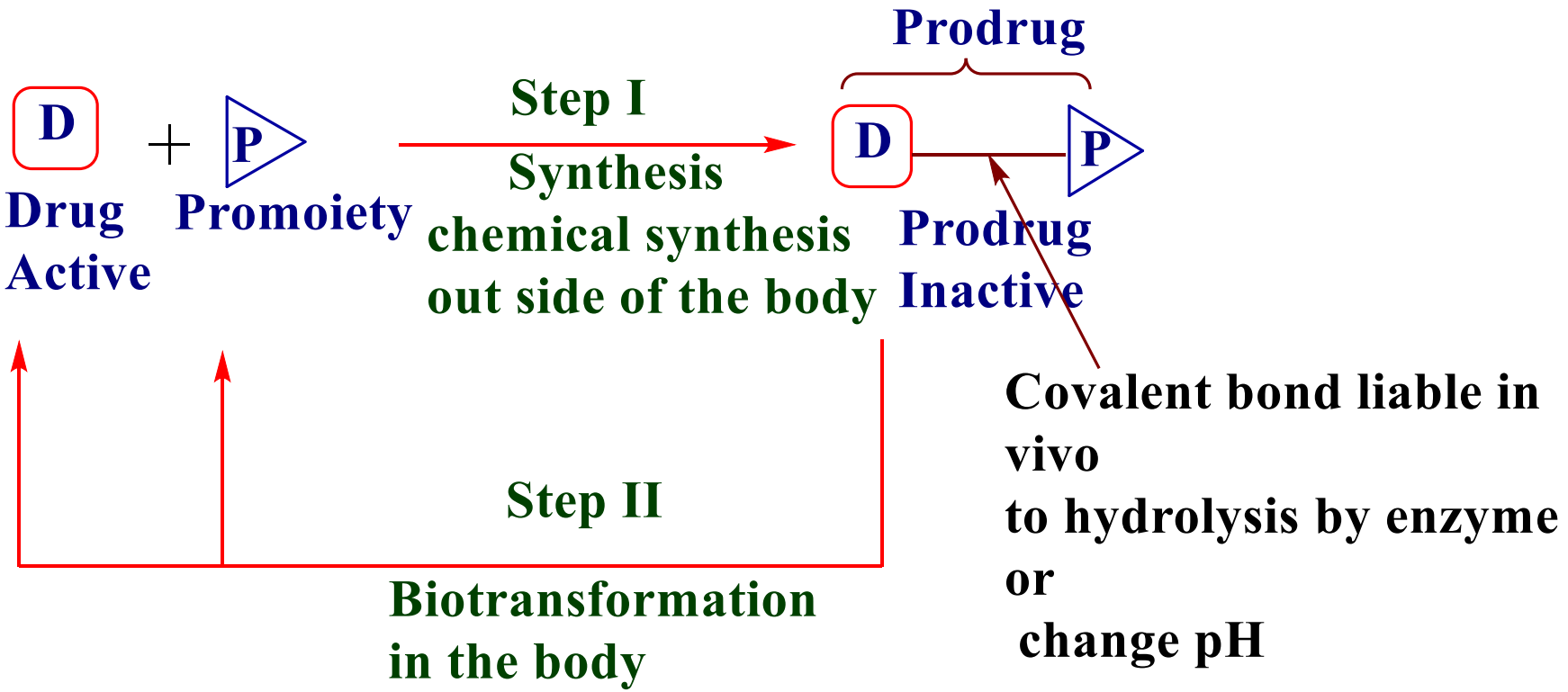


1) **Bioprecursor prodrugs:** which do not contain a promoiety but rather contain a latent functionality that is metabolically or chemically transformed to the active drug molecule.

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.


Prodrug
D
P
Step I
Synthesis
chemical synthesis
out side of the body
Drug
Active
Promoiety
Prodrug
Inactive
Covalent bond liable in vivo
to hydrolysis by enzyme
or
change pH
Step II
Biotransformation
in the body

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.

