Prodrug

Initial definition: A pharmacologically inactive chemical entity that when metabolized or chemically transformed by a mammalian system is converted into a pharmacologically active substance

• **Drug Latentiation" –** included later Process of purposely designing and synthesizing a molecule that specifically requires "bioactivation" to a pharmacologically active substance.

The term prodrug refers to a pharmacologically inactive compound that is converted to an active drug by a metabolic biotransformation.

The biotransformation or activation of a prodrug may occur prior, during, and after absorption, or at specific target sites within the body.

Prodrug design may be useful in circumventing problems associated with:

• Solubility

• absorption and distribution

• site non specificity

• Instability

• prolonged release

• Toxicity

• poor patient acceptability (unpleasant taste or odour)

• formulation problems.

Classification of Prodrugs

Non Intentional Prodrug:- After administration of the drug the metabolic studies indicate the prodrug nature of drug.

Eg. Sulindac (Active sulphide metabolite)

Carrier-linked prodrugs:

• contain a group that can be easily removed enzymatically (such

as an ester) to reveal the true drug.

• Ideally, the group removed is pharmacologically inactive and

nontoxic while the connecting bond must be labile for efficient activation *in vivo.*

Carrier-linked prodrugs can be further subdivided into:

• **bipartate:** composed of one carrier (group) attached to the drug.

• **tripartate**: carrier group is attached via linker to drug

• **mutual prodrugs:** two drugs linked together

Bioprecursors:

• metabolized into a new compound that may itself be active *or* further metabolized to an active metabolite (e.g. amine to aldehyde to

carboxylic acid).

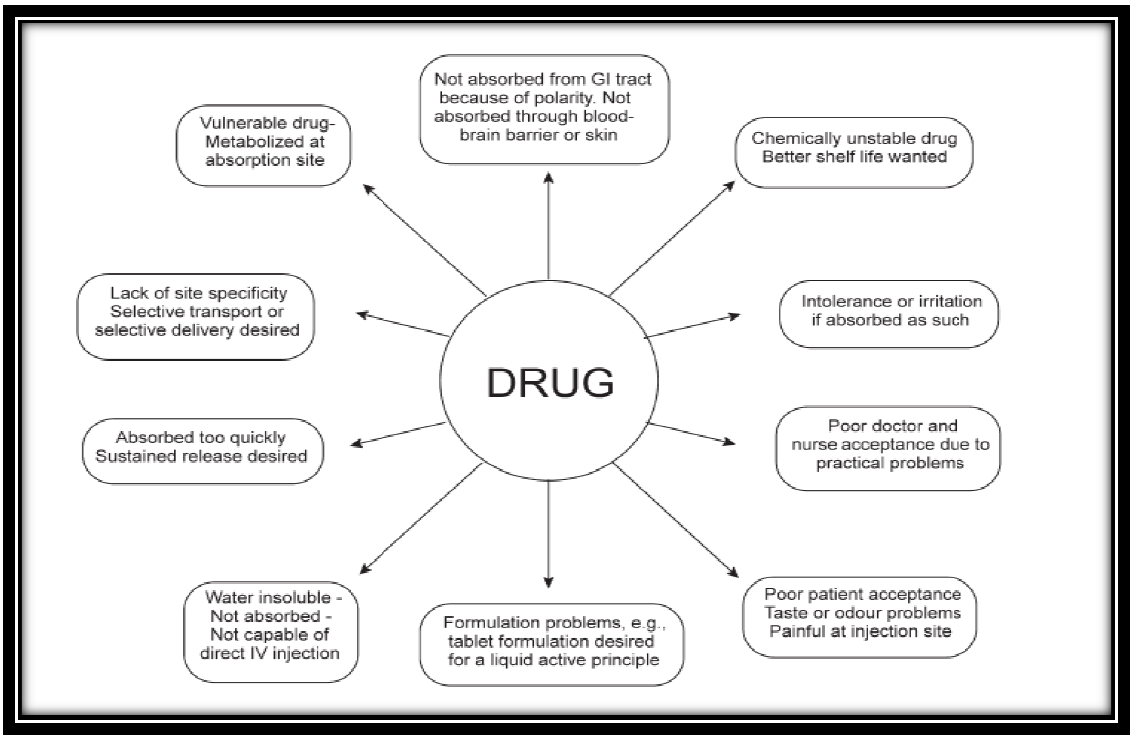

Fig: Circumventing problems associated with parent drug

1. Carrier Linked Prodrug

The carrier-prodrug principle consists of 'the attachment of a carrier group to the active drug to alter its physicochemical properties and then the subsequent enzyme attack to release the active drug moiety.

