Chapter

2

PRODRUGS

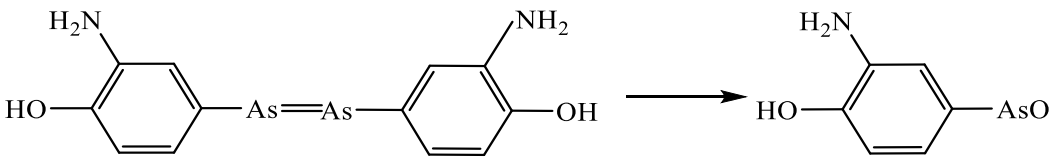
1. INTRODUCTION

The term prodrug is defined as a pharmacologically inactive compound that is converted into an active drug by a chemical or enzymatic process. The prodrug to drug conversion can occur before absorption, during absorption, after absorption or at a specific site in the body. A prodrug is also called as pro-agent, bio-reversible derivative, latentiated drug and congeners.

Drug + Cap (Prodrug) Drug Cap

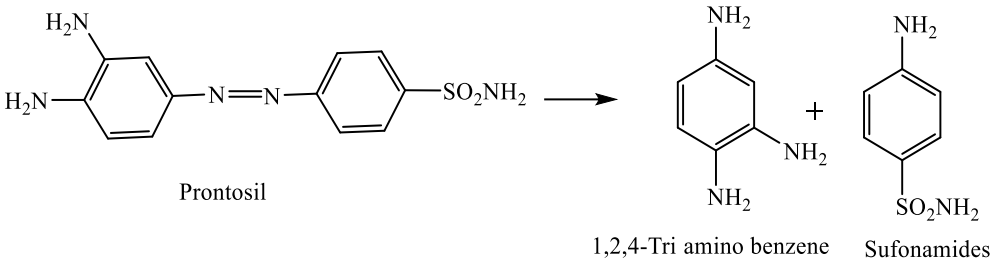
Fig. 2.1 Concept of Prodrug

The earliest example of prodrug is Arsphenamine which is used for the treatment of syphilis. Later on, it was found that, the activity of this compound was due to metabolic product Oxophenarsine. Arsphenamine was later replaced by Oxophenarsine in therapy as the metabolite was less toxic at the dose required for effective therapy.

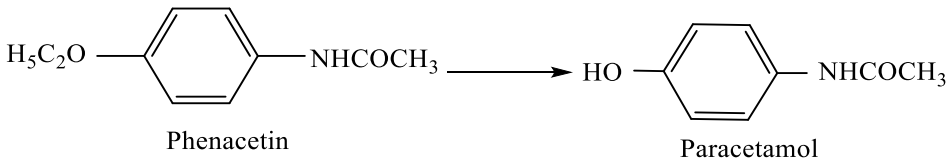


Arsphenamine Oxophenarsine

Azo-dye Prontosil had antibacterial activity, is a prodrug for sulphonamide which led to subsequent development of wide range of therapeutically superior sulfonamides through the modification of amino benzene sulfonamide.



Phenacetin, an analgesic and antipyretic agent is mainly metabolized in the body to active metabolite N-acetyl-p-amino phenol (Paracetamol). Paracetamol has replaced Phenacetin therapy, because it is free from toxic effects associated with Phenacetin (Methemoglobin formation).



2. PRODRUGS STRATEGY IN DRUG DESIGN

There are numerous reasons why one may wish to utilize a prodrug strategy in drug design. Few examples are

i) Solubility

Consider an active drug that is insufficiently soluble in water, so that it cannot be injected in a small dose. A water-soluble group could be attached which could be metabolically released after drug administration.

ii) Absorption and Distribution

If the drug is not absorbed and transported to the target site in sufficient concentration it can be made more water soluble or lipid soluble, depending on the desired site of action. Once absorption occurred or when the drug is at the appropriate site of action, the water or lipid soluble group is removed enzymatically.

iii) Site Specificity

Specificity for a particular organ or tissue can be made, if there are high concentrations of uniqueness of enzymes, present at that site which can cleave the appropriate appendages from the prodrug and unmask the drug.

iv) Instability

A drug may be rapidly metabolized and rendered inactive, prior when it reaches the site of action. The structure may be modified to block that metabolism until the drug is at the desired site.

v) Prolonged Release

It may be desirable to have a steady low concentration of a drug released over a long period of time. The drug may be altered, so that it is metabolically converted to the active form slowly.

vi) Toxicity

A drug may be toxic in its active form and would have a greater therapeutic index if it were administered in a nontoxic, inactive form that can be converted to the active form only at the site of action.

vii) Poor Patient Acceptability

An active drug may have an unpleasant taste or odor, produces gastric irritation, or causes pain, when administered (eg. when injected). The structure of the drug can be modified to alleviate these problems, but once administered; the altered drug can be metabolized to the active drug.

viii) Formulation Problems

If the drug is a volatile liquid, it would be more desirable to prepare it in a solid form, so that it could be formulated as a tablet. An inactive solid derivative could be prepared which would be converted in the body to the active drug.

3. IDEAL REQUIREMENTS OF PRODRUGS

An ideal prodrug must meet the following requirements

i) The prodrug should be inactive or less active than the parent compound.

ii) It should not have intrinsic pharmacological activity.

iii) The linkage between the drug and the carrier must be cleared *in vivo.*

iv) The carrier molecule released *in vivo* must be non-toxic.

4. TYPES OF PRODRUG

Depending upon the constitution, lipophilicity, method of bio-activation and catalyst involved in bio-activation, prodrugs are classified into two types

a. Carrier linked prodrugs

b. Bio-precursors

4.1 Carrier Linked Prodrug

Carrier linked prodrug is a compound that contains an active drug linked to a carrier group that can be removed enzymatically, such as ester which is hydrolyzed to active carboxylic acid containing drug. The bond to the carrier drug must be labile enough to allow the active drug to be released efficiently *in vivo* and the carrier must be non-toxic and biologically inactive when detached from the drug. Carrier linked prodrug can be further subdivided into bipartate, tripartate and mutual prodrug.

A bipartate prodrug is a prodrug comprised of one carrier attached to the drug. When a carrier is connected to a linker that is connected to the drug is called a tripartate prodrug. (Fig. 2.2)

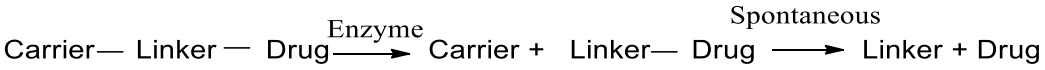


Fig. 2.2 Tripartate Prodrug

Bipartate prodrug may be ineffective because the prodrug linkage is too labile or too stable. In order to overcome this problem, tripartate prodrugs are designed. The drug-linker connection must be designed in such a way that it cleaves spontaneously after the

carrier detached. One approach to accomplish this, has been termed as double prodrug (Fig. 2.3)

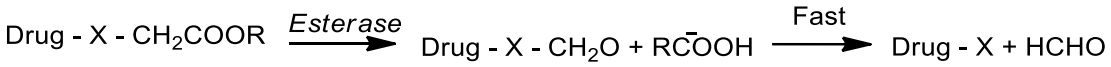
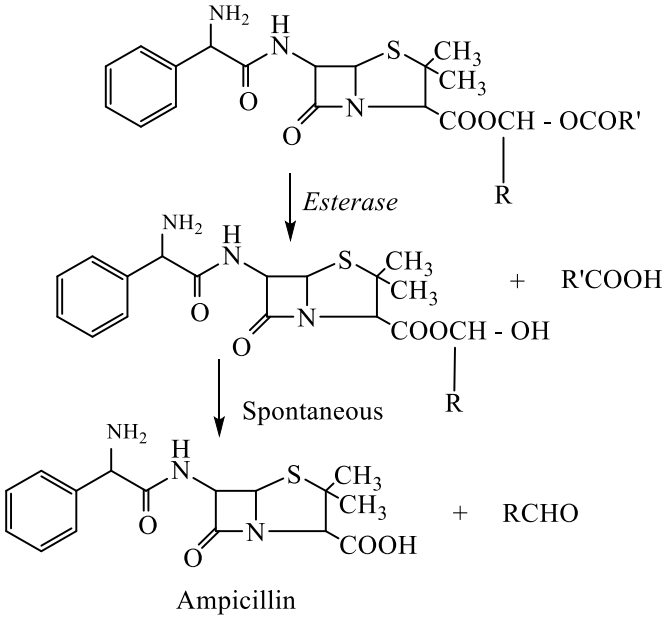


