Pro-drug Approach in Drug Design

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A prodrug is generally defined as a pharmacologically inactive derivative of parent drug which under physiological conditions may undergo spontaneous rearrangement or degradation or be converted enzymetically to a pharmacologically active drug. Prodrugs have also been called reversible derivatives, bio reversible derivatives and latentiated drugs. Three approach traditionally have been utilized in the search for new drugs such as screen approach, designing compounds that exert an effect similar to a naturally occurring substances; modifying a known drug to improve one property or minimize an undesirable one. This review highlights some organic compounds and their derivative, used as prodrug in different therapy, such as Esters and their derivatives, imides and other NH-acidic compounds, allopurinol, N-acyloxymethyl compounds etc.. Esters are used as a prodrug type of drugs containing carboxyl functions stems primarily from the fact that the organism in enzyme capable of hydrolysing esters. Eight aminoacid esters of metronidazole are prepared and evaluated for their potentiality as water soluble parental delivery forms of the parent drugs, whose solubility in water is limited (~ 1% w/v). Prodrug esters are used to improve various properties of parent drugs. A prodrug of Allopurinol suitable for parental administration with an aqueous solubility greater than 50%w/v. Prodrugs are used in cancer therapy. Prodrugs which overcome acquire resistance. Some tumours, which initially very responsive to this agent, become resistant due to overgrowth of cells which have lost the activating HGPRT enzyme.

Three approachs traditionally have been utilized in the search of new drugs and all embrace the concept of the lead compound. The first is the general screen approach in which substances from a wide variety of sources are tested for general pharmacological effect. Any promising leads are further tested for specific bioactivity. The second involves mimicking nature by designing compounds that exert an effect similar to a naturally occurring substance. The synthetic steroids, prostaglandins and anti-metabolites evolved from this approach. The third approach is chemical in nature and involves modifying a known drug to improve one property or minimize an undesirable one. The medicinal chemist has two options in this regards-
In conjuction with the biologist he can prepare analogs a lead compound in an attempt to increase potency, broden or narrow the spectrum of therapeutic activity, decrease or eliminate toxicity and side effects and/or enhance other desirable properties absent in the lead compound. Preparation of such analogs can be considered chemically and biologically irreversible since the lead compoundis not regenerated in vivo.
Preparation of prodrug derivatives of a parent drug molecule can be undertaken to modify some undesirable property of that molecule. In this instance, however, the parent molecule is regenerated in vivo.

Properties that can be modified using the Prodrug approach include :

to modify transport, tissue distribution, excretion and metabolism of drug in the body.
to enhance the bio-availability of the drug .
to reduce toxicity and undo unwanted effects.
to overcome difficulties encountered in pharmaceutical formulation procedures.
To increase the patient acceptance by eliminating pain on injection bitterness, tartness, odour and GIT irritation caused by drugs.
To obtain sustain drug action.

The emphasis of this area of medicinal chemistry has primarily been chemical in nature with rapid advances in the area of QSAR, biological and clinical pharmaco kinetic disciplines, the thrust in present and future efforts in this field logically will shift towards an interdisciplinary approach.

A prodrug is generally defined as a pharmacologically inactive derivatives of parent drug which under physiological condition may undergo spontaneous rearrangement or degradation or be converted enzymetically to a pharmacologically active drug. Prodrug have also been called reversible derivatives and bio reversible derivatives. Recent review concerning rational prodrug design have stressed an interdisciplinary approach involving Hansch correlations, chemistry, biology and clinical pharmaco kinetics.

Prior to embarking on a synthetic prodrug, one should consider the following factors :-

(1) What functional groups on the parent drug molecule are amenable to chemical modification? Molecules containing a alcoholic hydroxyl thiol , amine, carboxylicacids and ketones are customarily utilized for this purpose.
(2) Are synthetic methods available for selectively modifying a particular drug
Molecule ? Many drugs contain a variety of functional groups having similar chemical reactivity toward the modifying intermediate. Advantage may have to be taken of differences in stereochemistry or chemical reactivity of the groups involved.
(3) Are chemical intermediate available at reasonable costs? Drugs are frequently very expensive to produce and further chemical modification can become economically prohibitive if starting materials are expensive. Fortunately, most commonly used intermediates are available at reasonable costs.
(4) Synthesis and purification of the prodrug should ideally be simple synthesis involving many steps ultimately dcrease yields of prodrug and increase yield of side products. Unequivocal one or two steps synthesis permit optimal yield that involves a minimum purification.
(5) The prodrug should be chemically stable in bulk form and compatible with ingredients in the dosages formulation.
(6) Toxicity of the derivative portion of prodrug must be considered.

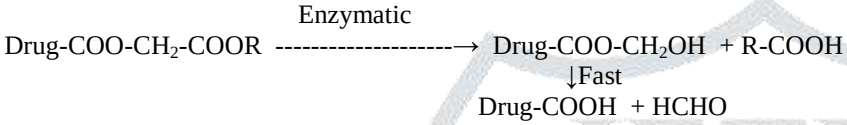
(7) The parent drug molecule must be regenerated from the prodrug in vivo.