A well-designed carrier-prodrug satisfies the following criteria:

(1) The linkage between the drug substance and the transport moiety is usually a covalent bond.

(2) As a rule the prodrug is inactive or less active than the parent compound.

(3) The linkage between the parent compound and the transport moiety must be broken in vivo.

(4) The prodrug, as well as the in vivo released transport moiety, must be nontoxic.

(5) The generation of the active form must take place with rapid kinetics to ensure effective drug levels at the site of action and to minimize either direct prodrug metabolization or gradual drug inactivation.

• What types of groups are the easiest to link to a carrier?

• What types of groups are the easiest to cleave from a carrier?

Alcohols -Containing Drugs (Linked as Esters)

• esters are readily synthesized from an alcohol-containing

parent drug and a carboxylic acid (or acid halide or anhydride)

• Esters are easily hydrolyzed by various and ubiquitous

esterases.

• Great range of hydrophobicity, hydrophilicity, and stabilities available through the carrier group (carboxylic acid).

• As a result, it is relatively easy to alter the water solubility and consequently, absorption and distribution may also be effected as desired. Sulfates and phosphates are also included in this category and can be cleaved by sulfatases and phosphatases, respectively.

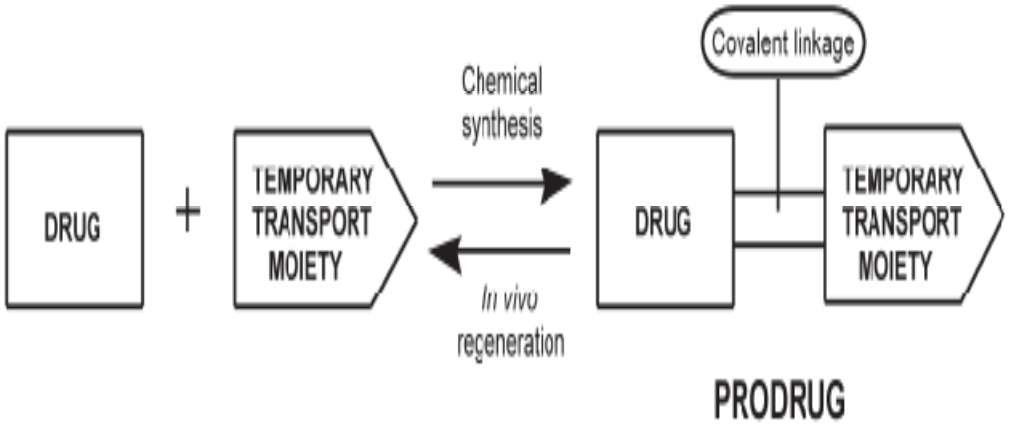

Fig: Principle of carrier-prodrug

Carrier linked prodrug

Improvement of the bioavailability and the biomembrane passage

The biomembrane passage of a drug depends primarily on its physicochemical properties and especially on its partition coefficient. Thus the transient attachment of a lipophilic carrier group to an active principle can provide better bioavailability, mostly by facilitating cell-membrane crossing by passive diffusion.

Derivatization of drugs containing alcoholic or phenolic hydroxy groups.

Starting from hydroxylic derivatives, high lipophilicity can simply be obtained by esterification with lipophilic carboxylic acids. Dipivaloyl-epinephrine for examplecrosses the cornea and is used in the treatment of glaucoma. Esterification of hydroxylic functions with poly-acids (e.g. succinic acid, phosphoric acid) represents an excellent way to prepare water-soluble prodrugs.