Fig. 2.3 Concept of Double Prodrug

Example for double ester is Bacampicillin or Pivampicillin an ester of Ampicillin. The β-lactam antibiotic Ampicillin is poorly absorbed when administered orally, so 2.5 times more drug must be administered orally than by injection. The extra dosage of the drug may lead to more rapid onset of resistance and may destroy the important intestinal bacteria. A lipid-soluble prodrug of Ampicillin would be a useful approach to increase the absorption of this drug. The various simple alkyl or aryl ester of thiazolidine carboxyl group of Ampicillin are stable and therapeutically useful. But steric hindrance occurs at ester carbonyl group of the thiazolidine ring with enzyme. This problem is overcome by double ester acyloxy methyl ester such as Bacampicillin or Pivampicillin which would extent the carbonyl group away from thiazolidine ring and steric hindrance with the enzyme. Hydrolysis of terminal ester gives an unstable hydroxy methyl ester, which spontaneously decomposes to Ampicillin and either acetaldehyde (Bacampicillin) or formaldehyde (Pivampicillin). Bacampicillin is absorbed to the extent of 98%, so only one half to one-third of Ampicillin dose is required orally.



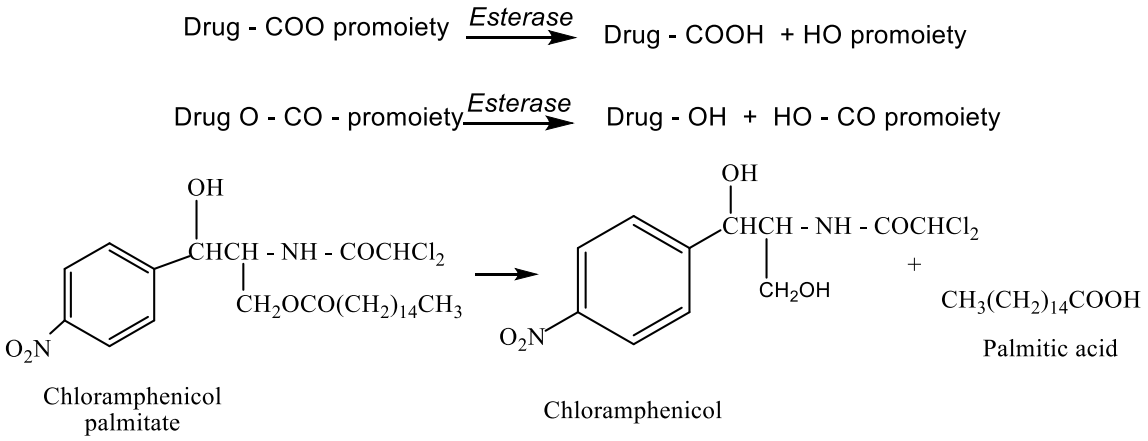
Prodrugs	R	R’
Bacampicillin	CH_3	C_2H_5
Pivampicillin	H	t-butyl

4.1.1 Carrier Linkage for Various Functional Groups

a) Carboxylic Acids and Alcohols

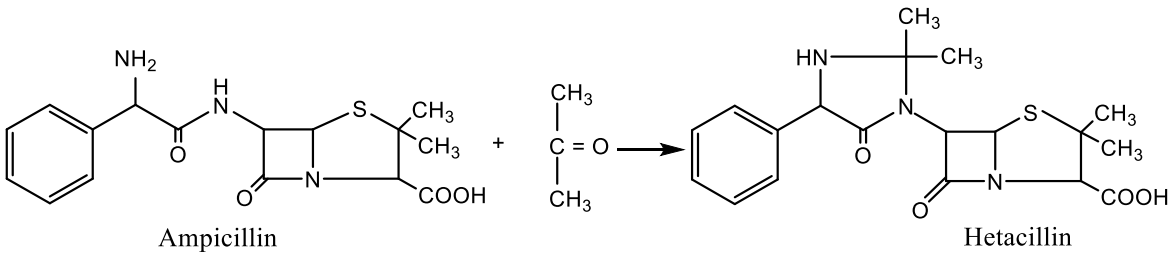
Prodrugs of carboxylic acid and alcohol functionalities can be prepared by conversion to esters. The esters can be easily hydrolyzed by esterase enzymes *(lipase, cholesterol esterase, acetylcholine esterase, carboxy peptidase)* present in plasma and other tissues to give active drug. Alcohols containing drugs can be acylated with aliphatic or aromatic acid to decrease water solubility (increases lipophilicity) or with carboxylic acids containing amino or additional carboxylate groups to increase water solubility and also conversion to phosphate or sulfate esters increases water solubility.

Carboxylic acid containing drugs can be esterified with various alcohols. The pKa of a carboxylic acid can be raised by conversion to choline ester or amino ester.



b) Amines

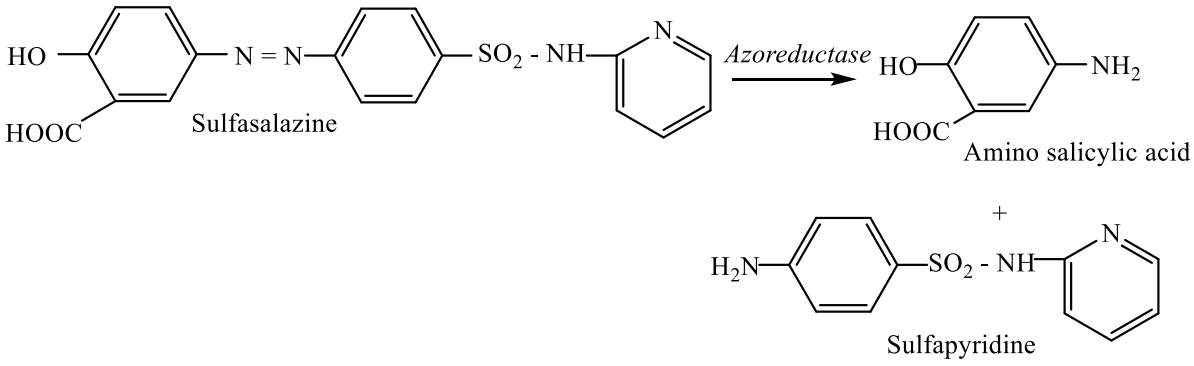
Derivatization of amines to give amide has not been widely used as a prodrug, because of high chemical stability of amide and lack of amidase enzyme necessary for hydrolysis. A more common approach is to use Mannich bases as prodrug form of amines. This lowers the basicity of amines, so that at physiological pH few of the prodrug molecule are protonated, thereby increases its lipophilicity. Hetacillin is a prodrug form of Ampicillin in which amide nitrogen and α-amino functionality have been allowed to react with acetone to give a Mannich base [imidazolidine ring system]. This decreases the basicity and increases the lipophilicity and absorption. Another approach to lower the pKa of amine is making them more lipophilic by converting in to imines (Schiff's base).



Ampicillin Hetacillin

c) Azo Linkage

Amines are derivatized to azo linkage prodrug occasionally. Sulfasalazine by the action of *azo reductase* releases the amino salicylic acid and Sulfapyridine. The generation of anti-inflammatory amino salicylic acid prior to absorption prevents the systemic absorption of the agents and concentrates it in active site. Sulfasalazine is an example of mutual prodrug. A mutual prodrug consists of two usually synergistic drugs attached to each other *i.e.*, one drug carrier for the other and vice versa. It is a bipartate or tripartate prodrug in which the carrier is a synergistic drug with the drug to which it is linked. A mutual prodrug is well absorbed, both components are released concomitantly and quantitatively after absorption, the maximal effect of the combination of the two drugs occurs and distribution and elimination of the two components are similar.