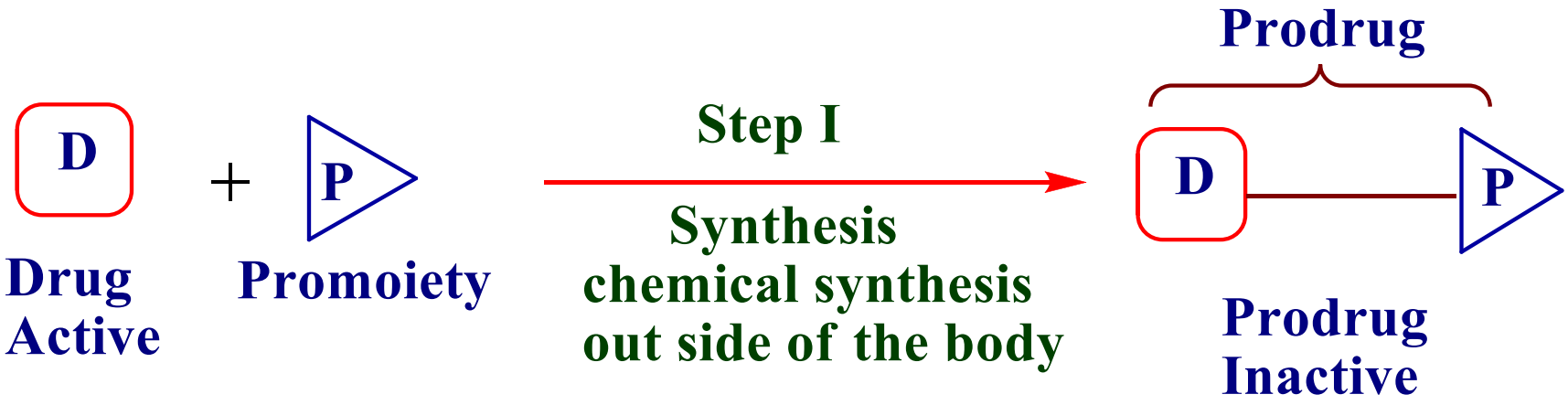
The polymer mainly uses which is either natural or synthetic, the natural polymer such as carbohydrate (Dextran), protein or poly peptide or poly amino acid, while there is limited synthetic polymer use for medical use.

Criteria of promoiety :-

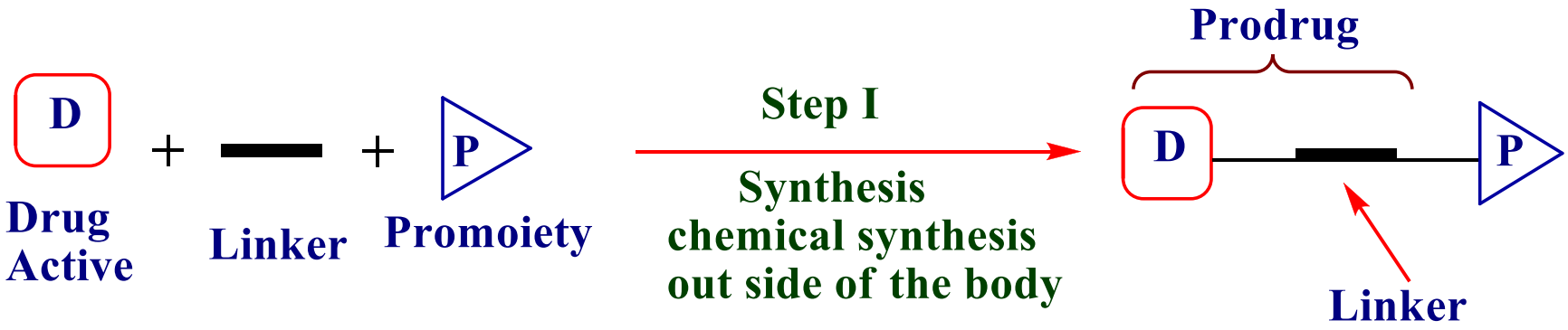
1) Should contain functional group that can interact chemically with the drug.
2) Must solve drug problem
3) Must be safe
4) Not toxic
5) Biodegradable
6) Excretable
7) Not accumulate(moderate MW)