Esters are readily synthesized from an alcohol-containing parent dr ug and a carboxylic acid (or acid halide or anhydride)

- Esters are easily hydrolyzed by various and ubiquitous esterases.
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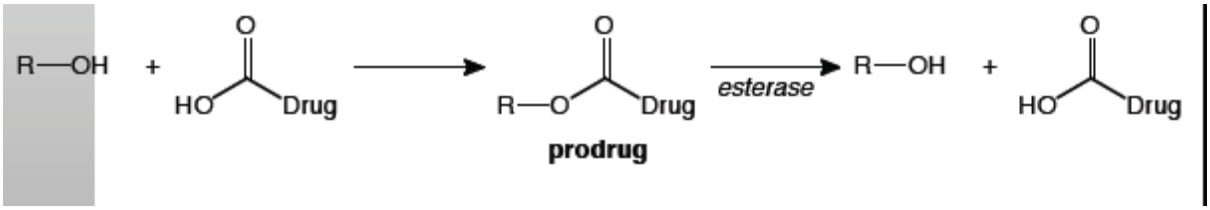


Derivatization of drugs containing a carboxylic acid function

Lipophilic prodrugs can also be derived from a carboxylic function, the most commonly used derivatives being carboxylic esters. Simple esters of aliphatic alcohols are attractive as they are cheap to prepare, chemically stable, and yield harmless hydrolysis products. Typical representatives of such prodrugs are tyrosine methyl ester, levodopa ethyl ester etc.

Ester are readily synthesized from carboxylic acids-containing parent drug and an alcohol-containing carrier.

Esters are easily hydrolyzed by various and ubiquitous esterases.

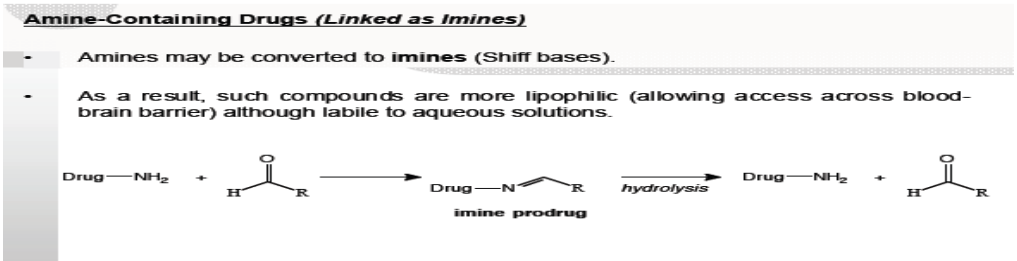
Large library of alcohols allow great variety of properties to the prodrug (e.g., pKa and water solubility).

- slow rate desired: long-chain aliphatic or sterically hindered alcohols
- faster rate desired: EWG on the alcohol
- increased pKa or solubility: choline-type or amino esters.

Derivatization of amines

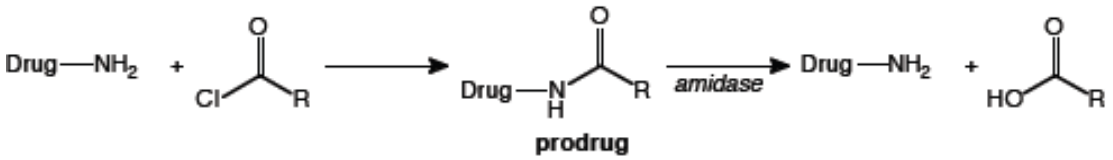
Owing to the slow in vivo cleavage rate of the N-substituted amides, acylation of amines is generally not recommended. Better possibilities are offered by activated amides, peptides, imines and soft quaternary ammonium salts.

However, the use of simple N-acyl derivatives must not systematically be discarded. The N-benzoyl- or N-pivaloyl derivatives of the inhibitory neurotransmitter GABA are examples of compounds able to penetrate the blood–brain barrier.



Amine-Containing Drugs *(Linked as Amides)*

Amides are **readily synthesized** from an amine-containing parent drug and a carboxylic acid *(or acid halide or anhydride)*



prodrug

Simple **amides** are more stable than esters toward hydrolysis. However, **activated amides** or **amides of amino acids** are more susceptible to enzyme-mediated cleavage.

Derivatization of drugs containing a carbonyl function: aldehydes and ketones.