Sulfasalazine Amino salicylic acid

Sulfapyridine

d) Carbonyl Moiety

Carbonyl functionalities such as aldehyde and ketones conversion to prodrug have not found wide clinical utility. These are converted into derivatives in which the sp^2 carbonyl carbon is converted to a sp^3 hybridized carbon attached to hetero atoms. These prodrugs are reconverted to carbonyl compound by hydrolysis. The most important

prodrug form of aldehydes and ketones are oximes, acetals, enol esters, oxazolidines, Schiff base and thiazolidines. For example, hexamine releases formaldehyde in the urine (acidic pH), which acts as an antibacterial agent.

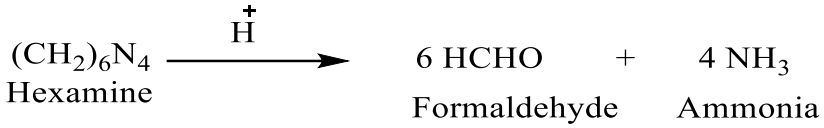
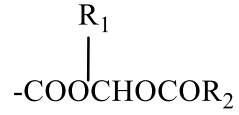
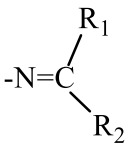
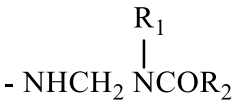
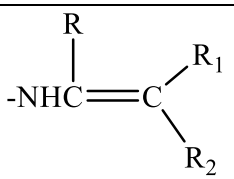
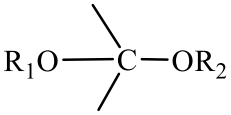
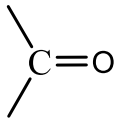
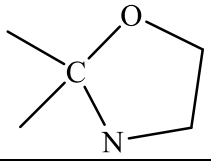
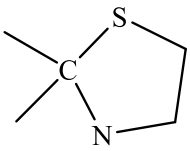
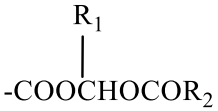
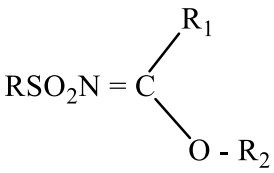
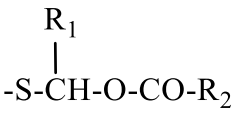
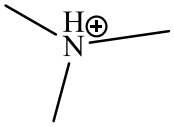
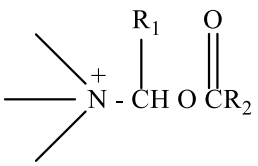


Table 2.1 Carrier linkage for various functional groups

Functional groups	**Prodrug**	**Name of groups**
-COOH	-COOR	Ester
	-CONHR	Amide
		α- Acyloxy alkyl esters
-NH₂	-NHCOR	Amide
	-NHCOOR	Carbamates
		Imines
		N-Mannich bases
		Enamines
		Ketals

		Oxazolidines
		Thiazolidines
-OH	-OCOR	Esters
	OPO_3H_2	Phosphate ester
		α-Acyloxy alkyl esters
	-OR	Ethers
$-SO_2NH_2$		N-Sulphonyl imides
	$-SO_2NHCH_2OR$	N-Sulphonyl imides
-SH	-S-CO-R	Thioesters
		α-Acyloxy alkyl thioethers
	-S-S-R	Disulfides
		N-Acyloxy alkyl derivatives

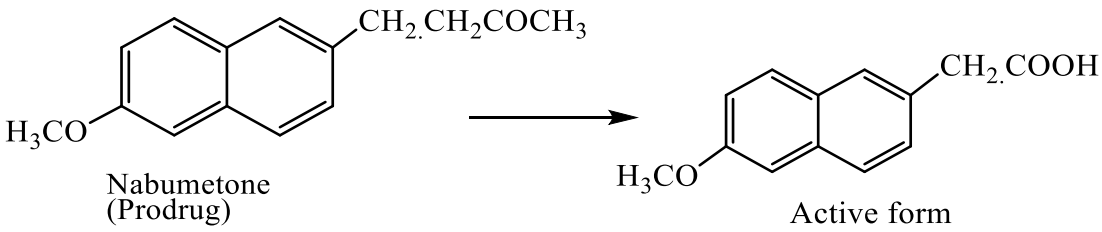
4.2 Bio-precursor Prodrug

Bio-precursors are inert molecule obtained by chemical modification of the drugs but do not contain a carrier. For example, if the drug contains carboxylic acid group, the bioprecursor may be primary amine, which is metabolized by oxidation to aldehyde which is further metabolized to carboxylic acid drug.

Bio-precursor prodrug does not contain a carrier or promoiety, but rather contains a latent functionality that is metabolically or chemically transformed to active drug molecule. The types of activation involve oxidation, reduction, phosphorylation or chemical activation. The examples given below are arranged according to the type of metabolic activation reaction involved.

a) Oxidative Activation

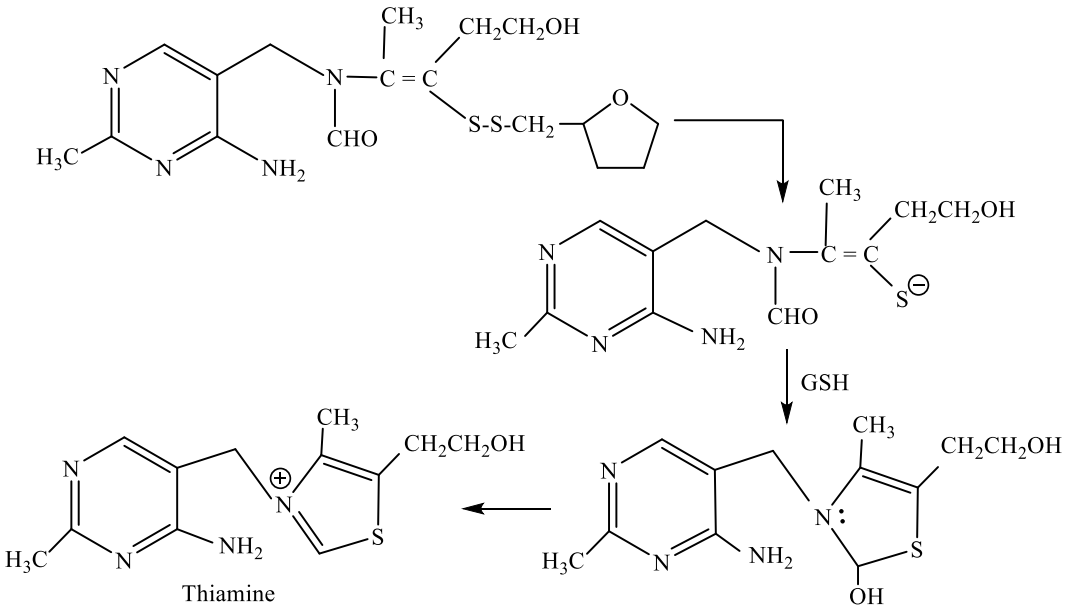
Nabumetone is an anti-inflammatory drug. NSAIDs normally produce stomach irritation. This is due to the presence of carboxylic acid group present in the drug. This functional group is essential for activity. Nabumetone contains no acidic functionality and so it passes through the stomach without producing irritation. After absorption the drug is metabolized in the liver to active substance.



Nabumetone (Prodrug) Active form

b) Reductive Activation

Thiamine is a quaternary ammonium salt, it is poorly absorbed into CNS and from gastro intestinal tract. To increase the lipophilicity of Thiamine, tetrahydro furfuryl disulphide was designed as a prodrug. The prodrug permeates rapidly through red blood cell membranes and reacts with glutathione to produce Thiamine.