Rapid regeneration to the parent drug is essential since the pharmacokinetic behaviour of parent molecule should be maintained as closely as possible. The only difference between the prodrug and parent drug should be the elimination of the undesirable property in question. Thus, situation of this type necessitate a short half-life for prodrug. When one wants increased depot bioavailability or localized drug activity then extended half- life for the prodrug is desirable.

Esters as prodrugs for compounds containing –COOH and –OH groups :

The popularity of using esters as a prodrug type for drugs containing carboxyl or hydroxyl functions stemps primarily from the fact that the organism in rich in enzymes capable of hydrolysing esters. The distribution of esterases is ubiquitous and several types can be found in the blood, liver and other organs or tissues in addition by appropriate esterification of containing –OH or –COOH group, it is fearible to obtain derivatives with almost any desirable hydro-philicity or lipophilicity being dictated by electronic & steeric factor. Accordingly a great number of alcoholic or carboxylic acid drugs have been modified for multitude of reasons using the ester prodrug approach.

Some times, simple aliphatic or aromatic esters may not be sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. This is the case with penicillin esters. Although various simple alkyl and aryl esters of the thizolidine carboxyl group are hydrolysed rapidly to the free penicillin acid in animals such as rodents, they proved to be for too stable in man to have any therapeutic effect. A solution to this problem was found that a special double esters type of benzyl penicillin was hydrolysed rapidly in the blood and tissues of several species including man.



A reason for the different enzymatic stabilities of the acyloxy methyl ester and simple alkoxy esters of penicillin is certainly that the penicillin carboxyl group is highly sterically hindered. The terminal ester in the acyloxy methyl derivatives is less hindered and thus should be more accessible to enzymatic attack. Ampicillin is in completely absorbed after its oral administration. The above principle has been used successfully to improve the oral bioavailability of ampicillin.

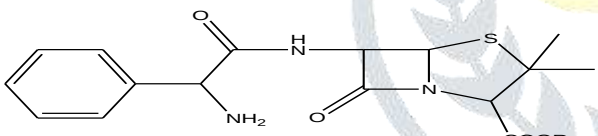
Various prodrug forms of ampicillin are :

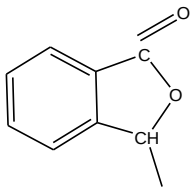
(a) Pivaloyloxy methyl ester. (b) Phthalidyl ester

(c) ethoxy carbonyloxy ethyl ester

(a) $–CH_2-OOC-C(CH_3)_3$ (b) $-CH(CH_3)-OOC-OC_2H_5$

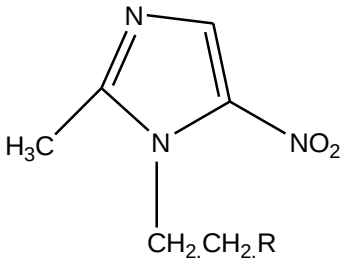
(c)

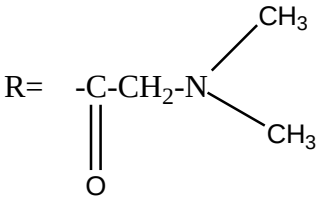




Amino acid esters of metronidazole :

Eight amino acid esters of metronidazole prepared and evaluated for their potentiality as water soluble parentral delivery from the parent drug whose solubility in water is limited (≈ 1% w/v). Hydrochloric salts of the esters exhibited a water solubility greater than 20% w/v but their susceptibility to undergo enzymatic hydrolysis varied rapidly.





Ester	t ½ in plasma mts.
N,n-dimethyglycinate	12
n- propylglycinate	8
3- amino propionate	207
3-dimethyl amino propionate	46
3- dimethyl amino butyrate	334
4- morpholino acetate	30
4- methyl-1- piperzinoacitate	523
Glycinate	41

Due to its facile cleavage in plasma excellent solubility properties (> 50% w/v in water) and case of synthesis and purification the hydrochloride salt of metronidazole N,N-dimethyl glycinate appears to be the most promising prodrug candidate. Following intervenous administration to days the ester was converted rapidly (T1/2=5mr) and completely to metronidazole. A disadvantage of this prodrug is that it is not sufficiently stable for formulation as ready to use a solution and must be used as a formulation to be reconstituted as the solution prior to be use.

Other examples :
Prodrug ester used to improve various properties of parent drug.

Parent drug	Ester type	Route administered	Property modified
Prostaglandin	Glyuride Alkyl Anhydrin	Oral	Increased half life Duration of activity Duration of activity
Clindamycin	Palmitate	Oral	Taste
Gitoxin	Pentaacetate	Oral	GI irritation

