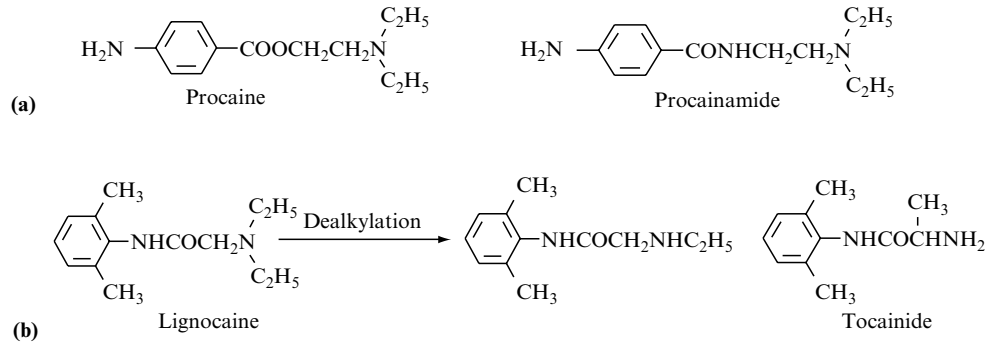


Figure 9.4 Examples of structural modifications causing changes in activity

9.8 Prodrugs

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 (see section 9.8.3).

9.8.1 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 (Figure 9.5).

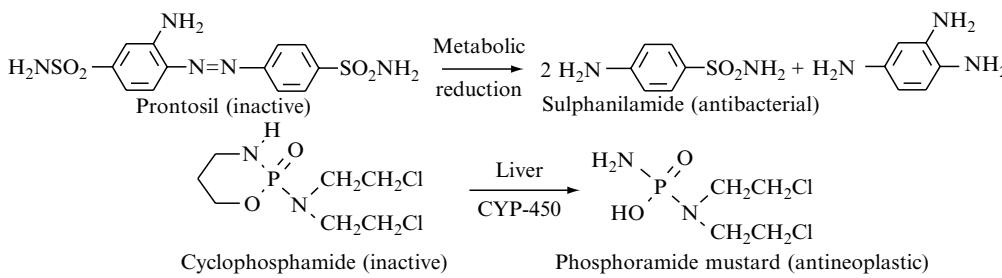


Figure 9.5 Examples of bioprecursor prodrugs

9.8.2 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:

$$\text{Carrier + Active species} \xrightarrow{\text{Synthesis}} \text{Carrier prodrug} \underset{}{\overset{\text{Metabolism}}{\rightleftharpoons}} \text{Carrier + Active species}$$

Carrier prodrugs that consist of the drug linked by a functional group to the carrier are known as **bipartate prodrugs** (Figure 9.6). **Tripartate prodrugs** are those in which the carrier is linked to the drug by a link consisting of a separate structure. In these systems, the carrier is removed by an enzyme controlled metabolic process and the linking structure by either an enzyme system or a chemical reaction.

The choice of functional group used as a metabolic link depends both on the functional groups occurring in the drug molecule (Table 9.5) and the need for the prodrug to be metabolized in the appropriate body compartment.

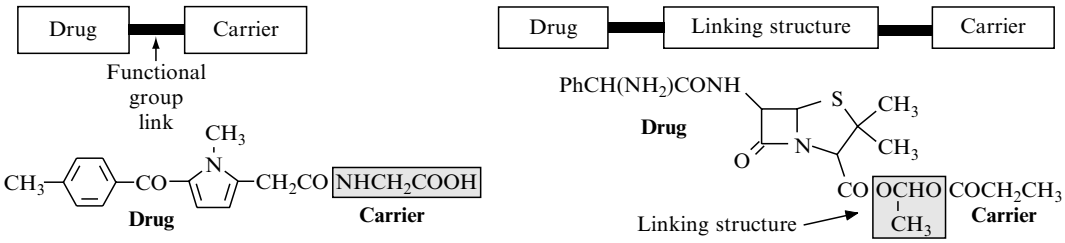
The precise nature of the structure of the carrier used to form a carrier prodrug will depend on the intended outcome (see section 9.8.3).

Table 9.5 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″.

9.8.3 The design of prodrug systems for specific purposes

The introduction of a carrier into the structure of a drug to form a prodrug may be used to change a drug's bioavailability. In some cases has been used to direct the drug to specific areas.



(a) Tolmetin-glycine prodrug

(b) Bacampicillin, a prodrug for ampicillin

Figure 9.6 Examples of (a) bipartate and (b) tripartate prodrug systems

Improving absorption and transport through membranes

The transport of a drug through a membrane depends largely on its relative solubilities in water and lipids (see section 2.7.1). 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 (Table 9.6). 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.