Carbonyl Compounds *(Linked as Hydrolyzable Derivatives)*

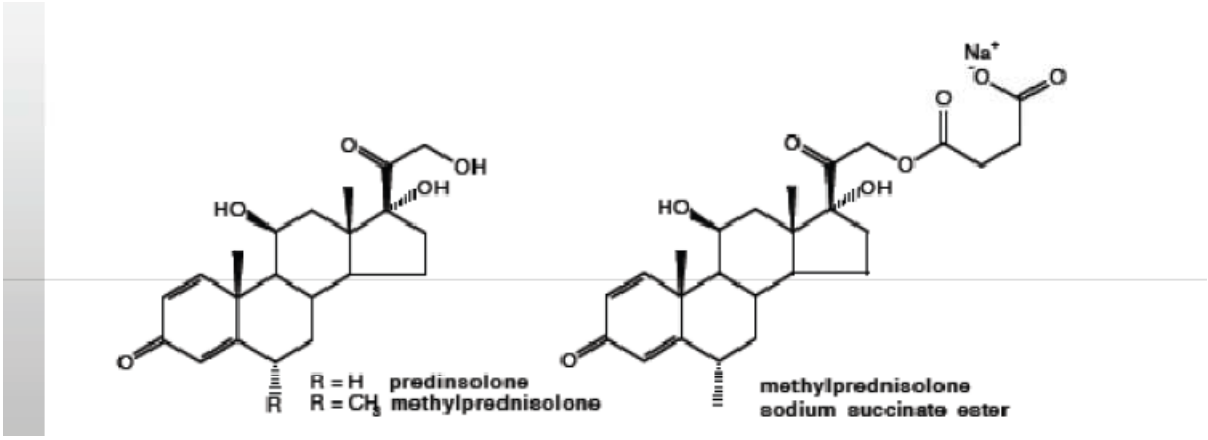
- The most common prodrugs of aldehydes and ketones are course **imines**, **oximes**, **acetals** (ketals), **enol esters**, **oxazolidines** and **thiazolidines**.

Table 8.3 Prodrug Analogs of Carbonyl Compounds

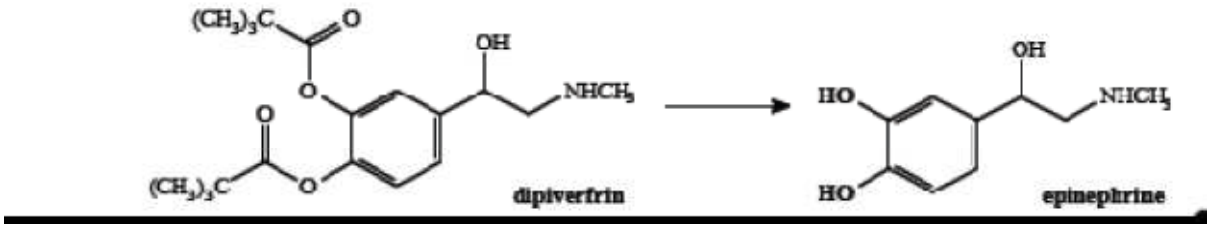
Examples of carrier linked prodrug

1. Prodrugs for Improved Absorption and Distribution

• Fluocinolone aceteonide and flucinonide are corticosteroid prodrugs that allow dermal absorption by "masking" the hydroxyl groups (that can interact with the skin or binding sites in the keratin) as either esters or acetonides. Once absorbed through the skin, the true drug is revealed by esterases or hydrolysis.



Dipivefrin is a prodrug for the antiglaucoma drug epinephrine. The dipivaloyl esters allow for greater corneal permeability which are hydrolyzed by corneal and aqueous humor esterases.

