PRODRUGS

Navneet F. Chauhan, Ph.D

Associate Professor,

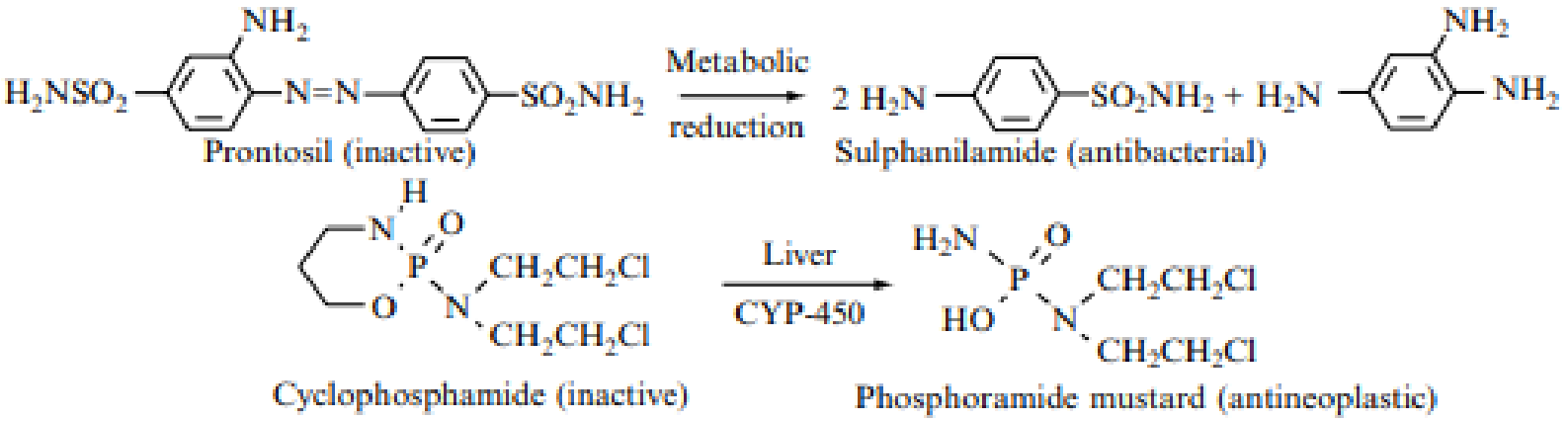
Saraswati Institute of Pharmaceutical Sciences, Gandhinagar

Definition

- Prodrugs are compounds that are biologically inactive but are metabolized to an active metabolite, which is responsible for the drug's action.
- They are classified as either bioprecursor or carrier prodrugs.
- Prodrugs may be designed to improve absorption, improve patient acceptance, reduce toxicity and also for the slow release of drugs in the body. A number of prodrugs have also been designed to be site specific.

Bioprecursor prodrugs

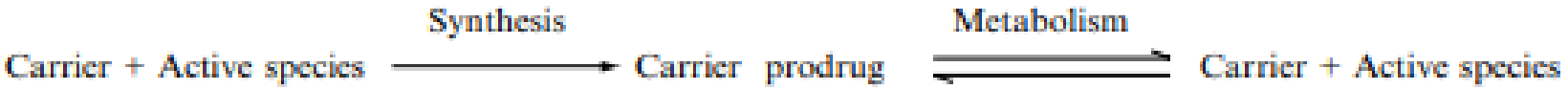
- Bioprecursor prodrugs are compounds that already contain the embryo of the active species within their structure. This active species is liberated by metabolism of the prodrug.



