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Prodrug

Introduction

✓The drug gives pharmacologic response by binding with receptor at the site of action.

✓There is a factor that limits its optimum entering into this site is considered as barrier.

✓The barrier can be overcome by chemically linking promoiety to form prodrug which undergoes biotransformation to release the parent drug which gives the pharmacologic response.

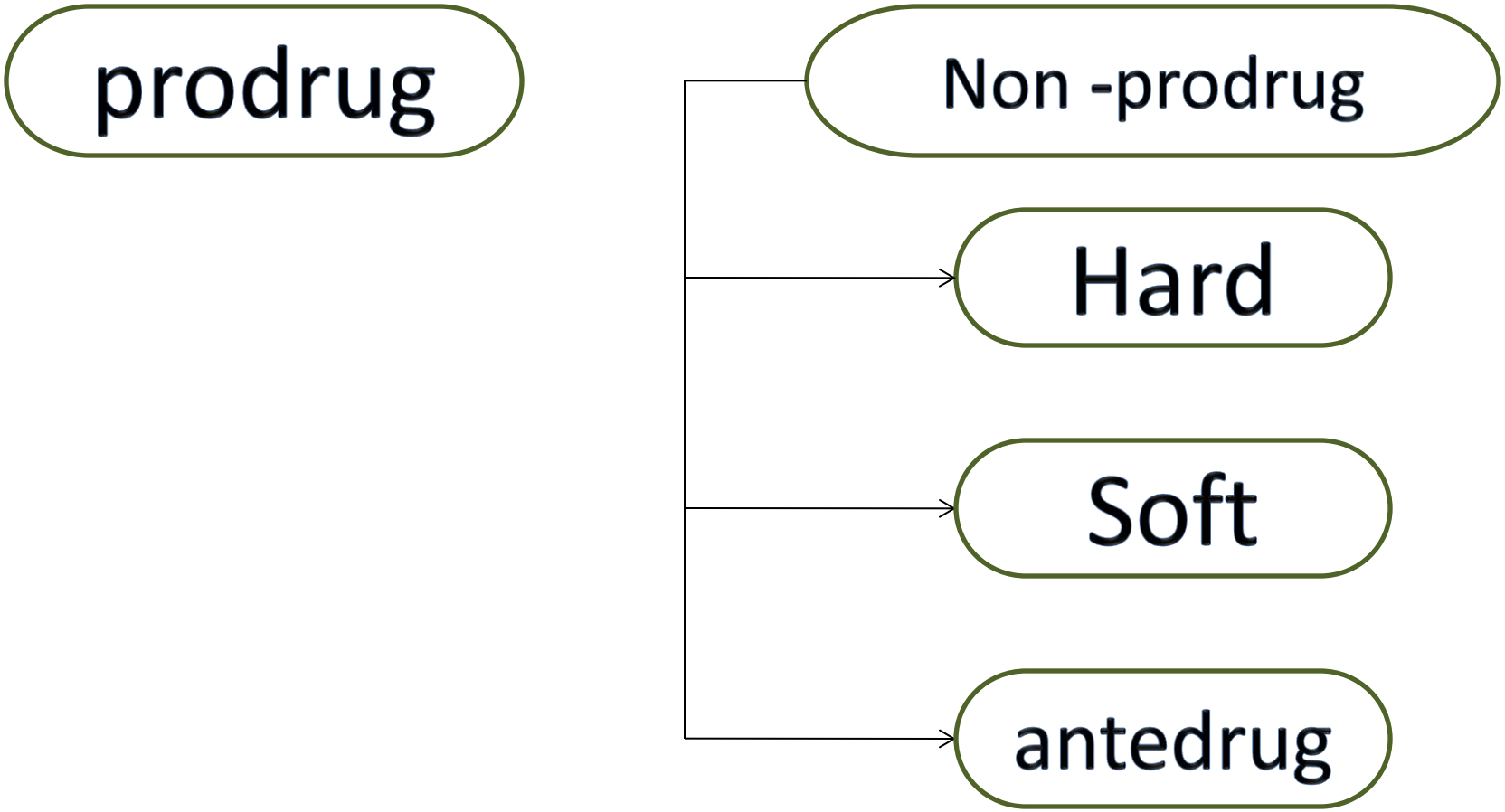
✓The term prodrug was first coined by Albert in1958 .Harper (1959) has promoted this concept by defining the term "DRUG LATENIATION" as the chemical modifications of a biologically activity compound to form a new chemical entity, the prodrug.

✓The drug is only identified as a prodrug after extensive drug metabolism studies ”Serendipity”

✓Currently, 5–7% of the drugs approved worldwide can be classified as prodrugs, and approximately 15% of all new drugs approved in 2001 and 2002 were prodrugs.by:Dr.Ali Gamal Al-kaf-Editorial board member of American Medicinal Chemistry Journal. Associate prof.of Med.Chem.Sana’a Univesity.Faculty of Pharmacy.Medicinal Chemistry Department.

Prodrug

Terms



Prodrug

➢Initial definitions :

prodrug:

a pharmacological inactive compound that is converted to an active drug by a metabolic biotransformation.

✓"Soft Drugs" : These are the ***opposite*** of prodrugs. These compounds are designed and synthesized as ACTIVE compounds that readily undergo metabolic inactivation to nontoxic products.