5. APPLICATIONS OF PRODRUGS

There are three main reasons for drug action, namely the pharmaceutical, pharmacokinetic and pharmacodynamic phases. Problems exist in all the three phases, but prodrug formation seeks to the problem in pharmaceutical and pharmacokinetic phases.

5.1 Pharmaceutical Applications

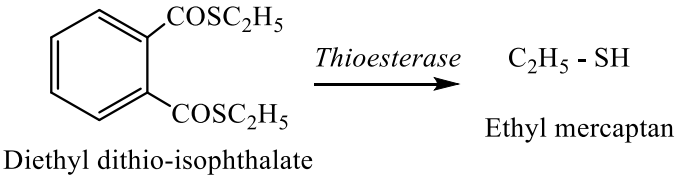
a) Prodrug to Improve Patient Acceptability

One of the reasons for poor patient compliance, particularly in case of children is bitterness, acidity or causticity of the drug. Two approaches can be utilized to overcome the bad taste of drug. The first is reduction of drug solubility in saliva and the other is to lower the affinity of drug towards taste receptor. Chloramphenicol has a bitter taste, so it is not well accepted by children. The palmitate ester of it is less soluble in saliva, so it masks the bitter taste. Some other examples are given in Table 2.2.

Table 2.2 Examples of Drugs and their Prodrugs

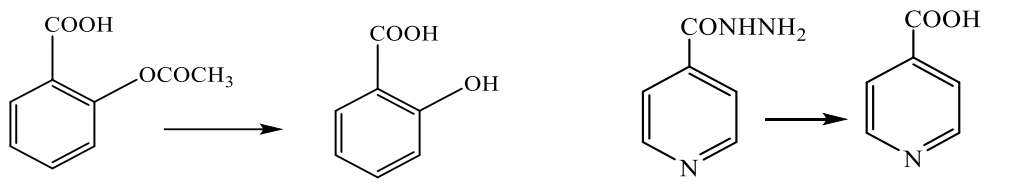
S. No	Parent Drug	Prodrug
1	Clindamycin	Clindamycin phosphate
2	Sulfisoxazole	N-acetyl sulfisoxazole
3	Erythromycin	Erythromycin estolate
4	Sulfamethoxy-pyridazine	N-acetyl sulfamethoxy-pyridazine
5	Metronidazole	Benzoyl metronidazole

The odor of a compound depends upon its vapor pressure; a liquid with high vapor pressure will have a strong odor. For example Ethyl mercaptan is a foul smelling liquid used in the treatment of leprosy. This is converted to phthalate ester, diethyl dithio-isophthalate which has higher boiling point and is odorless. The odourless inactive prodrug is metabolized to the active parent drug by *thioesterase*.



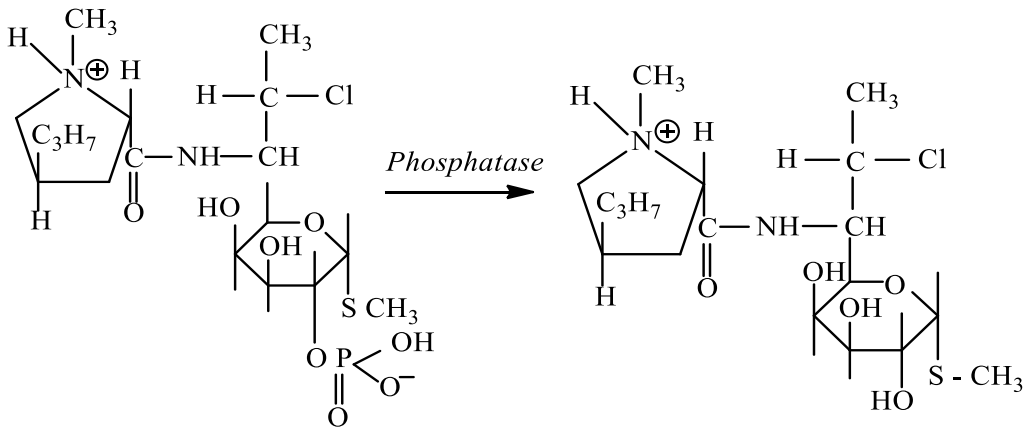
Diethyl dithio-isophthalate

Several drugs (NSAIDS, Nicotinic acid, Kanamycin, Diethylstilboestrol) cause irritation and damage to gastric mucosa. Examples of prodrug designed to overcome such problems of gastric distress are given below (Aspirin & INH).



Aspirin Salicylic acid Isonicotinic acid hydrazide Nicotinic acid

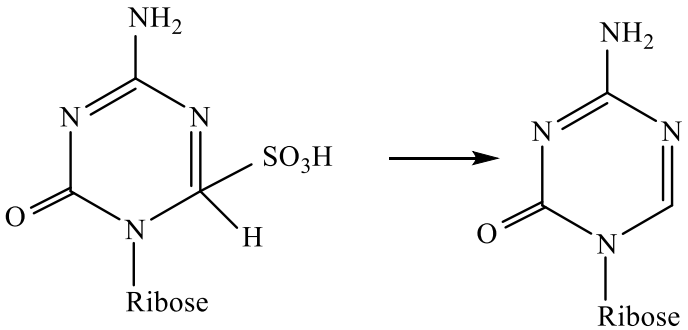
Intramuscular injection is particularly painful when drug precipitates or penetrates into the surrounding cell or when the solution is strongly acidic, alkaline or alcoholic. For example, Clindamycin hydrochloride causes irritation when given by intramuscular route. This can be overcome by use of more water-soluble prodrug Clindamycin - 2' - phosphate.



Clindamycin - 2' - phosphate Clindamycin

b) Prodrug to Improve Stability

Many drugs are unstable and may either breakdown on prolonged storage or are degraded rapidly on administration. Several drugs may decompose in GIT when used orally. Although enteric coatings may be used, it is also possible to utilize prodrug design to overcome this problem. An antineoplastic drug Azacytidine hydrolyses readily in acidic pH, but the bisulfite prodrug of it is more stable.

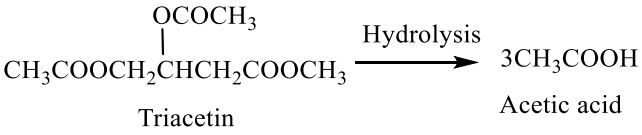


Bisulphite prodrug of azacytidine Azacytidine

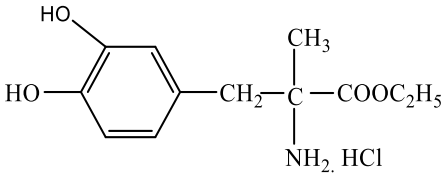
Erythromycin also has similar acid instability problem. Its stearate and estolate ester prodrugs are stable and hydrolyzed in stomach

c) Prodrug to Overcome Formulation Problem

Formaldehyde is a flammable, colourless gas which could not be used directly as medicine so a stable solid Hexamine (Methenamine) is used. In acidic pH, Hexamine (pH of urine in the bladder is mildly acidic) hydrolyzed to formaldehyde and ammonia which acts as urinary antiseptic. Another example is the topical fungistatic prodrug Triacetin owes its activity to acetic acid, the product of skin *esterase* hydrolysis to acetic acid.

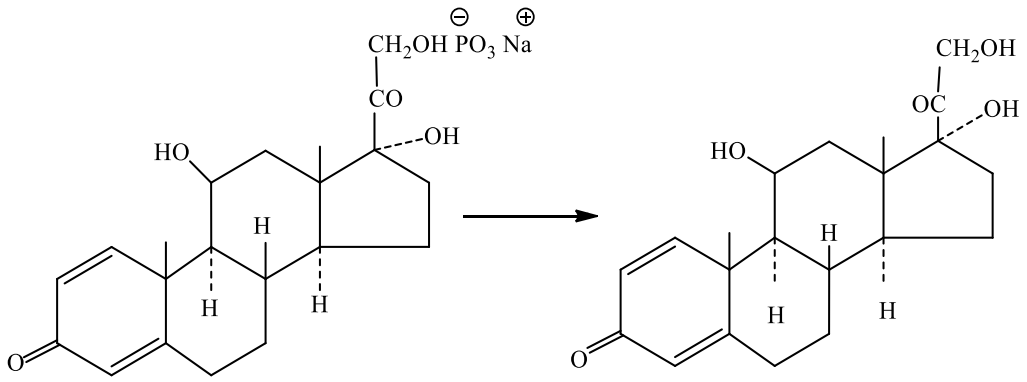


Some drug exists in a form which is unsuitable for formulation. For example, Methyl dopa is a Zwitterion and although charged, its crystal structure causes it to be only poorly water soluble. In order to formulate this drug for injection, it is converted into ethyl ester which may be formulated as hydrochloride salt.