Carrier linked prodrug can be further subdivided into:-

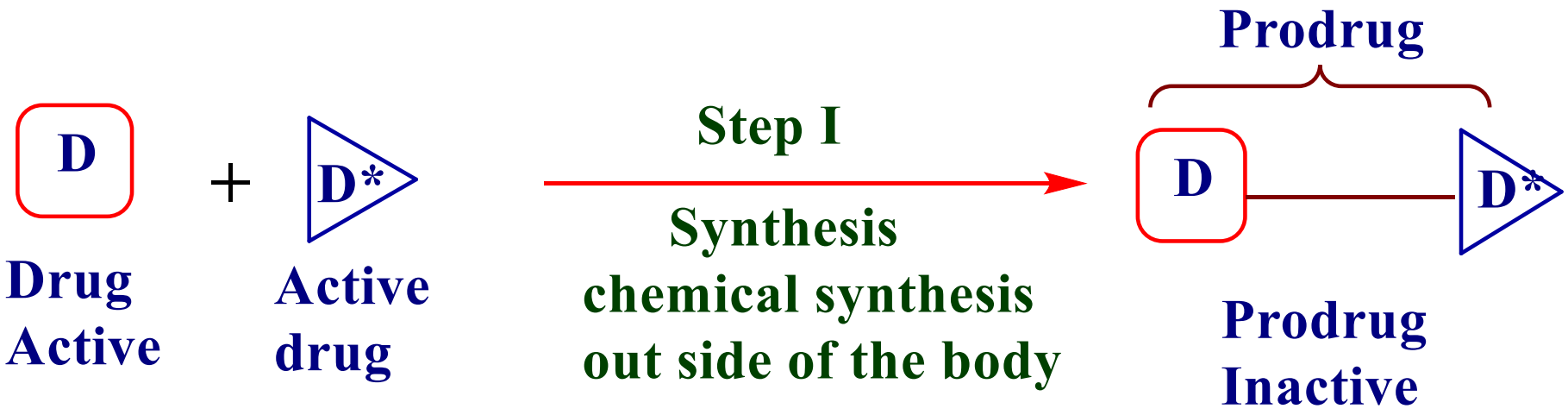
1- Bipartate:- composed of one carrier (group) attached to the drug.