Examples of bioprecursor prodrugs

Carrier prodrugs

- Carrier prodrugs are formed by combining an active drug with a carrier species to form a compound with the desired chemical and biological characteristics.
- For example, a lipophilic moiety to improve transport through membranes. The link between carrier and active species must be a group, such as an ester or amide, that can be easily metabolized once absorption has occurred or the drug has been delivered to the required body compartment. The overall process may be summarized by:



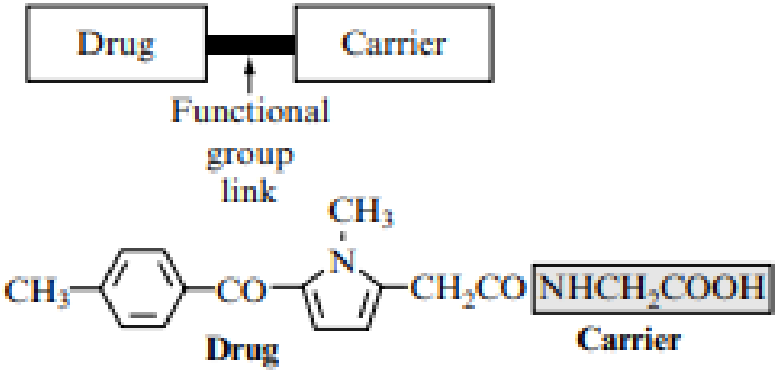
Carrier prodrugs that consist of the drug linked by a functional group to the carrier are known as bipartate prodrug.

Tripartate prodrugs are those in which the carrier is linked to the drug by a link consisting of a separate structure.

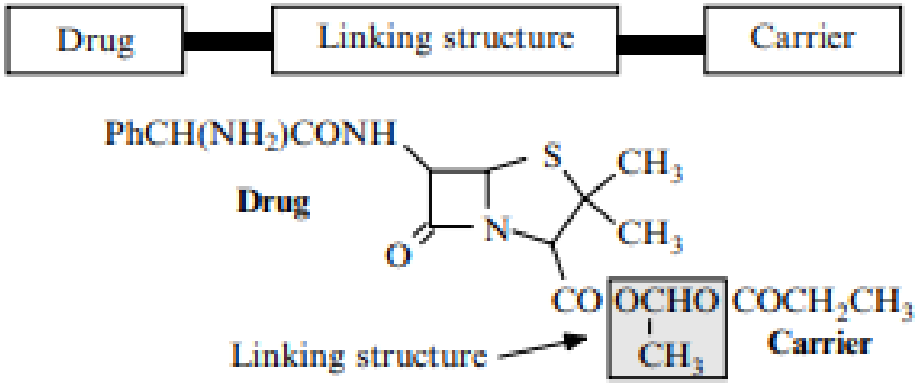
Examples of the functional groups used to link carriers with drugs

Drug group (D–X)	Type of group linking carrier to the drug	Examples of R groups
Alcohol, phenol (D–OH)	Ester: D–OCOR	Alkyl, Phenyl, $-(CH_2)_2NR_2$, $-(CH_2)_n$ CONR′R″, $-(CH_2)_nNHCOR$, $-CH_2OCOR'$.
Amines (all types), imides and amides (>NH)	Amide: >NCOR	Alkyl, Phenyl, $-CH_2NHCOAr$, $-CH_2OCOR''$.
	Carbamate: >NCOR	$-OCHR'OCOR''$, $-OCH_2OPO_2H_3$.
	Imine: >N = CHR	Aryl.
Aldehydes and ketones (>C = O)	Acetals: $>C(OR)_2$	Alkyl,
	Imine: >C = NR	Aryl, – OR.
Carboxylic acids (D–COOH)	Ester: D–COOR	Alkyl, Aryl, $-(CH_2)_nNR'R''$, $-(CH_2)_nCONR'R''$, $-(CH_2)_nNHCOR'R''$, $-CH(R)OCOR$, $-CH(R)OCONR'R''$.

The design of prodrug systems for specific purposes



(a) Tolmetin-glycine prodrug



(b) Bacampicillin, a prodrug for ampicillin

Examples of (a) bipartate and (b) tripartate prodrug systems

1. Improving absorption and transport through membranes

The transport of a drug through a membrane depends largely on its relative solubilities in water and lipids.