Ex: Insulin.

✓"Hard Drugs" : compounds having high lipid solubility or high water solubility having long biological half-life and not susceptible to metabolism.

Due to their avoiding to metabolism, they have high efficiency but less readily eliminated due to lack of metabolism.

Ex: . Cocaine and heroin.

✓"Antedrug":compounds that are designed and synthesized to exert their pharmacological activity "**locally**" and when enter the systemic circulation must to be susceptible to metabolic or chemical transformation to inactive compound

(e g steroidal drug that used topically to treat some allergic condition)

Prodrug

Classification of prodrugs

Type	Converting site	Subtype	Tissue location of conversion	Examples
Type I	Intracellular		Therapeutic target tissues/cells	Zidovudine, 5-Flurouracil
Type I	Intracellular	Type IB	Metabolic tissues (liver/lung etc)	Captopril, Cyclophosphamide
Type II	Extracellular	Type IIA	GI fluid	Sulfasalazine, Loperamide oxide
Type II	Extracellular	Type IIB	Systemic circulation	Fosphenytoin, Bambuterol

Prodrug

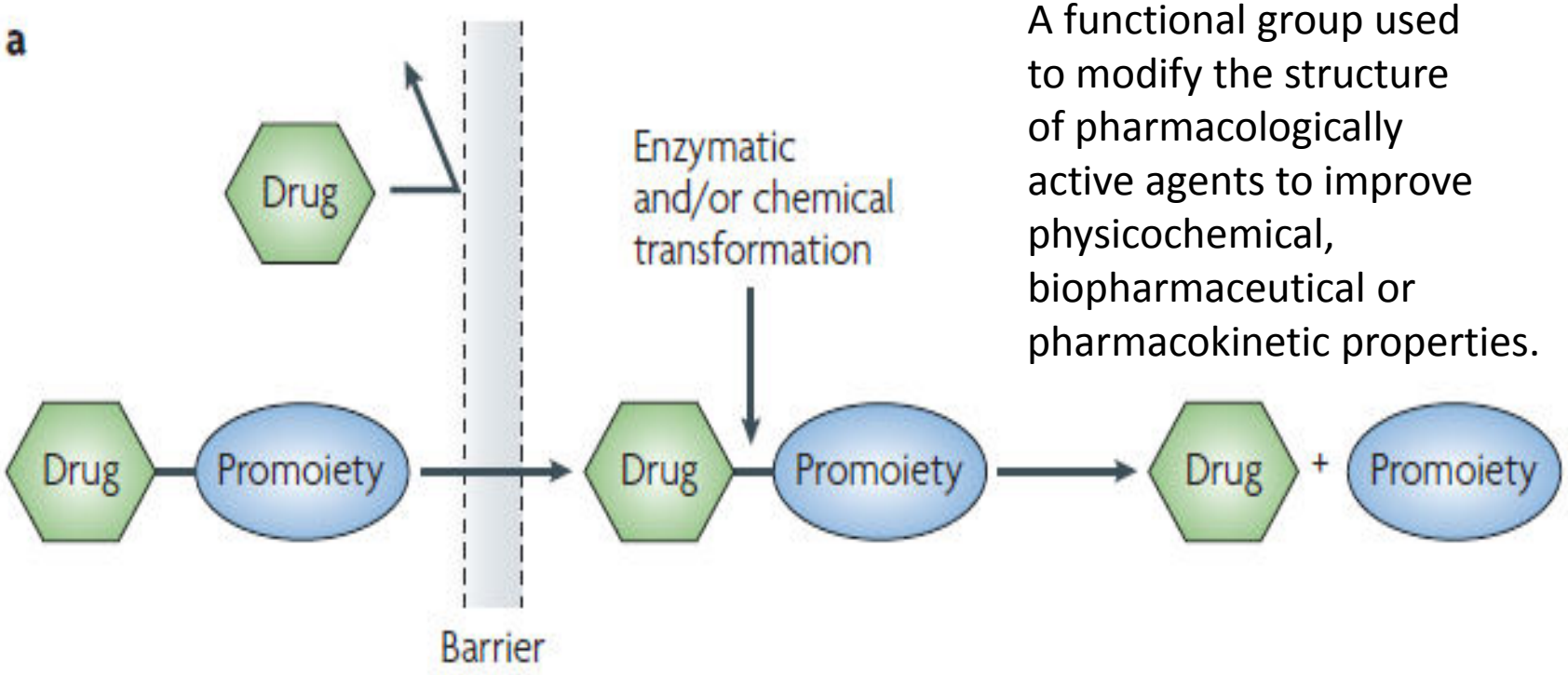
➢Why use prodrugs?

Prodrugs are used when drugs have unattractive physicochemical properties ((undesirable properties)).

1. Poor aqueous solubility.
2. Low lipophilicity.
3. Chemical instability.
4. poor patient acceptability.
5. formulation problems.
6. Good substrate for first-pass metabolism.
7. Rapid absorption/excretion.
8. Not site-specific.
9. Pain at the site of injection.

Prodrug

Prodrug Concept



Promoiety
A functional group used to modify the structure of pharmacologically active agents to improve physicochemical, biopharmaceutical or pharmacokinetic properties.