Methyl dopate hydrochloride

Hydrophilicity or water-soluble drugs are desired when parenteral or ophthalmic formulation of such agent is desired. Drugs with hydroxyl functional group can be converted to their hydrophilic form by use of half ester such as hemi-glutarate or hemi-phthalates; the other half of this acid carries sodium, potassium or amine salts and renders the moiety more soluble. Prednisolone and Methyl prednisolone are poor water-soluble corticosteroid drugs. Prednisolone phosphate is a water-soluble prodrug of Prednisolone that is activated *in vivo* by *phosphatase*.



Prednisolone sodium phosphate Prednisolone

5.2 Pharmacological Applications

Pharmacological problems may be either related to pharmacokinetic, pharmacodynamic or toxic properties of the drug.

a) Prodrug to Improve Absorption

Therapeutic agents have to permeate one or more biological membranes in order to reach the target site. Although drugs are administered by a number of quite different routes, prodrugs designed to solve delivery problems related to some of the mostly used route of administration e.g. oral, dermal and ocular delivery system.

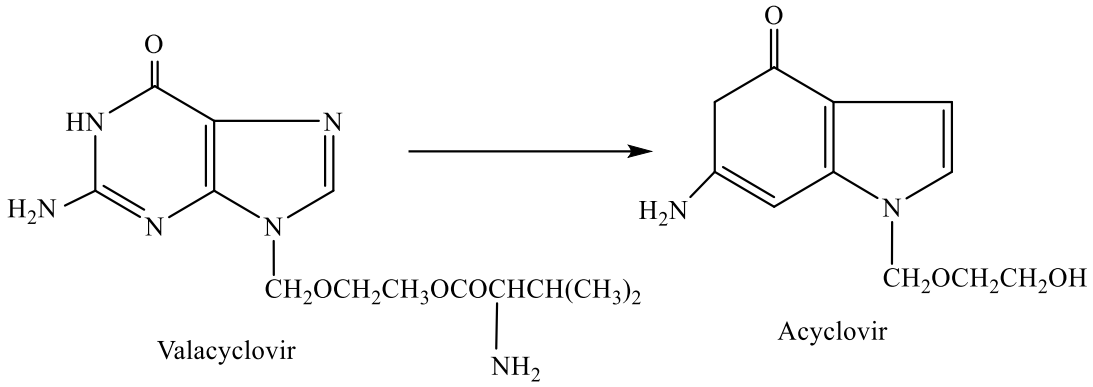
(i) Oral Absorption

For orally administered drugs one major challenge of reaching their site of action is that, they have to cross the intestinal epithelial cells to enter the systemic circulation. Poor transport properties may lead low bioavailability, which may also result from low water solubility, low stability in gastro intestinal juices or extensive first-pass metabolism. Prodrug design has been utilized in a number of cases to optimize the absorption of such drugs, thereby improving their bioavailability.

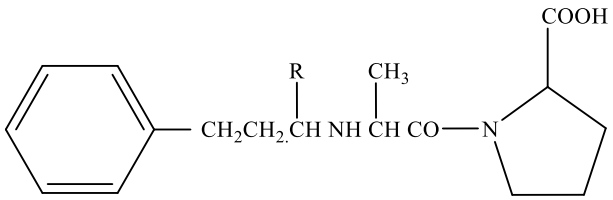
Well known example of prodrug to enhance absorption of polar drug modification is Ampicillin derivative (Discussed in tripartate prodrug). Ampicillin a wide spectrum antibiotic is readily absorbed orally as the inactive prodrug, Pivampicillin, Bacampicillin and Talampicillin which are then converted by enzymatic hydrolysis to Ampicillin.

The low absorption of antiviral Acyclovir is increased by orally active prodrug Valacyclovir, the L-valyl ester of Acyclovir, which is rapidly hydrolyzed by first pass

intestinal metabolism. The prodrug is converted into Acyclovir in human by the hydrolase enzyme present in the liver and gut.

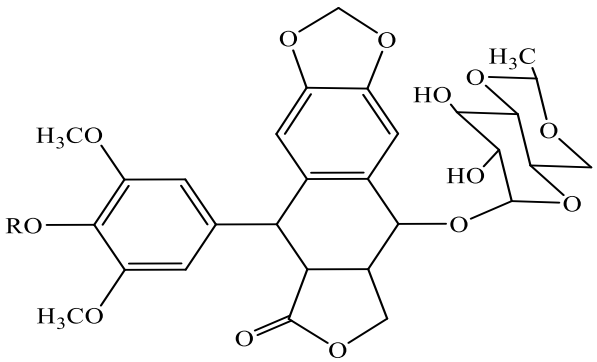


In antihypertensive drug Enalaprilat oral absorption has been improved by conversion to more efficiently absorbed ethyl ester Enalapril. The prodrug Enalapril is converted *in vivo* to an active Enalaprilat by hydrolysis in the liver.



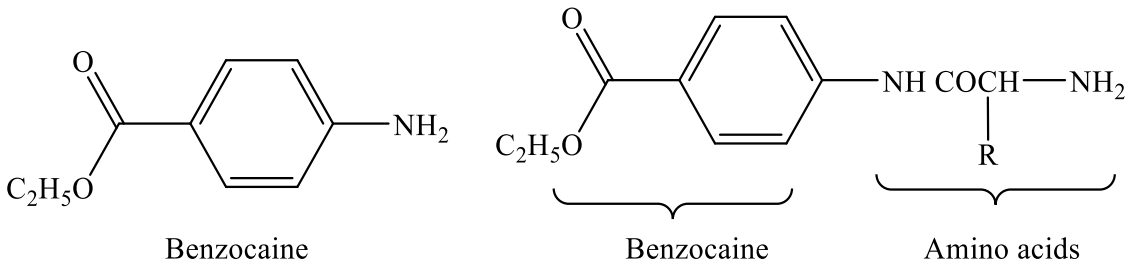
Name	R
Enalapril	-$COOC_2H_5$
Enalaprilat	-COOH

Several drugs show poor and variable oral absorption characteristics as a result of insufficient water solubility leading to dissolution rate-limited absorption. The antitumor drug Etoposide is toxic due to its poor water solubility. Conversion to corresponding phosphate ester, Etoposide phosphate allows the drug to be delivered in a more concentrated form over a much shorter period to time.



Name	R
Etoposide	-H
Etoposide phosphate	-PO_3H_2

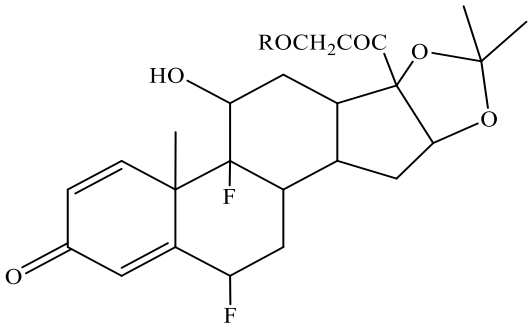
The local anesthetic Benzocaine has been converted into water soluble amide prodrug form with various amino acids; *amidase*-catalyzed hydrolysis in human serum occurs rapidly.