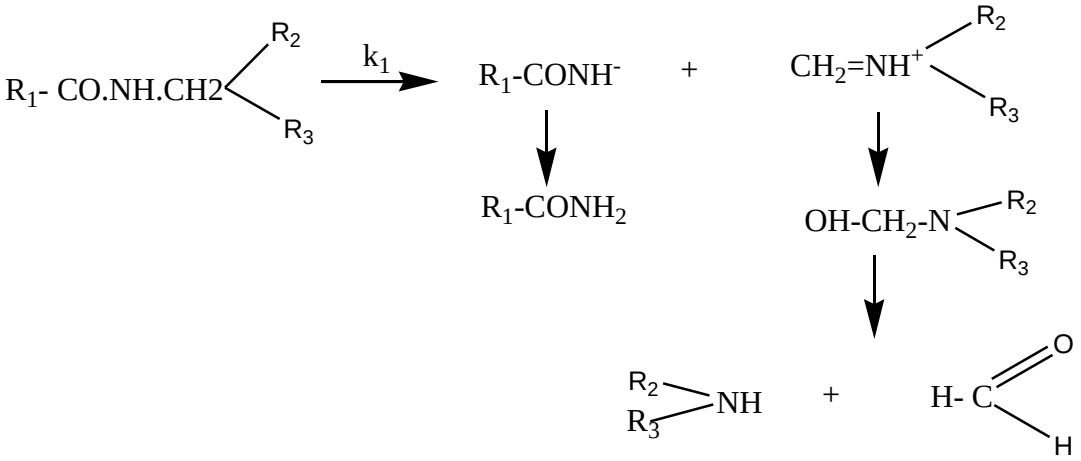
Prodrugs for amides, imides and other NH-acidic compounds -

N-mannich bases have been proposed as potentially useful prodrug candidate for NH-acidic compounds such as various amides, imides carbamate, hydantoins and urea derivatives as well as aliphatic or aromatic amines. They are generally formed by reacting an NH-acidic compounds with formaldehyde and 1 or 2 aliphatic or aromatic amines.

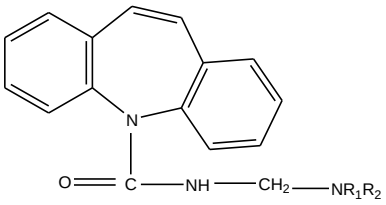
$RCONH_2 + HCHO + R_1.\ R_2.NH = R.CO.NH.CH_2.NR_1R_2 + H_2O$

At constant pH and temperature, the decomposition rate of N-Mannich bases followed strict first order kinetics and all reactions went to completion. The reaction mechanism proposed for the decomposition involves as rate determining step on unimolecular N-C bond cleavage with formation of amide (or imide) anion and an immonium cation.

$R_1\text{-}CONH\text{-}CH_2\text{-}\ NHR_1R_3 = R_1CONH\text{-}CH_2\text{-}NR_2R_3 + H^+$

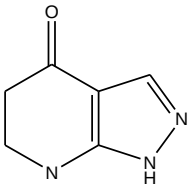


Various N-Mannich bases of carbamazipine have been developed as water-soluble prodrug for parental administration. The solubility of the hydrochloric salts of these n-Mannich bases in water was found to exceed 50% w/v, i.e. more than ten fold greater solubility than following intramascular administration in rats higher and more rapidly appearing carbamazepine plasma levels were observed forms aqueous solutions of the dipropylamino N-Mannich base prodrug than from adminstring of the parent drug.

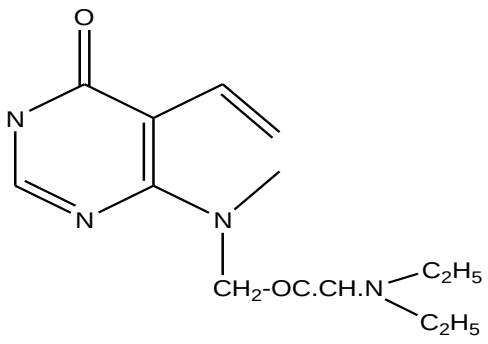


Allopurinol:

This compound is poorly soluble in water (0.05% w/v) and various polar or a polar organic solvents.



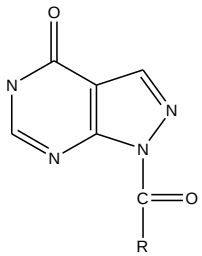
The x-ray interterogram of allopurinol shows a hydrogen bridge between the 1-NH group and 7-N of another molecule while 2-N is bound to the hydrogen of a 5-NH group. The strong crystal lattice energy of allopurinol due to these intermolecular hydrogen bonds which is the reflected in the high m.p. of compound (350^0C), is certainly responsible for the poor solubility behaviour. By blocking the 1-NH, 2-NH or 5-NH groups by N-acyloxy methylation the intermolecular hydrogen bonding is decreased and the water solubility is increased. N-acyloxy methyl derivatives which at the same time are both more lipophilic than allopurinol and passes a higher water solubility. By appropriate selection of the acyl moiety of the prodrug, it is possible to modify greatly the cleavage rate aqueous solubility and lipophilicity and hence delivery characteristics. A prodrug of allopurinol suitable for parental administration with an aqueous solubility greater than 50% w/v.