- The drug–promoiety is the prodrug that is typically pharmacologically inactive.
- limitation of a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic performance.
- The drug and promoiety are covalently linked via bioreversible groups that are chemically or enzymatically labile,

Prodrug

Ideal Property Of Prodrug:

1) The prodrug should be less toxic than the drug.

2) The pordrug should be inactive or significantly less active than the parant drug.

3) The rate formation of drug from the prodrug should be rapid enough to maintain the drug' conc. With its therapeutic window.
4) The metabolites from the carrier should be non-toxic or have a low degree of toxicity.

5) The prodrug should be site specific.

Prodrug

Limitation Of Prodrug:

The problem associated with prodrug design is its toxicity which is due to :

·Formation of unexpected metabolite from the total drug conjugates.

·Toxicity may be due to inert carrier generated by cleavage of promoiety and drug conjugate which is converted into toxic metabolite.

·The prodrug might consume a vital cell constituent such as glutathione during its activation stage which causes depletion of prodrug.

Prodrug

TYPES OF PRORDUG

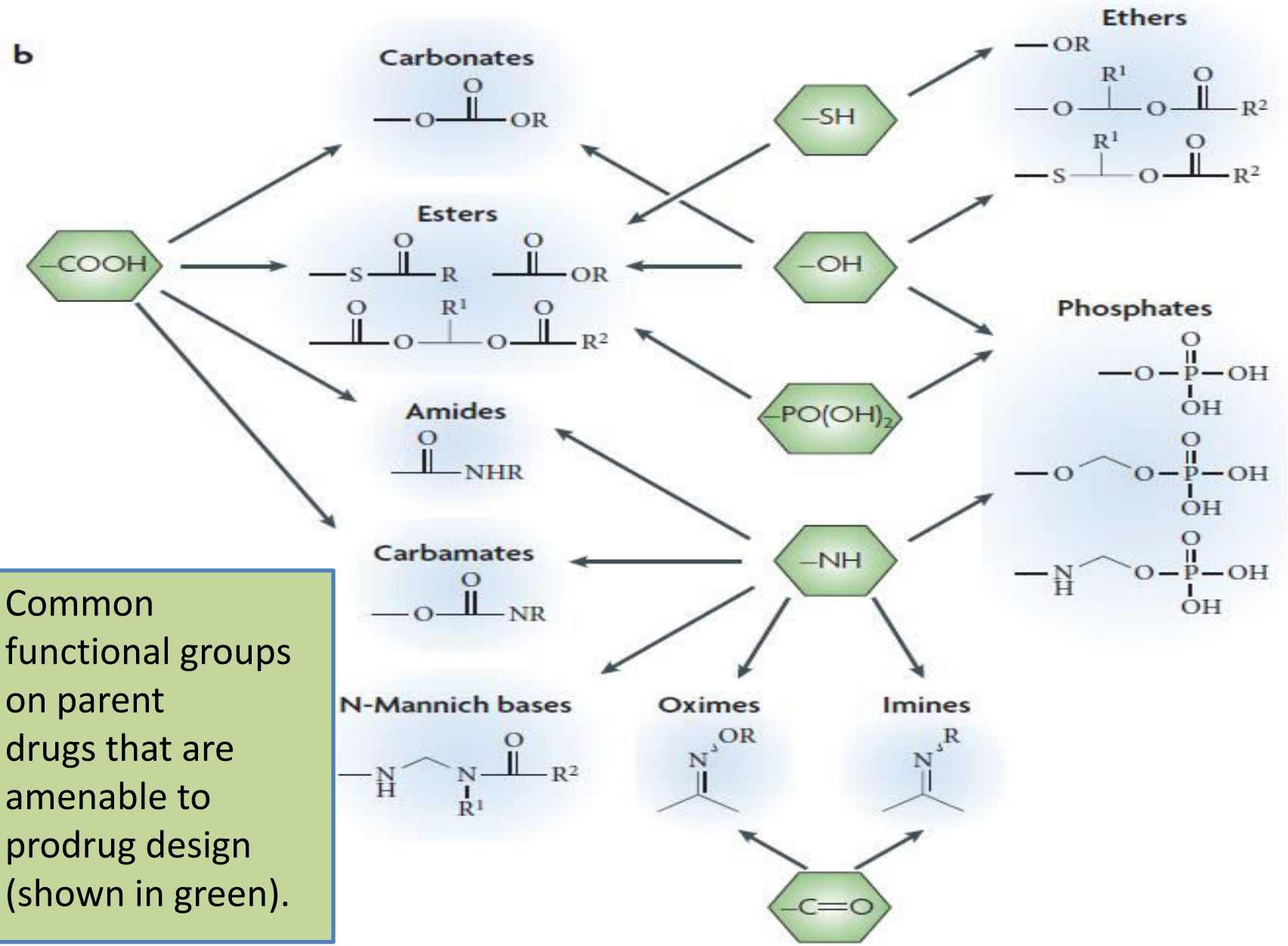
Promeioty
Carrier linked prodrug

Mutual prodrug

Bioprecursors

Prodrug

promoiety Prodrugs according to functional groups:



Common functional groups on parent drugs that are amenable to prodrug design (shown in green).

Prodrug

Related definitions

- **Double Prodrug or pro-prodrug :**

The double prodrug is a biologically inactive molecule which is transformed in vivo in two steps(enzymatically or chemically) to the active species.