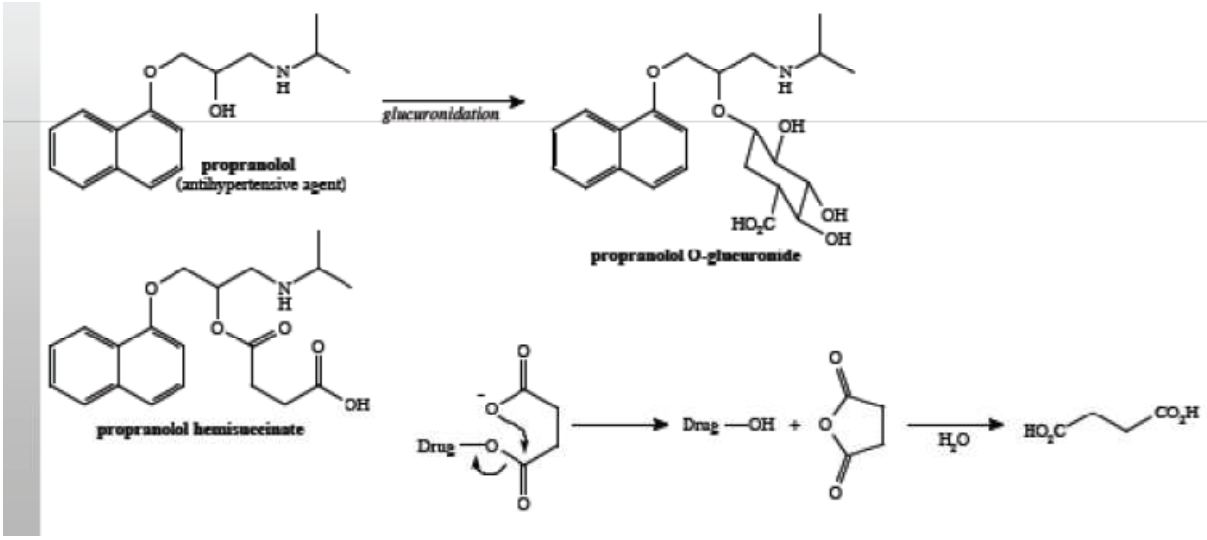


2. Prodrugs for Stability

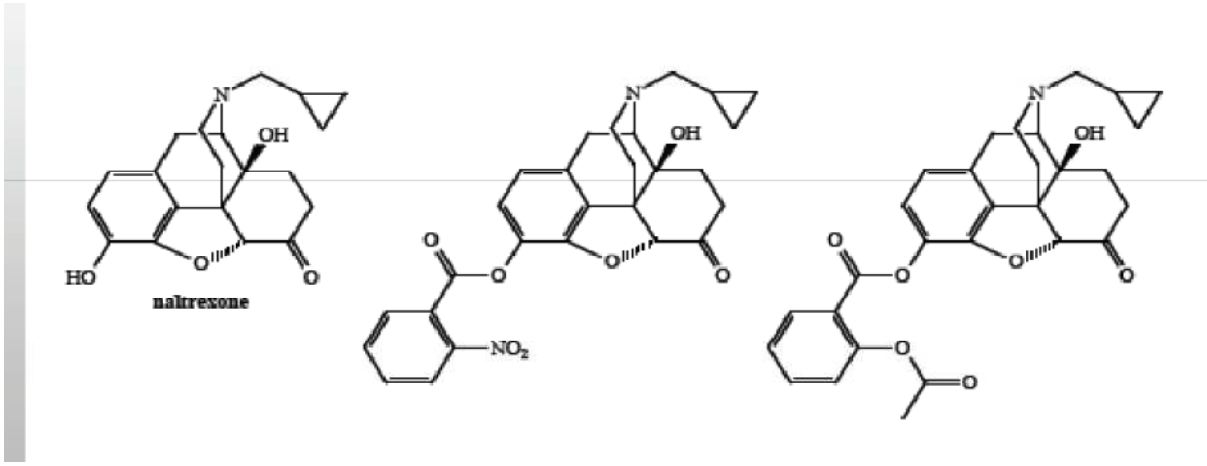
Prodrugs

- Prodrugs may protect a drug from 1st-pass effects.

  - Propranolol (antihypertensive drug) suffers from first-pass elimination resulting in decreased bioavailability of oral doses compared to i.v. injections. One of the major metabolites is the O-glucuronide. The hemisuccinate ester was designed to block glucuronide formation resulting in an 8-fold increase of plasma levels of propranolol.