N-acyloxymethyl compound:

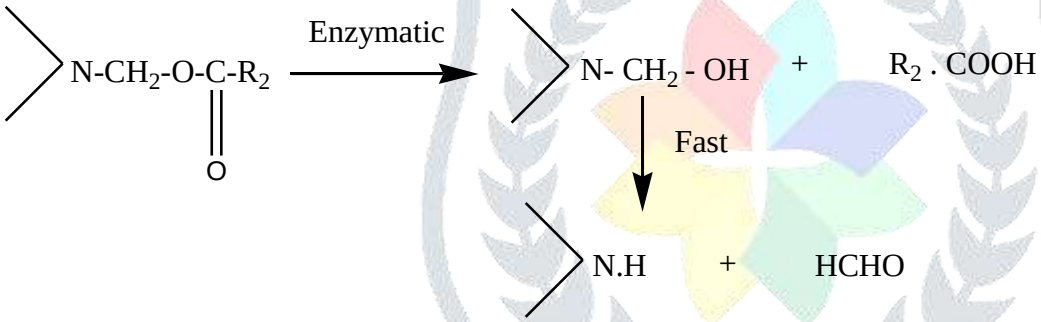
Allopurinol is only very slightly absorbed (<5%) upon rectal administration, and this is most probable due to its low lipophilicity and poor aqueous solubility preliminary experiments in rabbit showed that rectal administration of the N1-acetyl and N1-butyryl derivatives in form of fatty acid suppositories resulted in bioavailability of allopurinol of 20-30%, where as administration is allopurinol it self led to the bioavailability of less than 2%.

Compound	$T_{1/2}$ (Min.)
1-(Acetyl) Allopurinol	6.00
1-(Butyryl) Allopurinol	2.5



Conversion of N-acyloxy methyl derivatives of allopurinol to the NN-acidic (parent) drug takes place via two step reaction.

(i) Enzymatic cleavage of the ester grouping results in the formation of an N-hydroxy alkyl derivatives which subsequently is assumed to decompose instantaneously in the corresponding aldehyde and the NH-acidic drug.



N-acyl derivatives of allopurinol are easily cleaved to the allopurinol in aqueous solutions at physiological pH, the derivatives are susceptible to marked enzyme catalysed hydrolysis by human plasma.

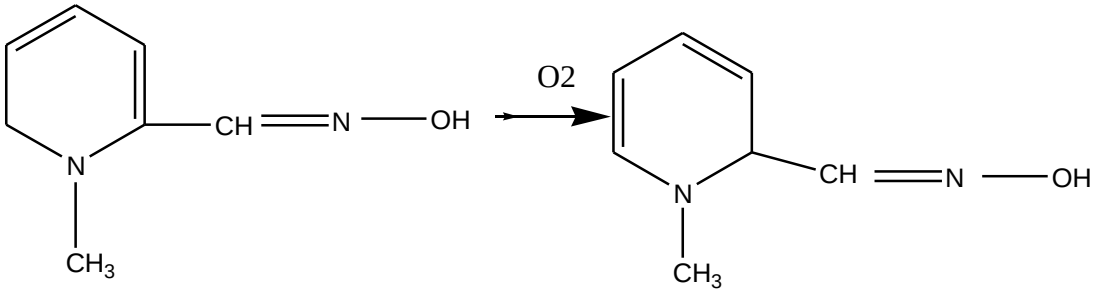
Site-specific drug delivery via prodrug :

Scientists have been attempting to design drugs and drug delivery systems that target drug for particular sites, be they a tissue organ, cell line, enzyme, bacteria or virus etc. with the hope that such site directed or site specific drug delivery would optimize therapy and minimize toxicity. The purpose of this chapter to address in a critical manner, whether prodrug can provide site specific delivery or this targeting of parent active drugs to their site of action. Site specific delivery via prodrug is possible when physicochemical properties of the parent drug and prodrug are optimized in accord with the properties of the target site.

Systematic site-specific transport by altered passive transport :

If drug availability to a site limits its activity, in such a case, a prodrug may be capable of reaching the site improve the effectiveness of the drug one tissue where improve passive permeability can lead to significant advantage in the drug delivery to the brain through blood-brain barrier. Entry of the drug in to cws through BBB is made difficult because unlike systemic capillaries, the endothelial all of CNS capillaries have very tight junctions, and are devoid of inter cellular spaces. The endothelial cells are also relatively void of pincocytotic activity. Therefore the drugs which are capable of entry into other systemic tissues have a greater difficulty entering the CNS. For example- the agent n-mrthyl pyridenium 2-carboldoxime chloride (2-PAM) used in the treatment of organophosphate poisonings by reactivating acetylcholinesterase by the nucliophilic attack of the amine oxygen on the phosphorous of the phosphorylated enzyme is not capable of entering the CNS because of its polarity of a patient has been exposed to an organophosphate poison capable of entering the CNS. CNS deactivated acetyl cholinesterase can not be reactivated by the administration of 2-PAM.

A prodrug of 2-PAM, the corresponding dihydropyridine was synthesised and evaluated. Pro-2PAM is relatively unstable and is oxidised rapidly in vivo (including in the CNS) to 2-PAM.