- Carrier linked prodrug subdivided into:

A. **bipartate :** in which the parent drug is attached to directly to promoiety.

comprised of one carrier attached to drug.

B. **tripartite prodrug :** there is a connector group between drug molecule and promoiety .

carrier connected to a linker that is connected to drugs.

Prodrug

Ideal Drug Carriers

- Protect the drug until it reaches the site of action.
- Localize the drug at the site of action.
- Minimize host toxicity.
- Are biodegradable, inert, and nonimmunogenic.
- Are easily prepared and inexpensive.
- Are stable in the dosage form.

Prodrug

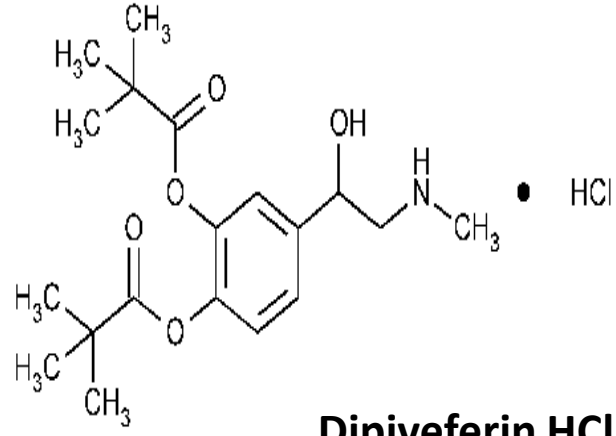
- **Examples :**

Carboxylic acid and alcohols :

a) Dipiveferin HCL :

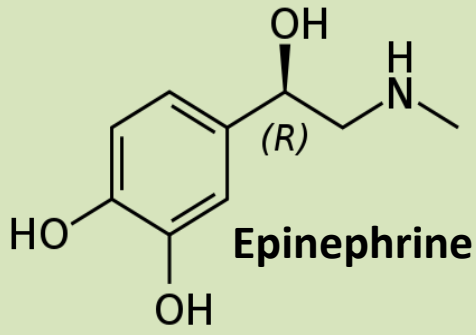
Dipivefrin HCL is a prodrug of epinephrine formed by the diesterification of epinephrine and pivalic acid.

The agent of use in the treatment of open angle glaucoma . the increased lipophilicity relative to epinephrine allows the agent to move across the membrane of the eye easily when applied .

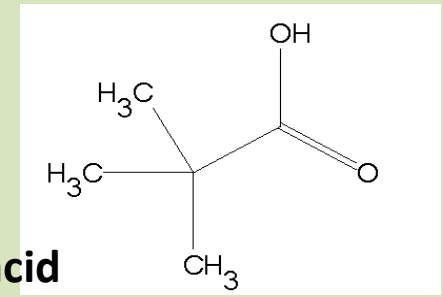


Dipiveferin HCl

Esterase



Epinephrine



Pivalic acid

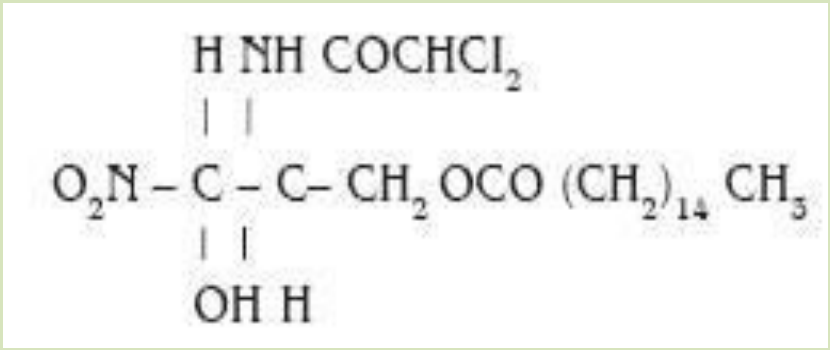
Prodrug

- **Examples :**

Carboxylic acid and alcohols :

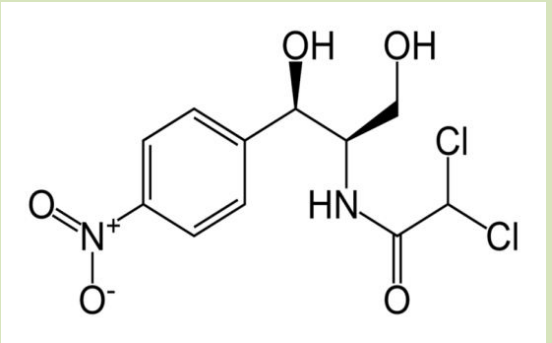
b) chloramphenicol palmitate :

A prodrug with reduced water solubility, The hydrophopic palmitate ester dose not dissolve to any appreciable extent in the mouth and therefore dose not interact with taste receptors.