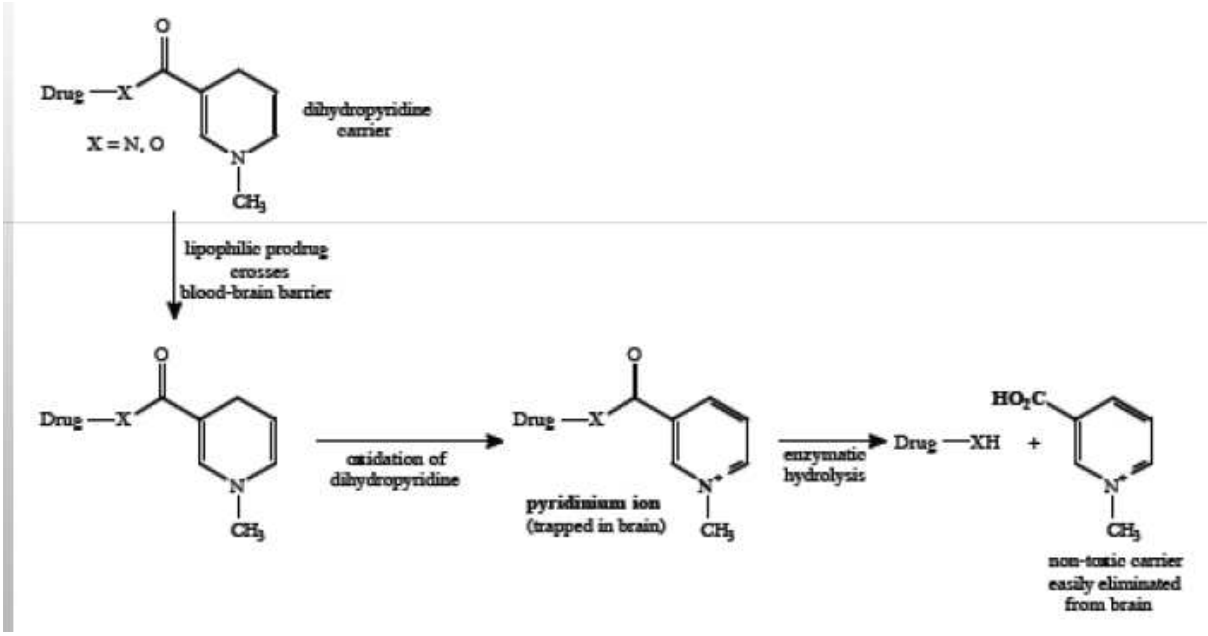


- **Naltrexone (treatment for opioid addiction)** is nonaddicting and is readily absorbed from the G.I. tract and as a result undergoes extensive first-pass metabolism. Ester prodrugs such as the anthranilate (o-nitrobenzoate) and the acetylsalicylate increased bioavailability 45- and 28-fold, respectively.

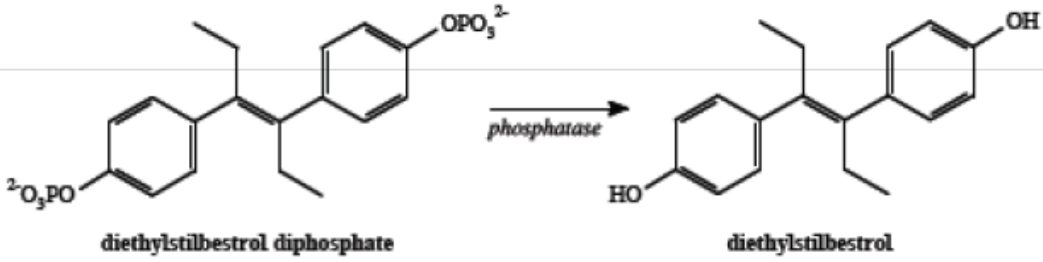


3. Prodrug for site specific drug delivery

- Bodor & coworkers developed a reversible redox drug delivery system for getting drugs into the CNS.



- Exploitation of enzymes found predominantly at the target site of action. For example, tumor cells posses higher concentrations of phosphatases and amidases than normal cells. Diethylstilbestrol diphosphate was designed for such site- specific delivery of deithylstilbestrol in the treatment of breast cancer.



Bioprecursor prodrugs

Bioprecursor prodrugs result from a molecular modification of the active principle generating a new compound, able to be a substrate for the metabolizing enzymes, the metabolite being the expected active principle. The bioprecursor-prodrug approach exemplifies the active metabolite concept in the prospective application.