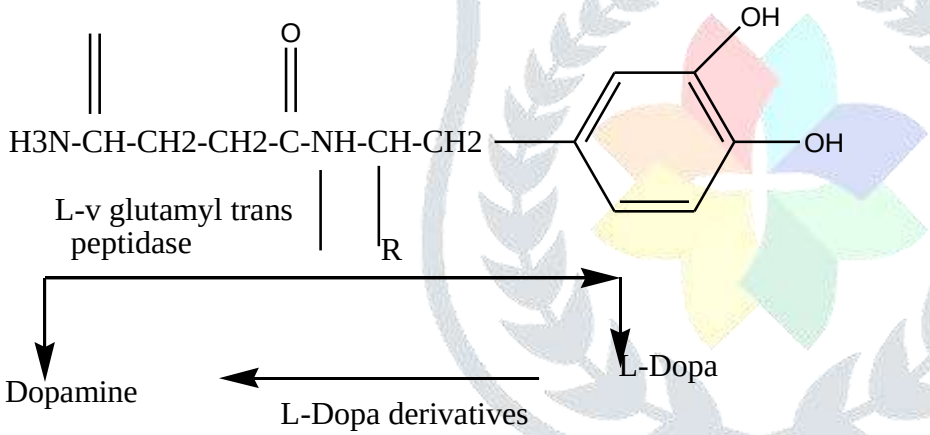


After systemic administration of Pro2-PAM and 2-PAM to mice, 13 times as much 2-PAM was present in mice brains after prodrug treatment compound to 2-PAM treatment. This was confirmed further by the fact that acetyl cholinsterate reactivation in mice brain after the mice had been pre-treated with di-isopropyl flurophosphate was far superior with the prodrug compared to the parent drug.

Enzyme mediated drug-release :

There are some good example of site specific drug delivery where site-specific drug release did play a very important role in achieving the selectivity, one of the best examples has been works on L-r-glutamyl derivatives of various aines and amino acids. L-r-glutymyl transpeptidase is an enzyme that is distributed very selectively through out the body. In particular, it is concentrated in the brush border in the cells of the proximal tubules in the kidney. The enzymes is primarily responsible for the transfer of the L-r-glutamyl group from the terminal end of a peptide to another peptide or amino acid or water. Therefore, it could be argued that the L-r-glutamyl derivative of the amino acid or amine will be selectively cleaved in the proximal tubules releasing a drug selectively in that tissue.

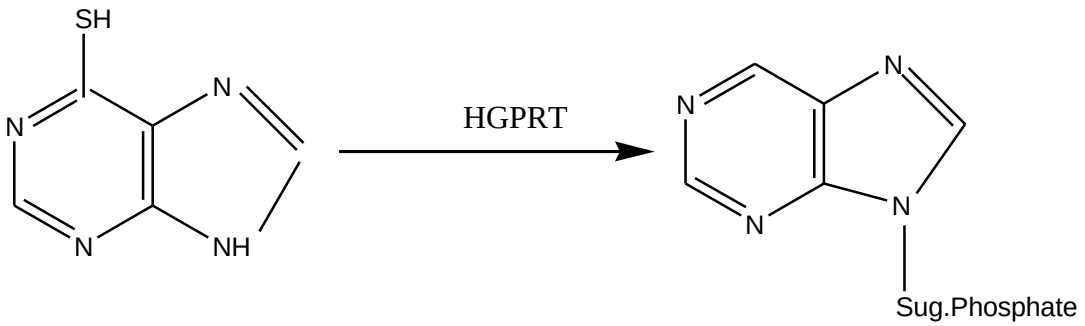
L-r-glutamyl derivatives of L-dopa and dopamine as kidney specific prodrug for the delivery of the renal vaso dilator dopamine. In the case of L-r-glutamyl the prodrug is cleaved slowly on passage through kidney. The dopamine is then metabolised rapidly and excreted into the urine without reentering the systemic circulation, where it could produce adrenergic stimulation of the heart and other side effects. L-r-glutamyl likage by L-r-glutamyl transpeptidase is decarboxylated by dopa decarboxilase, which is also abundant in the kidney.



Prodrug in cancer therapy:

Prodrugs which overcome acquired resistance:

Often the mechanism by which a cell aqueous resistance to a drug is understood it is possible to design a prodrug to overcome this resistance. Thus 6-mercaptopurine like any antipurines and anti pyrimidines, requires intracellular conversion to a nucleotide before it exerts its inhibitory action. 6-mercaptopurine is converted by hypoxanthine guanine phosphoribosyl transferase (HGPRT) to nucleoside mono phosphate, which interferes with all growth by number of mechanism.