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:-

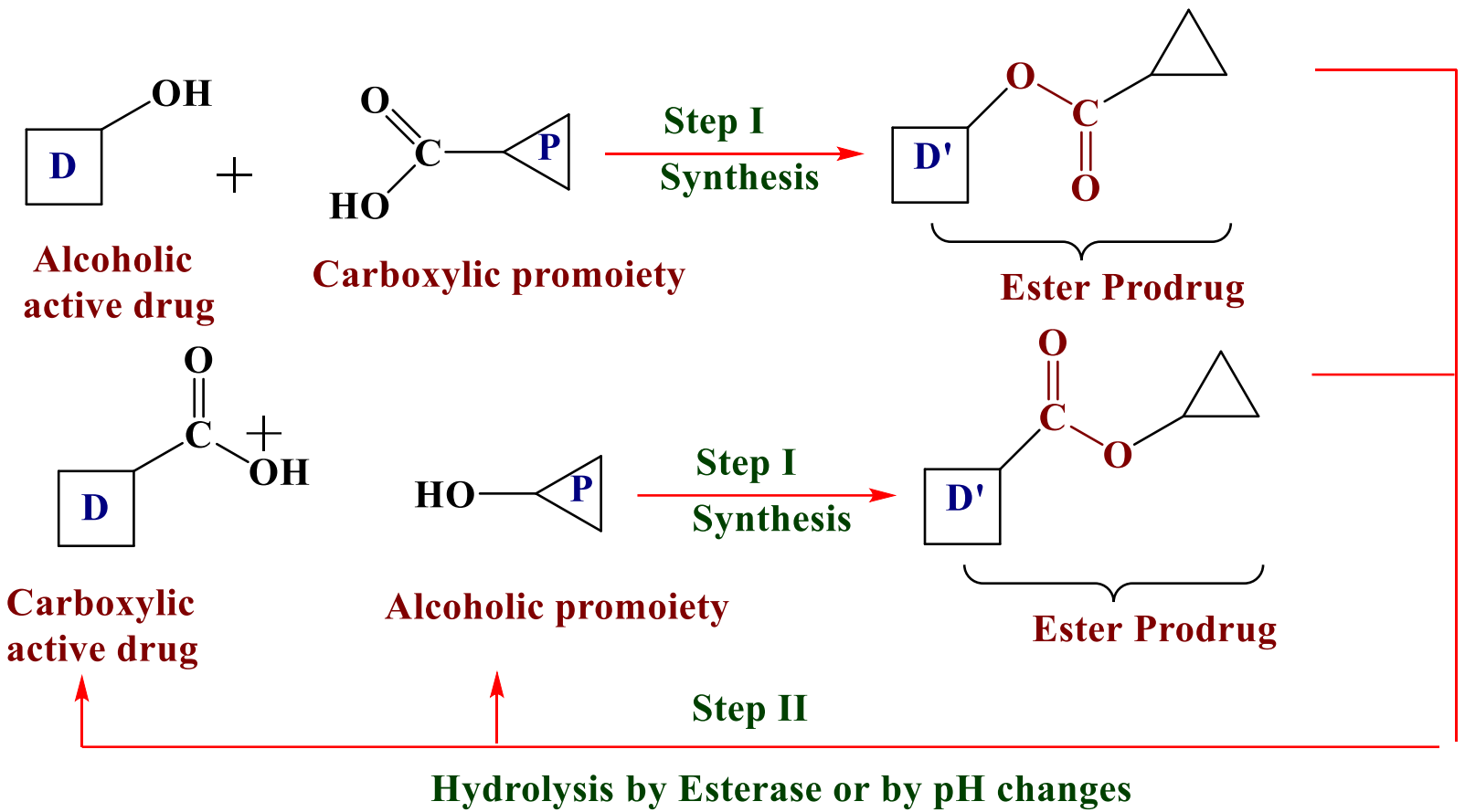
1) Chemical nature of the original drug (type of functional group)

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.