Good absorption requires that a drug's hydrophilic–lipophilic nature is in balance. The lipophilic nature of a drug may be improved by combining a lipophilic carrier with a polar group(s) on the drug.

However, it is difficult to select a lipophilic carrier that will provide the degree of lipophilic character required. If the carrier is too lipophilic, the prodrug will tend to remain in the membrane. Similarly, improving the water solubility of a drug may be carried out by introducing a carrier with a water solubilizing group or groups.

Examples of the reactions used to improve the lipophilic nature of drugs

Functional group	Derivative
Acids	an appropriate ester
Alcohols and phenols	an appropriate ester
Aldehydes	acetal
Ketones	acetal (ketal)
Amines	quaternary ammonium derivatives, amino acid peptides and imines

2. Improving Patient Acceptance

Odour and taste are important aspects of drug administration. A drug with a poor odour or too bitter a taste will be rejected by patients, especially children.

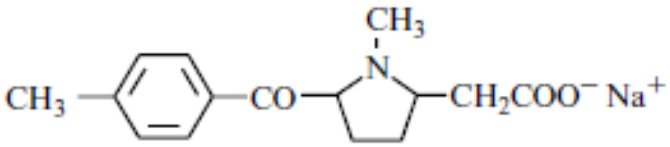
Furthermore, a drug that causes pain when administered by injection can have a detrimental effect on a patient.

The formation of a carrier prodrug can sometimes alleviate some of these problems. For example, palmitic acid and other long chain fatty acids are often used as carriers, since they usually form prodrugs with a bland taste.

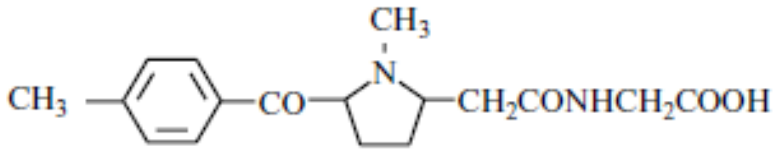
3. Slow release

Prodrugs may be used to prolong the duration of action by providing a slow release mechanism for the drug. Slow release and subsequent extension of action is often provided by the slow hydrolysis of amide and ester linked fatty acid carriers.

Hydrolysis of these groups can release the drug over a period of time that can vary from several hours to weeks. For example, the use of glycine as a carrier for the anti-inflammatory tolmetin sodium results in the duration of its peak concentration being increased from about one to nine hours.