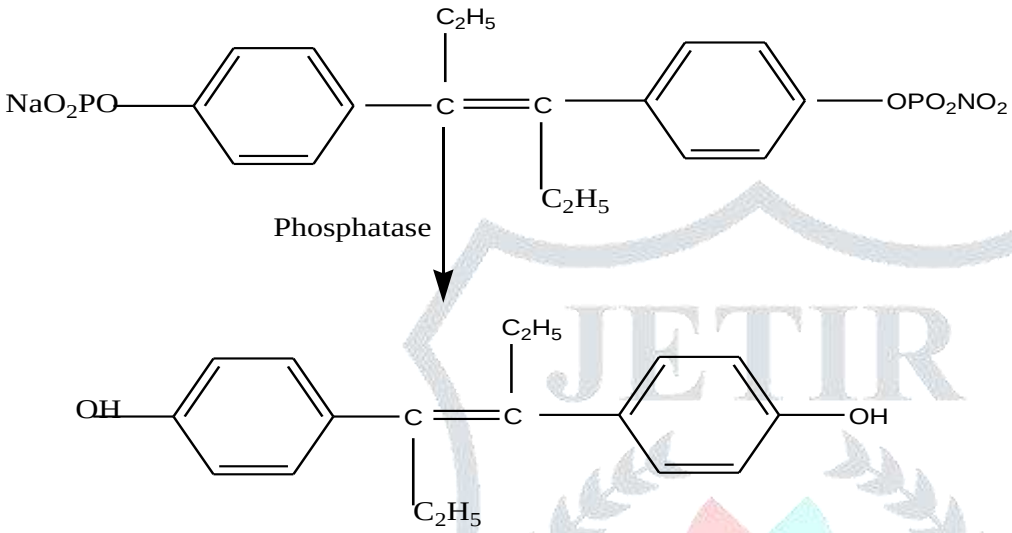


However, some tumours, while initially very responsive to this agent, become resistant due to over growth of cells which have lost the activating HGPRT enzyme. This resistance can not be overcome by using the nucleotide of 6-mercaotopurine since the conised form does not penetrate cells and quickly degraded by extracellular enzyme however the 2' - 0-acyl-f-thioinosine cyclic 3'5' - phosphate is very effective prodrug against cells with acquired resistance to 6-mercaptopurine. The lipophilic product is readily taken up by the resistant cells and is then concerted by phosphodiesterase to 2,-0-acythioinosine and by acylases to thioinosinic acid.

On this example the addition of the 2,-0-acyl group improves drug penetration.

Selective activation in cancer cells:

Many prodrugs have been synthesised which are themselves of low toxicity, but which may be converted enzymatically in tumor cells to an active drug. One of the first example of this approach was the synthesis of the diethylstilbestrol di phosphate. Which releases active diethyl stilbestrol in prostatic cancers high in acid phosphate.



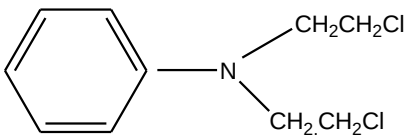
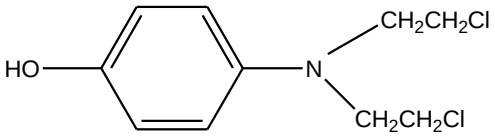
Diethylsilbestrol

Prodrug of nitrogen mustard:

The principal employed in the design of prodrugs activated in tumour cells are best illustrated using the alkylating mustards as example:

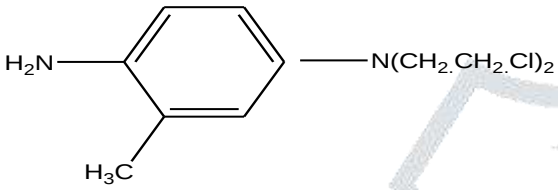
This class of antitumour agents acts by covalent bonding to cellular macromolecules and cases cytotoxicity principally because they cross link DNA. Highly reactive nitrogen mustards are likely to be very toxic and poorly reactive are much less toxic. Examples:

Compound	Alkylating activity K' $80x10^3$	LD_{50} micro mol/kg.
	13.00	367
	48.6	74

Compound	Alkylating activity K $80x\ 10^3$	LD50 umd/Kg
	13.0	367
	48.6	74

Very small changes in the structure eg. P-hydroxilation can greatly alter reactivity and hence toxicity. On this bans prodrugs can be designed which are poor alkylating agent and non-toxic, but which act as substrate for enzymes which transform the highly reactive and cytotoxic agents. Clearly, for there to be selective tumour cell kill. The prodrug must be a good substrate for enzyme under physiological conditions and the enzyme ideally should be present uniquely in the tumour cells, or at least at much higher levels in the tumour than in normal tissues, especially those which are also sencetive to this type of agent. A further prerequisite is that one formed the prodrug, the drug should react immediately and be unable to diffuse from the tumour and reach alkylating agent sensitive tissues.

This should be achieved by ensuring, for eg. That it would be in an inactive from if it diffused from the tumour, or perhaps charged so that it is trapped inside the cell. This approach may be illustrated by the design of prodrug activated by azo-reductase. The hepatocellular carcinoma in humans had azo-reductase levels almost as high as normal hepatocytes. A series of azobenzenes were designed to be activated by this enzyme. The plan was to design an inert prodrug which was a good substrate for the enzyme and which would form an alkylating agent so reactive that any drug diffusing from the tumour cell would hydrolyse or react in blood stream before reaching normal tissue sensitive to this agents. The following compounds are synthesized:



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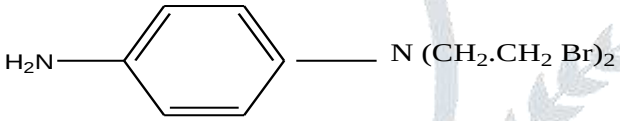