Benzocaine Benzocaine Amino acids

(ii) Dermal Absorption

The skin is designed to maintain the body fluids and prevent absorption of xenobiotics into the general circulation. Consequently, drugs applied to the skin are poorly absorbed. Corticosteroids for the topical treatment of inflammatory, allergic and pruritic skin conditions can be made more suitable for topical absorption by esterification or acetonidation. For example, both Fluocinolone acetonide and Fluocinonide are prodrugs used for inflammatory and pruritic manifestations.

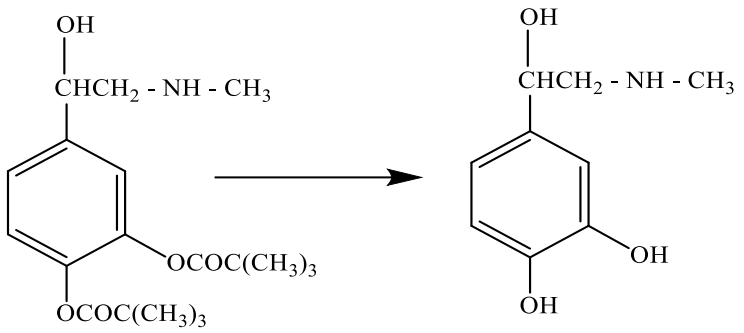


Name	R
Fluocinolone acetonide	-H
Fluocinonide	-$COCH_3$

(iii) Ocular Absorption

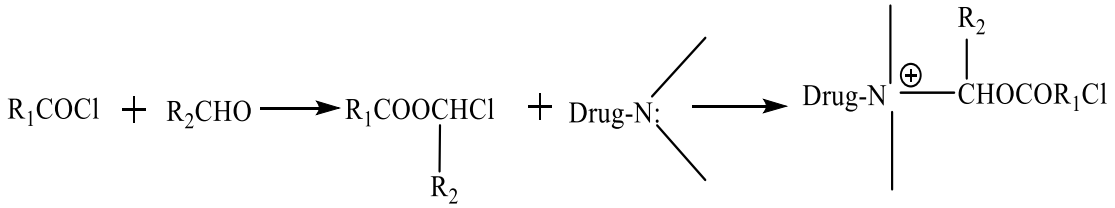
A major problem in ocular therapeutic is the attainment of an optional drug concentration at the site of action. The difficulty is largely due to the fact that all the existing drugs, many of which were originally developed for system use, lack the physio-chemical properties to overcome the severe constraints imposed by the eye on drug absorption. The net result is 1% or less of the instilled drug dose is ocularly absorbed.

Dipivaloyl epinephrine (Dipivefrin) a prodrug for the antiglaucoma is able to penetrate the cornea better than Epinephrine. The cornea and aqueous humor have significant esterase activity.



Dipivaloyl epinephrine Epinephrine

The approach of "soft" quaternary salt is utilized to achieve improved bio-availability of Pilocarpine on ocular administration. Pilocarpine is rapidly drained from the eye resulting in a short duration of action. The "soft" quaternary salt has a lipophilic side chain which has been shown to improve absorption in rabbits and gives a more prolonged effect at one tenth of the concentration of Pilocarpine. The "soft" quaternary salt is formed by reaction between α-chloromethyl ester and amino group of the drug. The quaternary salt formed is termed as "soft" quaternary salt since unlike normal quaternary salt it can release the active basic drug on hydrolysis. "Soft" quaternary salt increases the absorption since it has surfactant property and capable of forming micelles and unionized pair with bile acid etc., which are able to penetrate the intestinal epithelium more effectively. The prodrug after absorption rapidly releases the parent drug by hydrolysis process.



α- Chloromethyl ester Basic drug "Soft" quaternary salt

(b) Prodrug for Site Specific Drug Delivery

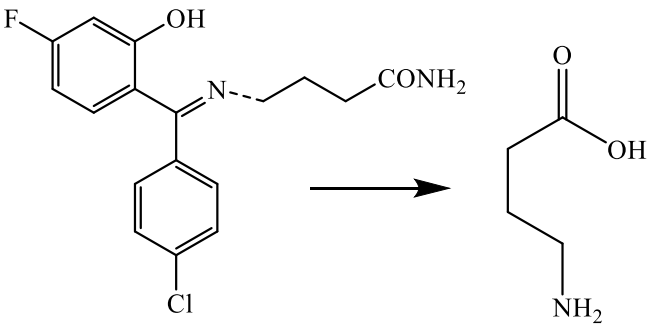
Targeting of drug for a specific site in the body by conversion to a prodrug are designed to ensure that, the release of active drug only occurs at its site of action thereby reducing toxic side effects due to high plasma concentration of the drug or non- specific update by other body tissues. Site specific drug delivery might achieve by site directed drug delivery or site-specific bio activation. Site directed delivery relates to design prodrug

that affords an increased or selective transport of the parent drug to the site of action. It can be further divided into localized or systemic site directed drug delivery. The objective of site-specific bio-activation is to accomplish bio-reversible derivatives, that are distributed throughout the organism but undergo bio-activation only in the vicinity of the target area.

(i) Site Directed Drug Delivery

Successful site-directed drug delivery has been achieved in the field of localized drug delivery. Compared to localized drug delivery, systemic site-directed delivery constitutes a much more difficult task, since the drug has to be transported via the systemic circulation to the desired organ or tissue, passing various complex and not easily predictable on the way. Drug targeting in cancer chemotherapy, an interesting approach to obtain site-directed delivery to the brain has been investigated.

One important membrane that must be trans-versed for drug delivery into the brain is the blood-brain barrier, a unique lipid-like protective barrier that prevents hydrophilic compounds from entering the brain unless they are actively transported. They also contain active enzymes to protect the central nervous system further. Anticonvulsant activity can be achieved by increasing concentration of γ-aminobutyric acid (GABA) in the brain which results in neurotransmission inhibition. GABA is too polar to cross blood brain barrier, so it's effective lipophilic analog of GABA that crosses the blood-brain barrier, releases GABA inside the brain and shows anticonvulsant activity. In the above example, the lipophilicity was increased, so that they could diffuse through the membranes.



Probabide γ - Amino butyric acid

Although lipophilic prodrug may be used, but increased lipid solubility may enhance uptake in other tissue with a resultant increase in toxicity. Furthermore, therapeutic levels of such lipophilic prodrug can only be maintained if there is a constant

plasma level. These problems may be overcome by utilizing a dihydropyridine-pyridine-pyridinium salt type redox system. (Fig.2.4). The drug (D) which is aimed to be delivered to the brain, is coupled to a quaternary carrier (i.e. N-methyl nicotinic acid) QC^+ to yield D-QC^+ which is reduced to neutral, lipophilic dihydro from (D-DHC).

After administration, this compound is distributed throughout the body including the brain. D-DHC is then enzymatically oxidized back to the original quaternary entity (D-QC^+). The later hydrophilic compound is prevented from passing through the blood-brain barrier. Thus, the ionic form is trapped in the brain and undergoes slow enzymatic cleavage releasing the active agent. Because of the facile elimination of D-QC^+ from the circulation, only small amount of the free drug is released in the blood. This concept has been applied to several drugs including Dopamine, Phenytoin and Penicillin.