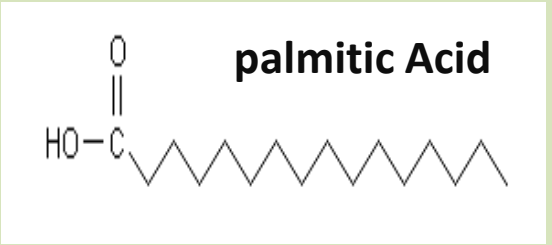


chloramphenicol palmitate

Esterase



chloramphenicol +



Prodrug

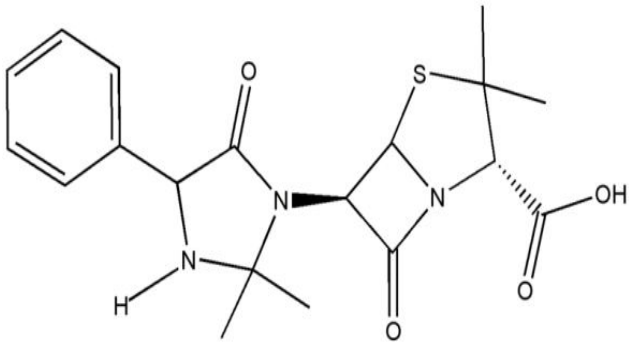
- **Examples :**

Amines

Hetacillin :

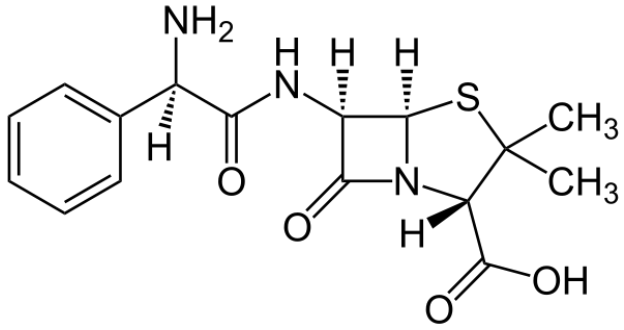
Hetacillin is a beta-lactam. Hetacillin is a activity, but is converted by the body to ampicillin, which is active against a variety of organisms.

The effect of forming the Mannich base is to lower the basicity of the amine and there by icrease lipophilicity and absorption .

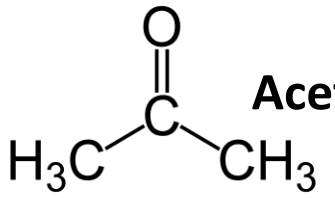


Hetacillin

water



ampicillin



Acetone

Prodrug

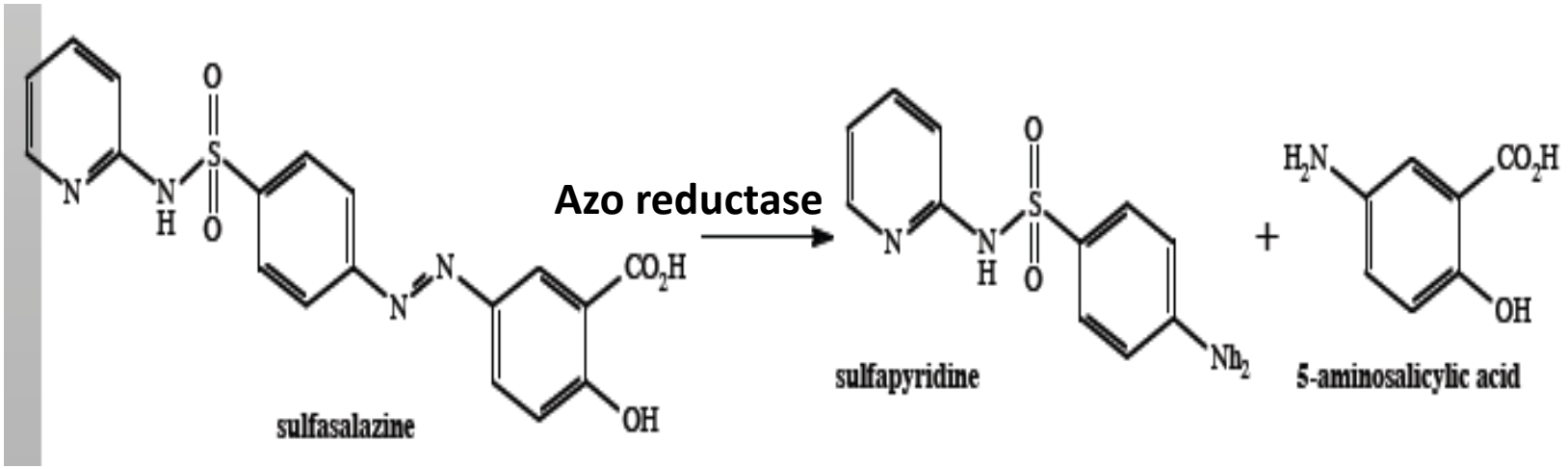
- **Examples :**

Azo linkage

Sulfasalazine :

is used in the treatment of *inflammatory bowel disease (ulcerative* colitis).