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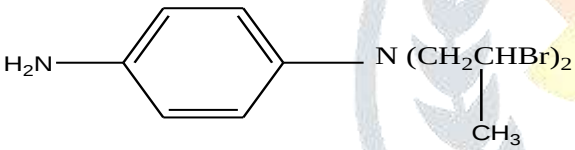

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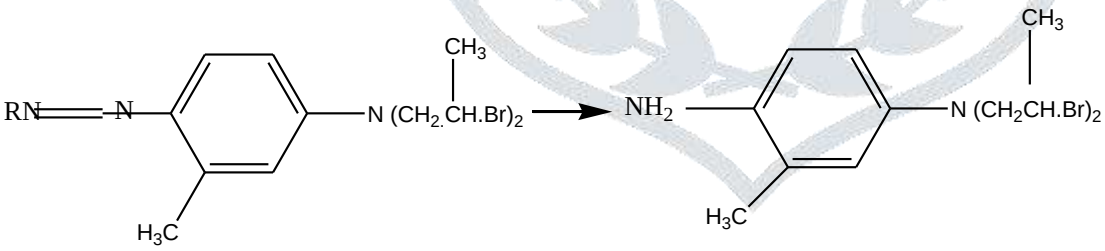
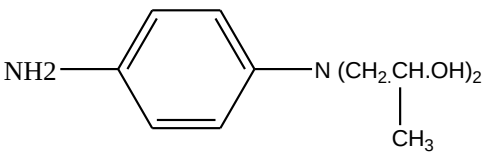


Toxic



Non- Toxic

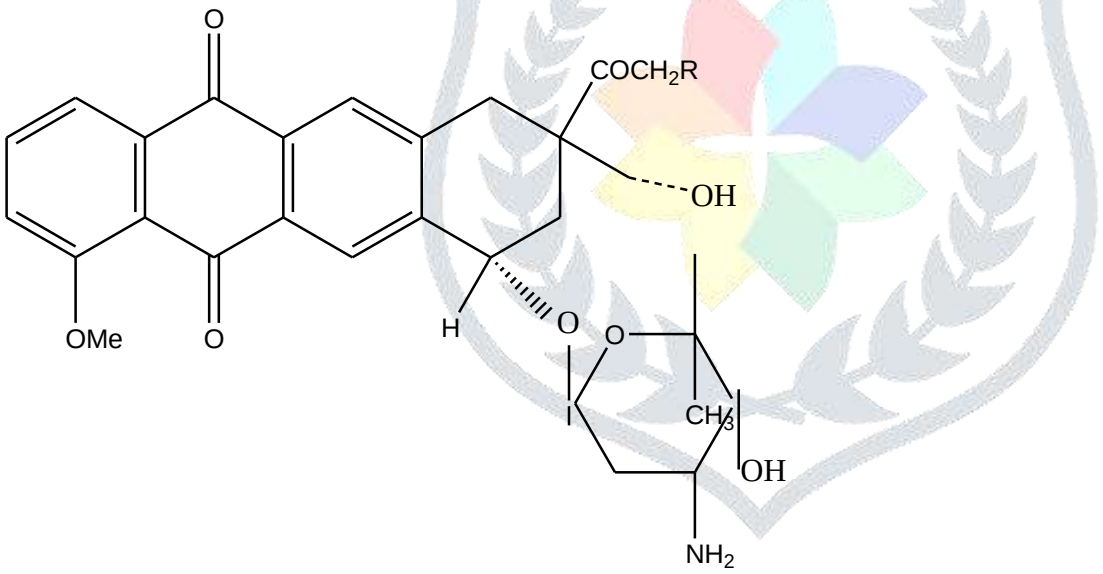
Any active drug diffusing from the normal or malignant hepatocyte will hydrolyse in blood to the innocuous di-2 hydroxy product before reaching other organs.
The reactivity of nitrogen mustards can be increased by replacing the chlorine atoms by bromine and also by inserting a methyl group on a carbon atom carrying the halogen. Both these modifications lead to enhanced alkylating activity. In both normal and malignant hepatocytes the prodrug will be activated normal hepatocytes are relatively resistant to nitrogen mustards and will service doses which are toxic to malignant hepatocytes.

Decreased toxicity and adverse reactions via prodrug:
Prodrugs have been extensively investigated as a means of targeting drugs directly to their site of action consequently minimizing the toxicological effects observed in target tissue. The prodrugs therapeutic index has been taken as a increase of the separation of the drugs therapeutic properties from its clinically limiting toxicological side-effects and as an indication of its potential clinical efficacy.
The simpler converse problem of minizing dug concentrations in particular toxicologically sensitive organs, which maintaining reasonable drug concentrations in other target tissue, seems to fall within the range of what is currently possible using prodrug techniques. Having this considered the delivery of the prodrug to the target tissue, a number of conditions need to satisfied before the drug can finally accomplish its therapeutic role, the drug must be released at a satisfactory rate from the latentiated form. The drug having been released must avoid the pitfall of becoming irretrievably bounds to large biological molecules, such as albumin, within the active organ. Most target organs, for example: The brain, are not homogeneous media and a further degree of location even within the target organ may be necessary before the desired biological effect is elicited.