Table 9.6 Examples of the reactions used to improve the lipophilic nature of drugs

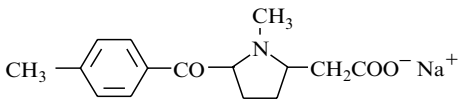
Functional group	Derivative
Acids	an appropriate ester
Alcohols and phenols	an appropriate ester
Aldehydes	acetal
Ketones	acetal (ketal)
Amines	quaternary ammonium derivatives, amino acid peptides and imines

Improving patient acceptance

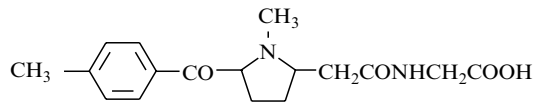
Odour and taste are important aspects of drug administration. A drug with a poor odour or too bitter a taste will be rejected by patients, especially children. Furthermore, a drug that causes pain when administered by injection can have a detrimental effect on a patient. The formation of a carrier prodrug 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.

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



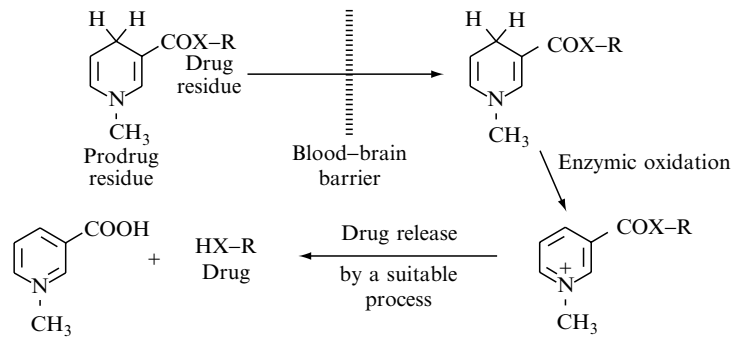
Tolmetin-glycine prodrug

Site specificity

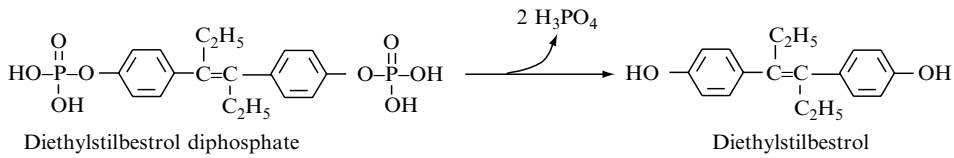
In theory, it should be possible to design a carrier prodrug that would only release the drug in the vicinity of its site of action. Furthermore, once released, the drug should remain mainly in the target area and only slowly migrate to other areas. In addition the carrier should be metabolized to nontoxic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

One area where the site specific carrier prodrug approach has been used with some degree of success is to design drugs capable of crossing the blood–brain barrier (Appendix 11). This barrier will only allow the passage of very lipophilic molecules unless there is an active transport mechanism available for the compound. 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. Carriers based on the dihydropyridine ring system have been found to be particularly useful in this respect. This ring system has been found to have the required lipophilic character for crossing not only the blood–brain barrier but also other membrane barriers. The dihydropyridine system is particularly useful, since it is possible to vary the functional groups attached to the dihydropyridine ring, so that the carrier can be designed to link to a specific drug. 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.



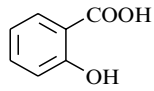
A method of approach followed by some workers is to design prodrugs that are activated by enzymes that are found mainly at the target site. This strategy has been used to design antitumour drugs, since tumours contain higher proportions of phosphatases and peptidases than normal tissues. For example,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



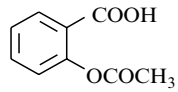
Unfortunately this approach has not been very successful for producing site specific antitumour drugs. However, site specific prodrugs have been developed to deliver drugs to a number of sites.

9.8.3.5 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

9.9 Questions

(1) Explain the significance of each of the members of following pairs of terms: (a) Phase I and Phase II reactions and (b) carrier and bioprecursor prodrugs.

(2) List the main biological factors that could influence drug metabolism. Outline their main effects.

(3) Outline the types of pharmacological activity that a metabolite could exhibit.

(4) Outline, by means of general equations, how conjugation with glycine is used to metabolize aromatic acids. Suggest a chemical reason for the product of this process being readily excreted by the kidney.

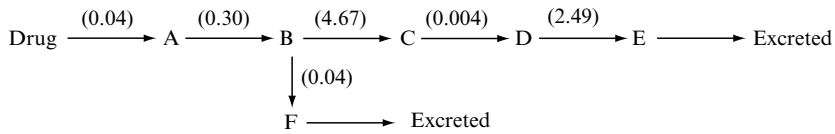
(5) Suggest, by means of chemical equations and/or notes, feasible initial steps for the metabolism of each of the following compounds: (a) pethidine and (b) 4-aminoazobenzene.

(6) (a) What is the desired objective of drug metabolism? How is this normally achieved?

(b) Suggest a series of metabolic reactions that could form a feasible metabolic pathway for N,N-dimethyl aminobenzene.

(*continued*)

(7) The following scheme represents the hypothetical metabolic pathway of a drug. The figures in brackets are the rate constants for the appropriate step.



(a) Explain the significance of the rate constants for the metabolism of the drug to stage B.

(b) What is the significance of the rate constants for the metabolism of B to F and C respectively?

(c) Where is the rate determining step of the series? What is its significance?

(8) Why is it necessary to design drugs with a very rapid rate of metabolism?

(9) Design a prodrug that could be used to transport the diethanoate ester of dopamine (A) across the blood–brain barrier. Show by means of notes and equations how this prodrug would function.