- Anaerobic bacteria in the lower bowel metabolically reduce sulfasalazine to the therapeutic agent **5-aminosalicylic acid.**



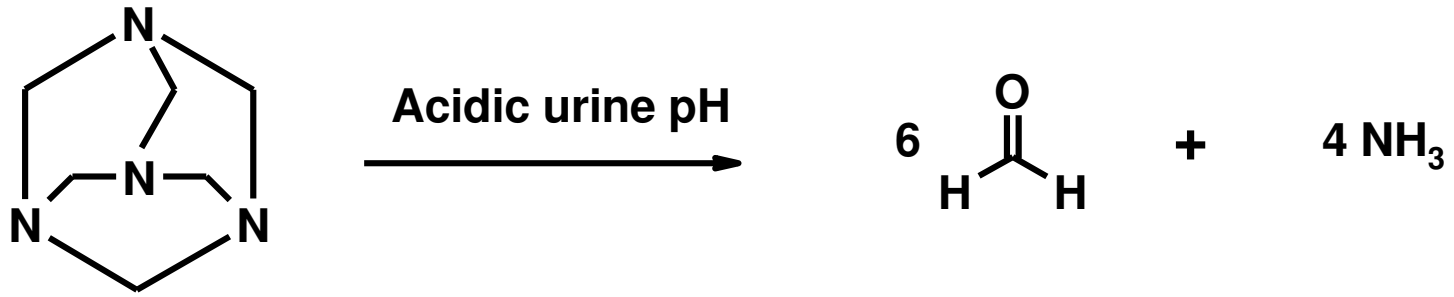
Prodrug

- **Examples :**

Carbonyl compounds

Methenamine :

Methanamine is prodrug in acidic pH , methamine is converted to formaldehyde , which act as an antibacterial agent.



Prodrug

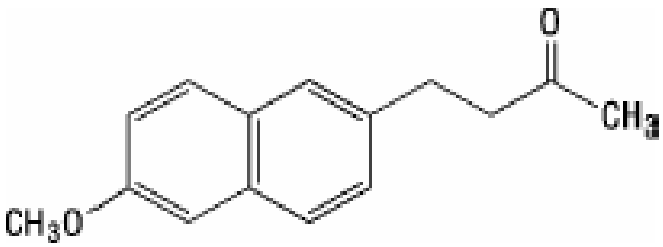
- **Examples :**

Bioprecursor Prodrug

Which result from a molecular modification of the active compound itself. This modification generates a new compound, which acts as a substrates for the metabolizing enzymes, and metabolite being the expected active agent.

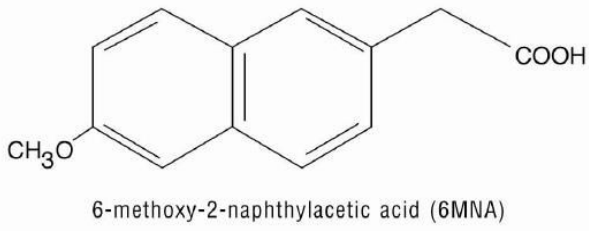
Nabumetone : (NSAID) (Relafen) prodrug that requires oxidative activation.

Nabumetone contains no acidic functionality and passes through the stomch without producing the irritation normally associated with this class agent .subsequent absorption occurs in the intestines.



Nabumetone

oxidation



Active Form

Prodrug

- **Examples :**

Bioprecursor Prodrug

Mitomycine C: Mutamycin® **(antineoplastic agent)** prodrug that requires Reduction of the **quinone to hydroquinone.**

✓is a potent DNA crosslinker. This crosslink has shown to be effective in killing bacteria.

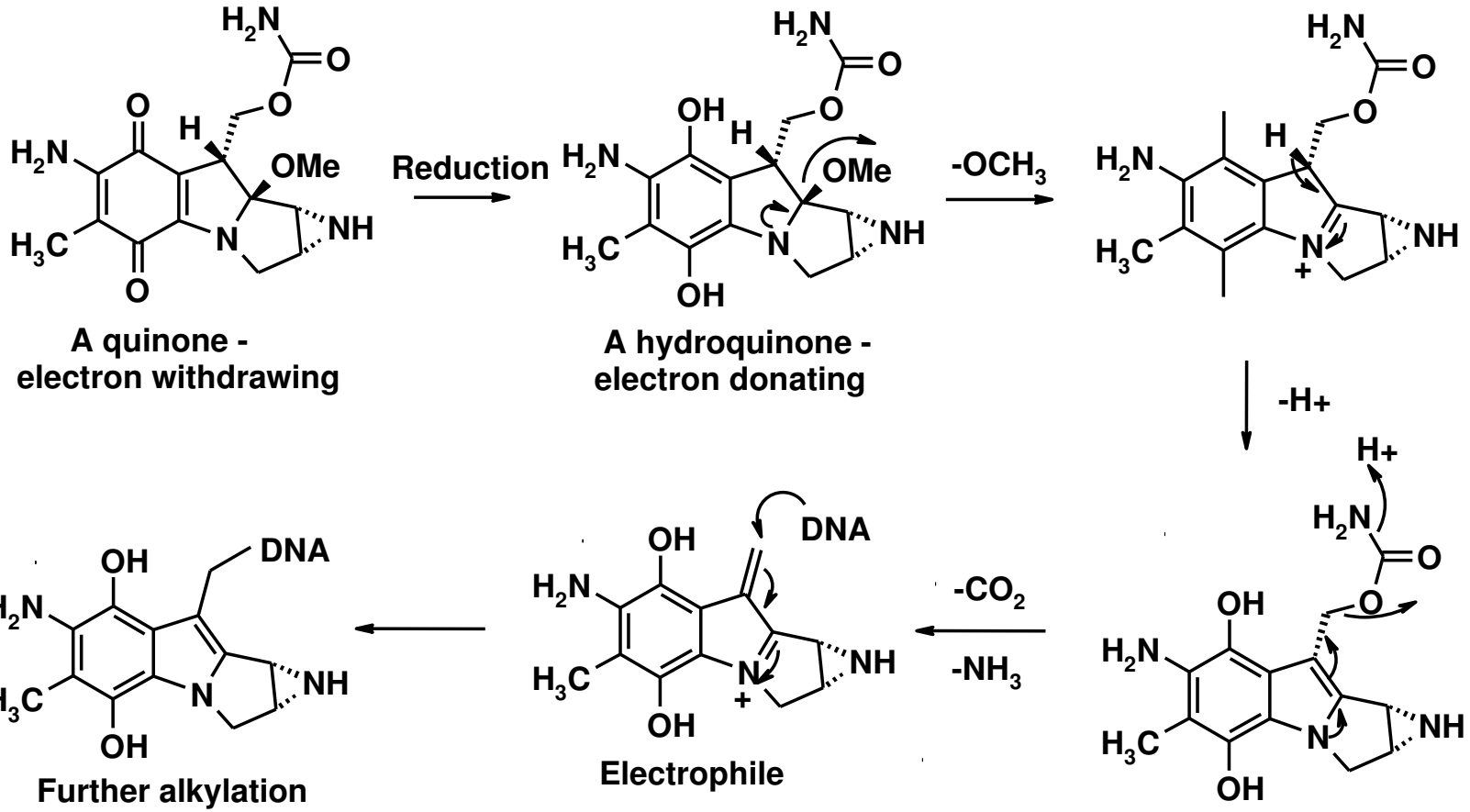
✓**Mitomycine C required a** reductive activation followed by two N-alkylations specific for a guanine nucleoside. Potential bis-alkylating heterocylic quinones were synthetised in order to explore the antitumoral activities of bacteria.