Leakage from, or metabolism within the target tissue must be slow compared to the rate of release of drug from the prodrug, thus ensuring that the target organ is exposed to the significant concentrations of drug for reasonable period of time. The design of prodrugs which satisfy all the varied criteria noted above cannot be realized easily in a single molecule. Each of the criteria often place conflicting structural demands are the nature of the latentiated form, leading to the need for compromise in the design process. This review documents the search for the optimum position for compounds.

Pepticlyl-latentiated forms of the anthracyclines and related antineoplastic agents with reduced toxicity:

The practical therapeutic use of daunorubicin and doxocarbicin, two antineoplastic drugs of anthracycline family is limited by the cordiotoxic effects produced by these agents. The cordiotoxic effects can be subdivided into acute, sub-acute and chronic depending upon their temporal relationship to the administration of the drugs



The acute effects consists of hypotension tachycardia and arrhythmias and develop with in minutes after i.v. infusion of the drug. The sub-acute effects are characterized by fibrinous pericardities or myocardial dysfunction and occure within weeks of the first or second dose of the drug. The chronic effects become evident only after several weeks months of the treatment and are manifested by the insidious onset of severe, often fatal, congestive heart failure. Peptide prodrug of numerous anti cancer drugs have been investigated in an attempt to increase the selective toxicity towards the malignant cells. Amino acid and dipeptide derivatives of daunorubicin and singled out the L-leucyl daunorubicin as being four times less toxic than daunorubicin, whilst being equipotent with the parent when tested against L1210 leuxemia in mice.

The amino acid di or tripeptide derivatives of daunorubucin were uniformly less toxic than the parent. In general, the hydrophobic amino acids such as alanine and leucine, producd more toxic derivatives than did the more hydrophilic, basic and acidic amino acids. The most promising therapeutic effect, in terms of both anti tumour activity and toxicity was found in a group consisting of the basic amino acids lysine, orginine, ornithine and in particular the 2, 4-diamino butylic acid derivative , all of these derivative being superior to the parent molecule.
These variations in toxicity and therapeutic index of the amino acid derivatives were attributed to the several parameters, namely differences in tissue distribution different rated of cellular uptake and different patterns of intracellular localization.

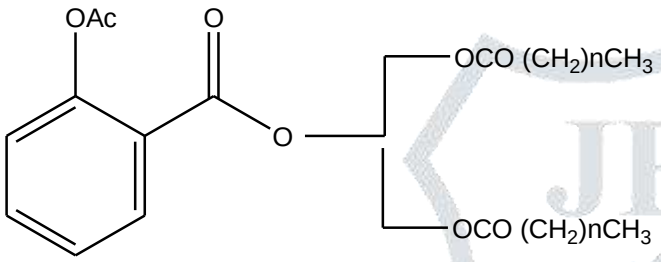
More recently, there has been a resurgence of interest in designing potential site specific anticancer prodrug based on the rationale that tumours that contain high level of some specific enzyme might convert the prodrug to the physiologically active drug in the vicinity of the tumour, resulting in lower drug concentrations at sites of limiting toxicity such as the heart in a case of anthracyclines.

Masked anti-inflammatory agents with reduced gastric irritation:

Despite the enormous amounts of work that has been carried out on the development of anti-inflammatory agents, their clinical usefulness is still restricted by their side effects. The non-steroidal anti-inflammatory drugs (NSAID) are limited by their gastric irritant properties while the steroidal agents, even when applied topically or used in appropriately , can produce an atrophy of the epidermis, steroid acne, stria, suprainfections impaired wound healing purpose and occasionally systemic side effects.

The need for a sefe anti-inflammatory agent remains and consequently the search for a prodrug with reduced toxicity has continued during recent years. The gastric lesions produced by the acidic no steroidal anti-inflammatory agents are produced by two different mechanism on the mucosa and a generalised systemic action which appears after adsorption and can be demonstrated following i.v. administration. The intensity of the mucosal contact effect varies from drug to drug and from drug to prodrug and is not related to the anti-inflammatory activity.

Aspirin , probably the most widely used drug in the world is a potent, effective and low cost analgesic anti-inflammatory agent. However, it produces occult gastrointestinal blood loss in a large percentage of patients. The administration of the aspirin as part of a triglyceride has been investigated by the number of groups . The rationale for the approach was based on the well stablished principles concerning the intestinal absorptions of the natural triglycerides. The actively absorbed species from natural triglycerides are micellar particles composed of 2-monoglycerides, free fatty acids and bile salts. The synthetic triglyceride prodrugs with the anti-inflammatory acid attached at 2position would be absorbed intact, without the intervention of significant quantities of the free gastric irritant anti-inflammatory acid. This hypothesis has now been generally confirmed.



Biological evaluation of the aspirin triglycerides having aspirin in the 2-position and fatty acids of intermediate chain length (C4-C8) in the 1 and 3 positions do not cause gastric lesions and have essentially all the systematic activity associated with aspirin.

Compound		anti-inflammatory activity ED_{25} micro mol/kg.	Unicerogenic UD_{50} micro mol/kg.
Aspirin		498	84
Aspirin triglycerides	a	368	>2562
	b	190	>2562

References

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