Tolmetin sodium

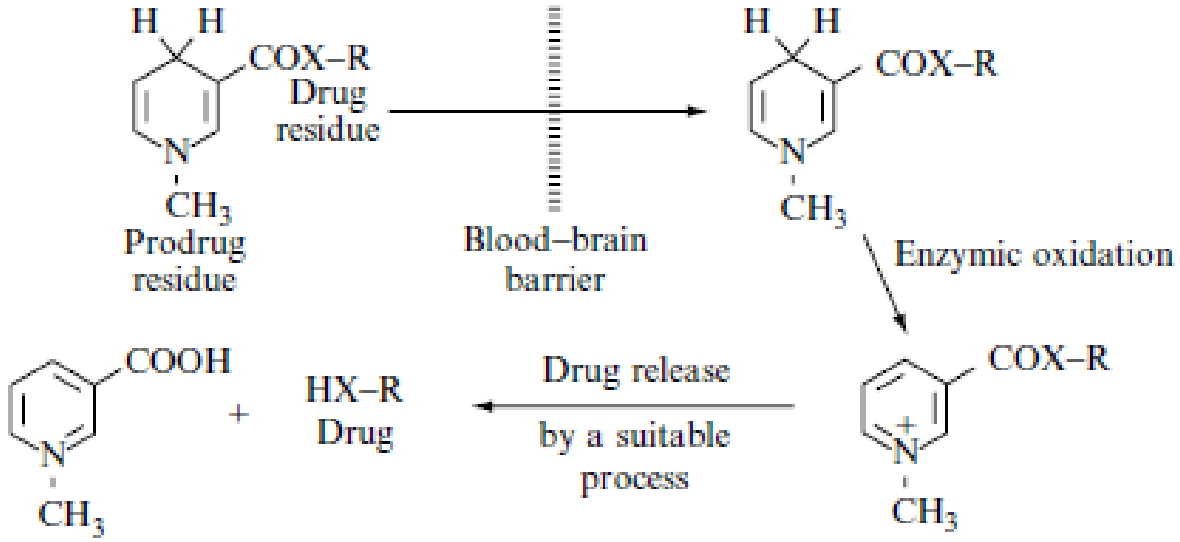


Tolmetin-glycine prodrug

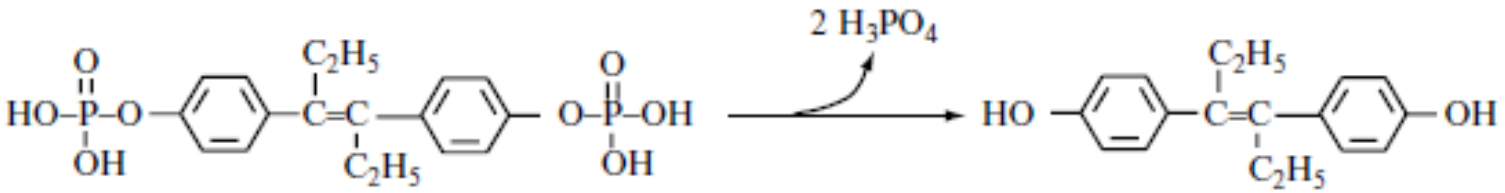
4. Site specificity

In theory, it should be possible to design a carrier prodrug that would only release the drug in the vicinity of its site of action. Furthermore, once released, the drug should remain mainly in the target area and only slowly migrate to other areas. In addition the carrier should be metabolized to nontoxic metabolites.

A method developed by **Bodor and other workers** involved the combination of a hydrophilic drug with a suitable lipophilic carrier, which after crossing the blood–brain barrier would be rapidly metabolized to the drug and carrier. Once released, the hydrophilic drug is unable to recross the blood–brain barrier. The selected carrier must also be metabolized to yield nontoxic metabolites.



Once the dihydropyridine prodrug has crossed the blood–brain barrier it is easily oxidized by the oxidases found in the brain to the hydrophilic quaternary ammonium salt, which cannot return across the barrier, and relatively nontoxic pyridine derivatives in the vicinity of its site of action.



Diethylstilbestrol diphosphate

Diethylstilbestrol

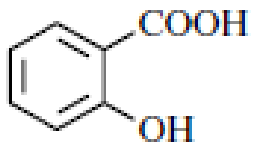
A method of approach followed by some workers is to design prodrugs that are activated by enzymes that are found mainly at the target site. This strategy has been used to design antitumour drugs, since tumours contain higher proportions of phosphatases and peptidases than normal tissues. For example, diethylstilbestrol diphosphate (Fosfestrol) has been used to deliver the oestrogen agonist diethylstilbestrol to prostatic carcinomas.

5. Minimizing side effects

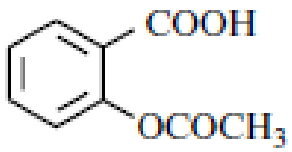
Prodrug formation may be used to minimize toxic side effects. For example, salicylic acid is one of the oldest analgesics known. However, its use can cause gastric irritation and bleeding.

The conversion of salicylic acid to its prodrug aspirin by acetylation of the phenolic hydroxy group of salicylic acid improves absorption and also reduces the degree of stomach irritation, since aspirin is mainly converted to salicylic acid by esterases after absorption from the GI tract.

This reduces the amount of salicylic acid in contact with the gut wall lining.



Salicylic acid



Aspirin