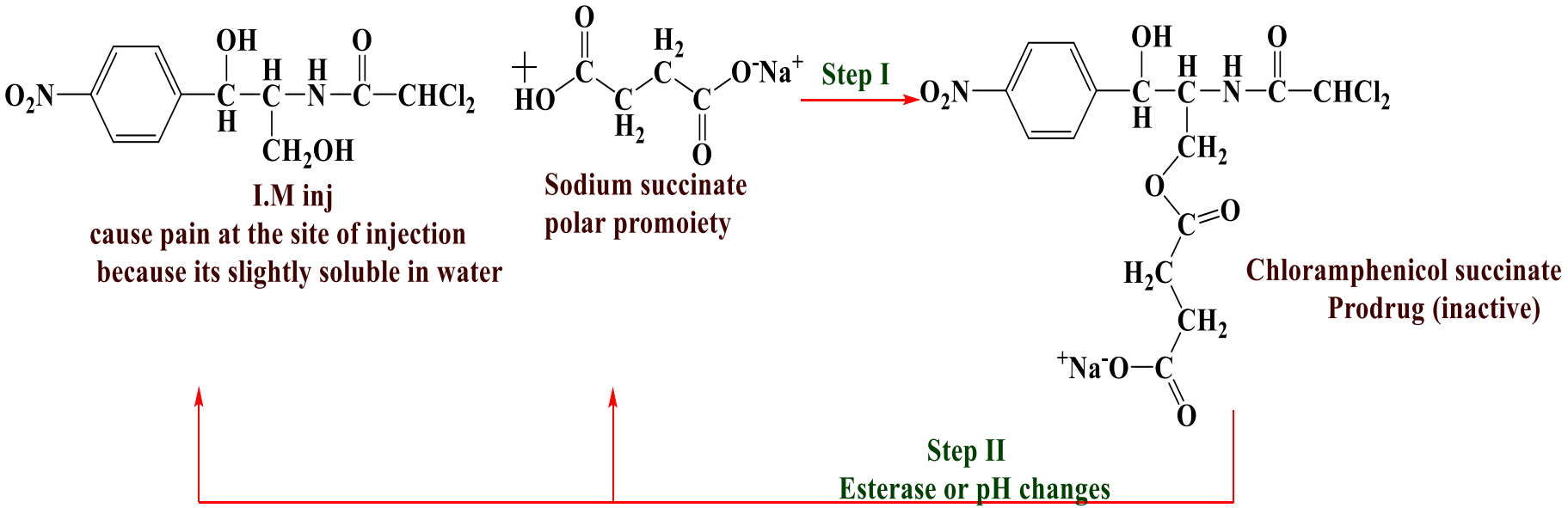


The ester prodrug is the most common type of prodrug because:-

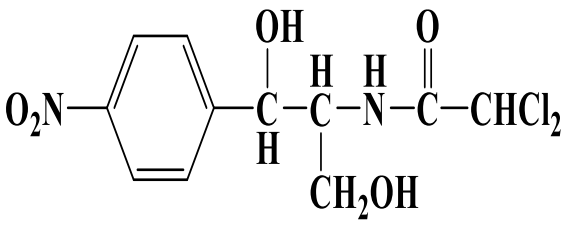
1. The ease of formation the ester prodrug.
2. The ester prodrug can be hydrolyzed easily to give the active drug.
3. Hydrolysis is take place by esterase enzyme.
4. Esterase enzyme present in must tissue that are capable of hydrolyzing a wide variety of ester linkages.
5. Chemical hydrolysis of the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

Examples:-

Chloramphenicol(antibiotic)



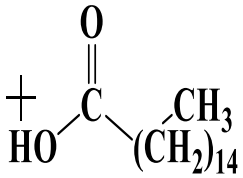
Chloramphenicol when given parentrally by IM inj. it is painful ,since it ppt. at site of injection because of its low water solubility, so when polar functional group like succinate was added lead to increase water solubility and reduce pain.



Oral administration

cause bitter taste

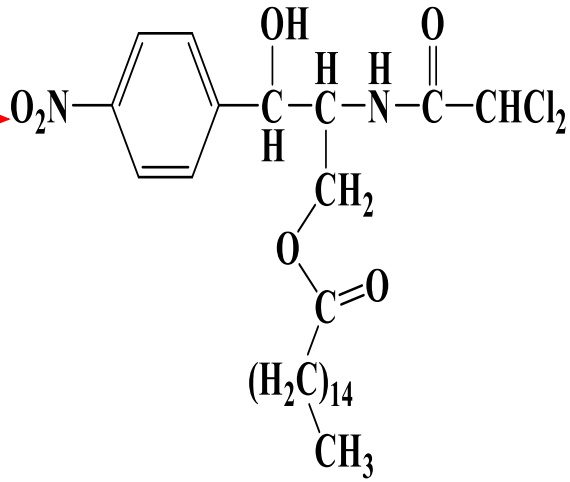
because water solubility 2.5mg/ml



Palmitic acid

Non polar promoiety

Step I



Chloramphenicol palmitate

ester prodrug

water solubilty 1.05mg/ml

it can formulated as suspension that

pass over the taste receptor on the tongue

Step II

Esterase or pH changes