Prodrug

- **Examples :**

Bioprecursor Prodrug

Mitomycine C: Mutamycin® **(antineoplastic agent)** prodrug that requires Reduction of the **quinone to hydroquinone.**



Prodrug

- **Examples :**

Bioprecursor Prodrug

Vidarabine : (antiviral agent) prodrug that requires phosphorylation.

✓works by interfering with the synthesis of viral DNA.

✓vidarabine is sequentially phosphorylated by kinases to the triphosphate ara-ATP ((active form)). This active form is both an inhibitor and a substrate of viral DNA polymerase.

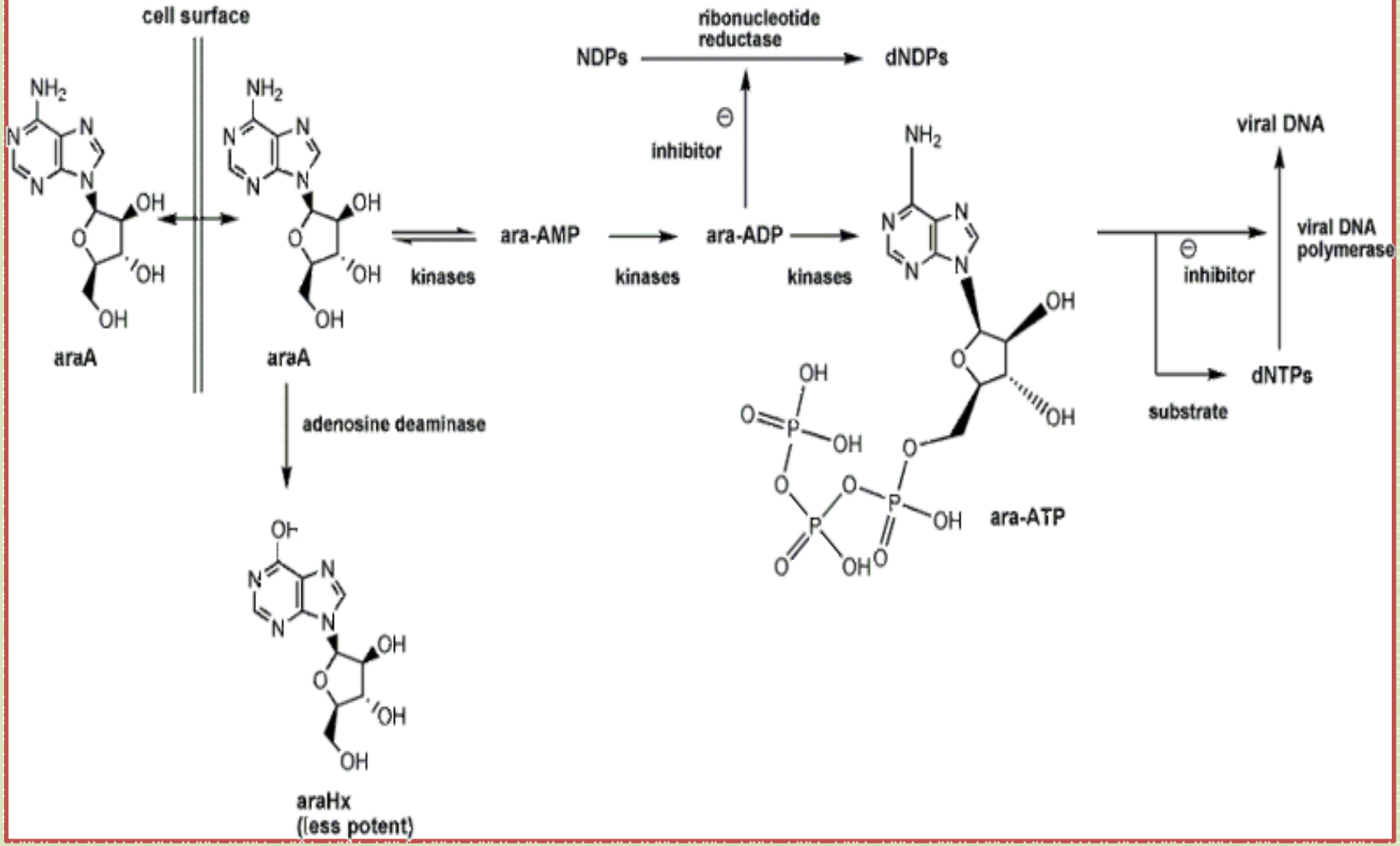
✓ara-ATP competitively inhibits dATP leading to the formation of 'faulty' viral DNA.