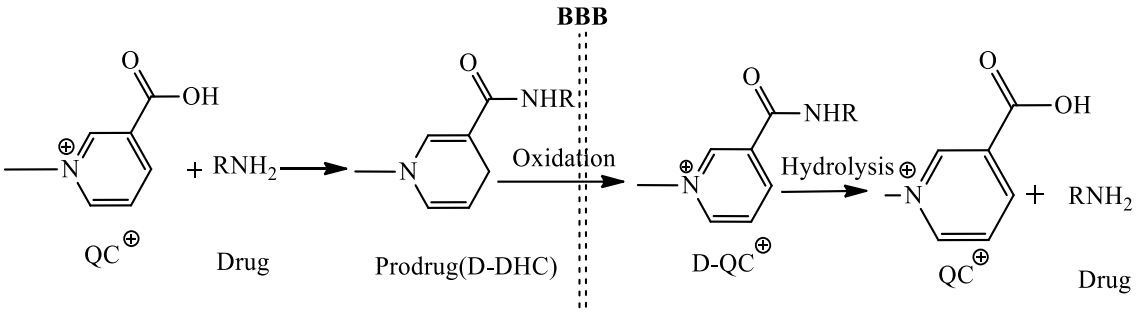


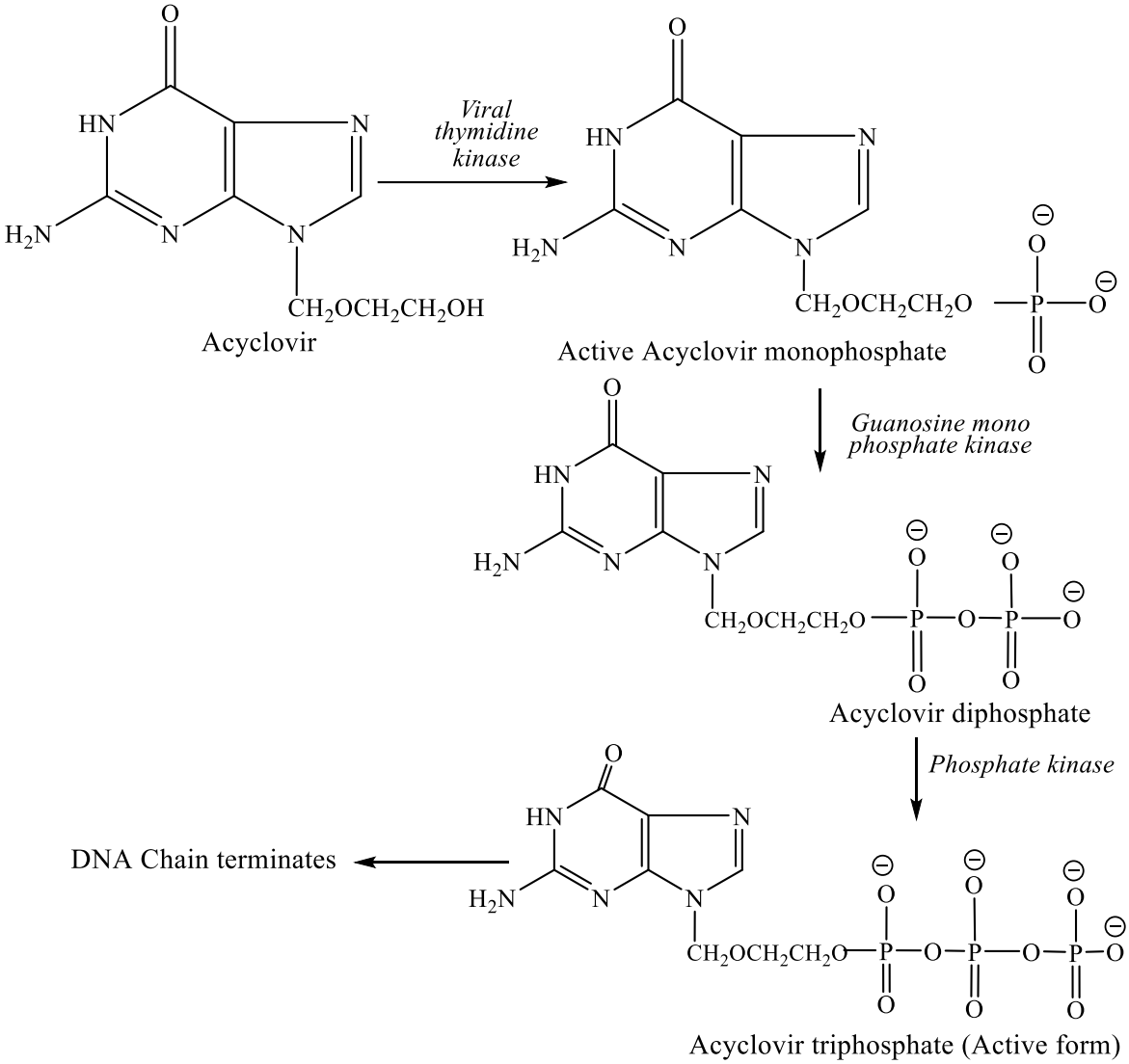
Fig. 2.4 Quaternary Ammonium Carrier Prodrug

(ii) Site Specific Bio-activation

Quantitative or qualitative difference between the target and non-target sites might be exploited in prodrug design to activate or release the active agents in the vicinity of the target area. Difference in pH or more often in enzyme levels have founded the platform for the synthesis of bio-reversible derivatives, which after the distribution phase are selectively activated in the desired organ within the body.

Site specific bio-activation can be explained by action of Acyclovir as antiviral agent. The herpes virus encoded *thymidine kinase* converts Acyclovir to its mono phosphate, which by the action of cellular enzyme results in the formation di and tri phosphorylated species. The Acyclovir triphosphate is active one. The triester formation takes place much greater extent in the herpes-infected cells, than the uninfected host cells.

The selectivity of action is manifested in the fact that, a 3000-fold higher concentration of Acyclovir is needed to inhibit uninfected cell multiplication.



An example of pH dependent bio-activation relates to the action of the antiulcer drug Omeprazole. The drug is an effective inhibitor of gastric acid secretion by inhibiting the gastric H^+, K^+-ATPase. This enzyme is responsible for the gastric acid production and is located in the secretary membrane of the parietal cell. Omeprazole is inactive but requires transformation within the acidic compartment of the parietal cell into the active inhibitor a cyclic sulfonamide. This intermediate reacts with thiol groups in the enzyme forming a disulphide complex thereby inactivating the enzyme (Fig. 2.5).

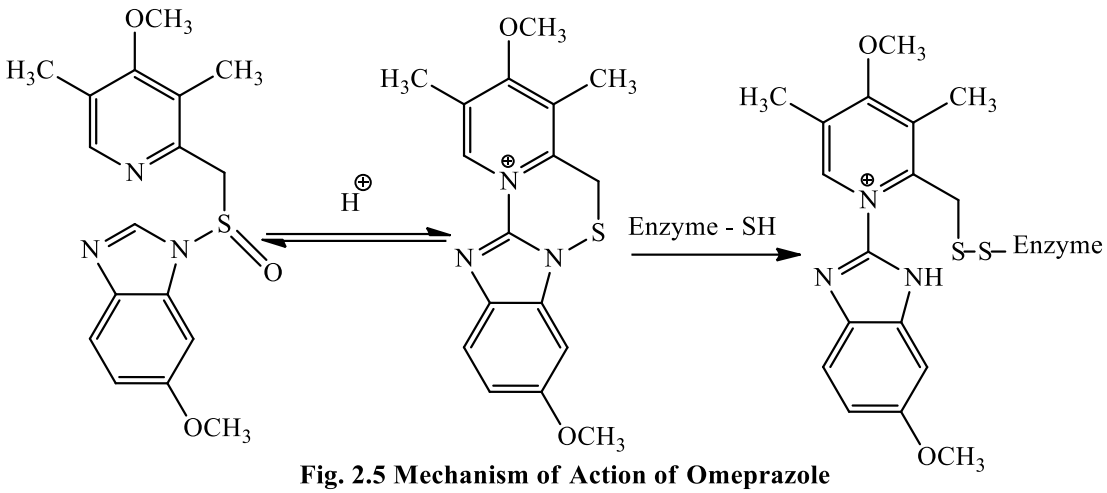
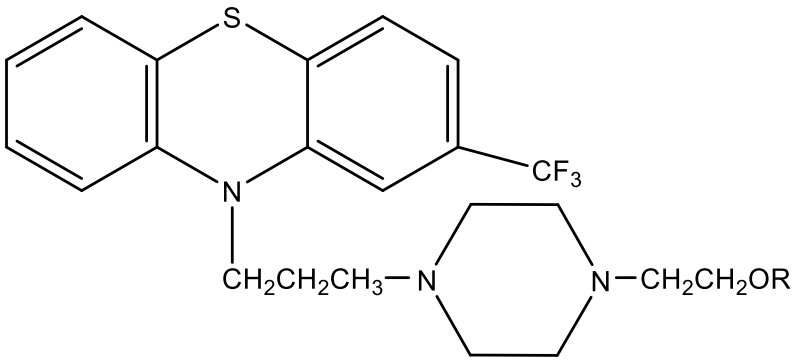


Fig. 2.5 Mechanism of Action of Omeprazole

(c) Prodrug for Slow and Prolonged Release (Sustained Release Action)

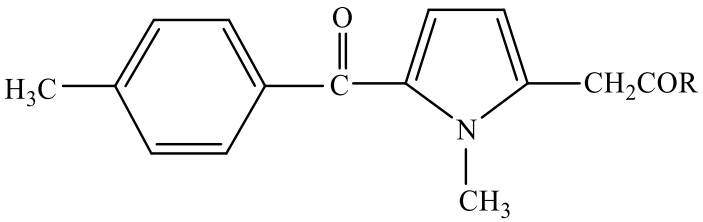
A common strategy in the design of slow-release prodrug is to make long-chain aliphatic esters, because these esters hydrolyze slowly and to inject them intramuscularly. The phenothiazine group of drugs acting as tranquillizer has been converted into long acting prodrug which is administered by intramuscular injection. Not only the frequency of administration reduced, but also the problem associated with patient compliance is also eliminated. For example, Fluphenazine has shorter duration of action (6-8h), but prodrugs Fluphenazine decanoate have duration of activity about month.

Conversion of non-steroidal anti-inflammatory drug Tolmetin sodium to corresponding glycine conjugate increases the potency and extend the peak concentration of Tolmetin from 1hr to about 9hr because of the slow hydrolysis of the amide linkage.



Fluphenazine R = H

Fluphenazine decanoate R = CO $(CH_2)_8CH_3$



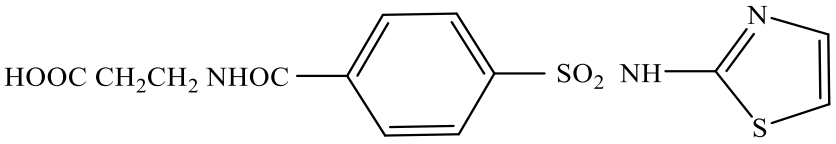
Tolmetin sodium R = $\overset{\ominus}{O}\overset{\oplus}{Na}$

Tolmetin prodrug R = $NHCH_2C\overset{\ominus}{O}O\overset{\oplus}{Na}$

Vasopressin has been used for the treatment of bleeding varicose veins in the lower end of the esophagus a condition that affects 1000 individuals annually. The vasoconstrictor action of the drug stops the bleeding, but the action is of short duration and cannot be prolonged by the use of higher doses due to the development of toxic side effects. Glypressin, Gly-Gly-Gly-Lys-Vasopressin is an inactive prodrug of Vasopressin. After injection the glycyl of Vasopressin is obtained, which is sufficient to produce the required vasoconstriction effect on the portal blood pressure, while minimizing the possibility of unwanted effects caused by high blood pressure.

d) Prodrug to Improve Membrane Transport

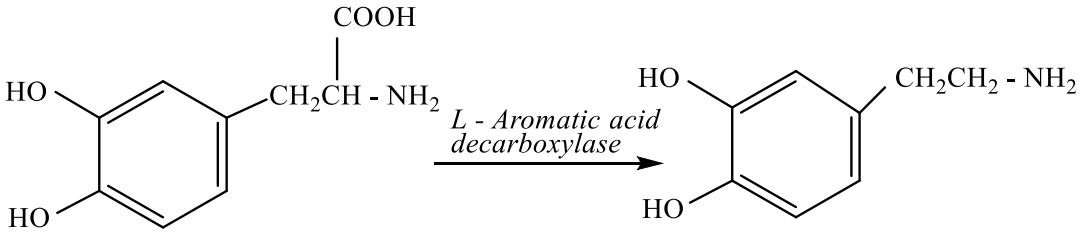
Interference with transport characteristic can serve many purposes. The introduction of a hydrophilic moiety can restrict a drug to the gastro intestinal tract and prevent its absorption. For example, Succinyl sulfathiazole.



Succinyl sulfathiazole

On the other hand introduction of lipophilic group decreases the rate of hydrolysis, which liberates the active drug slowly, in depot preparation for a period of days or weeks. The antimalarial Cycloguanil pamoate can deliver the drug Cycloguanil for longer time (for several months). The membrane transport characteristic of the neurotransmitter Dopamine used for the treatment of Parkinson's disease can be improved by administering its prodrug 3, 4-dihydroxy phenyl alanine (Levodopa). This derivative has better blood-

brain permeation characteristic, since it uses amino acid channels for transportation. Once it enters the cell, decarboxylase enzyme removes the acid group to generate dopamine.



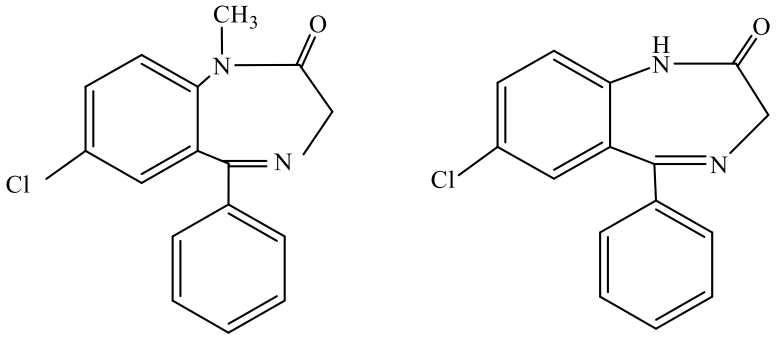
L - Dihydroxy phenyl alanine Dopamine

e) Prodrug for Prolonged Duration of Action

Frequent dosing is required for drugs having short biological half life; this can also be overcome by prodrug approach. This can be achieved by either controlling the release rate of drug from the site of application or the conversion of prodrug into active drug. For example, the diester of Pilocarpine has prolonged therapeutic effect than the Pilocarpine. The diester of the drug when applied as ophthalmic solution showed better intraocular penetration due to improved lipophilicity and slow conversion of ester prodrug to active Pilocarpine prolong the activity.

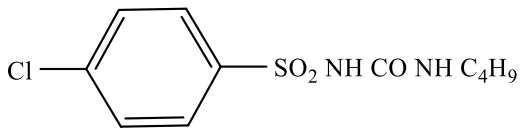
The prodrug by its improved characteristics get closer to the receptor site for longer period of time and the conversion to the active drug takes place at the site of action.

Nordazepam, a sedative drug loses activity quickly due to metabolism and excretion. A prodrug Diazepam improves the retention characteristics, due to the presence of N-methyl group. Slow release of the Nordazepam in the liver by demethylation prolongs the activity.

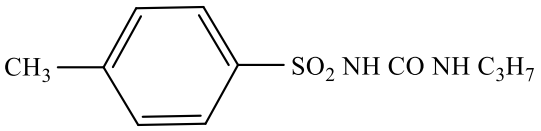


Diazepam Nordazepam

Replacement of less oxidizable chlorine group by vulnerable moiety-a methyl in Tolbutamide results in long acting prodrug Chlorpropamide, with half-life six-fold greater than its parent.



Tolbutamide



Chloropropamide

The utility of slow and prolonged release of prodrug is

i. It reduces the number and frequency of dose required
ii. It eliminates night-time administration of drugs.
iii. Because the drug is taken frequently, it minimizes patient non-compliance.
iv. When fast release drug is taken, due to metabolism the concentration of the drug diminished. A slow release drug would eliminate these peaks and valleys of fast-release drugs, which place a strain on cells.
v. Because a constant lower concentration of the drug is being released, the toxic level of drug in reduced.
vi. It reduces the gastro intestinal side effects.