Prodrug

- **Examples :**

Bioprecursor Prodrug

Vidarabine : (antiviral agent) prodrug that requires phosphorylation.



- **Examples :**

Mutual Prodrug

Prodrug comprises of two pharmacologically active agents coupled together to form a single molecules such that each act as the carrier for the other prodrug of two active compounds are called as mutual prodrug.

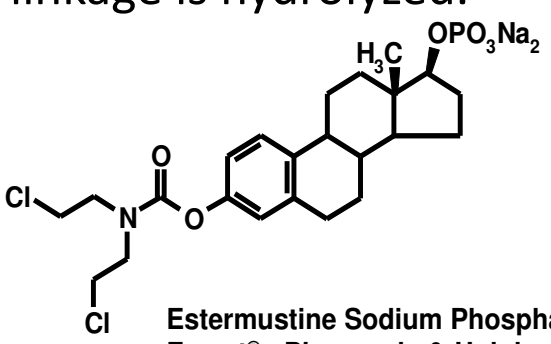
- **Examples :**

Mutual Prodrug

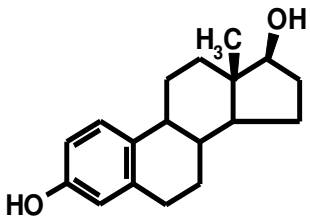
Estramustine:

✓**Used for the** treatment of progressive carcinoma of the prostate.

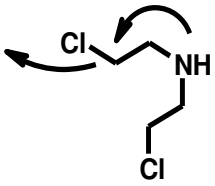
✓Prodrug is selectively taken up into estrogen receptor positive cells then linkage is hydrolyzed.



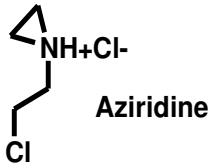
Estermustine Sodium Phosphate
Emcyt® - Pharmacia & Upjohn



Sodium phosphate
and
Carbon dioxide



Nornitrogen mustard



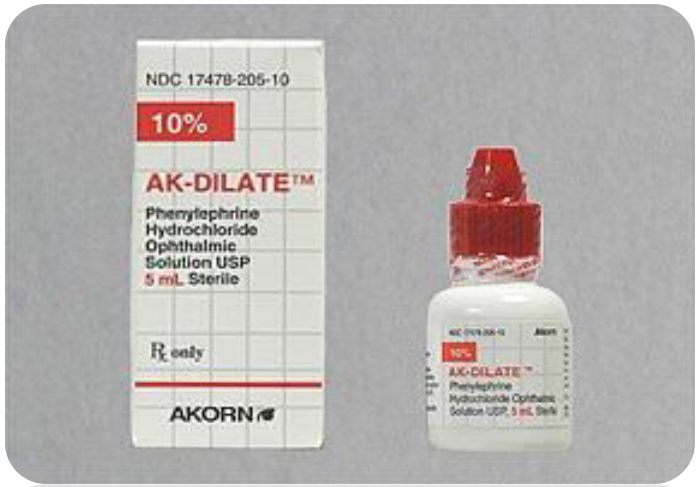
Aziridine

Actual alkylating species

17-alphaestradiol slow prostate cell growth

Nornitrogen mustard is a weak alkylating agent

Prodrug



DIPIVEFRIN HCl 0.1%, Alcon® ophthalmic solution

KLORAN is packed in tins of 1000 capsules. KLORAN suspension is available in a glass jar of 60ml.

KLORAN SUSPENSION contains 125mg of Chloramphenicol Palmitate.

Hetacin-K

Relafen ®

Prodrug

Mandelamine ®

(methenamine)

Sultamicillin ®

(Sultamacillin)

Prodrug

APPLICATIONS

(a) PHARMACEUTICAL APPLICATIONS

- Improvement of taste.

Ex: Parent drug	prodrug
Chloramphenicol	Palmitate ester

- Improvement of odor.

e .g; Ethyl mercaptan which is a foul smelling liquid, is converted in to its drug ester ,which has higher b.p. and odorless

- Reduction of pain on injection.

E.g. the low aqueous solubility of clindamycin Hcl is responsible for pain on injection. This can be overcome by use of more water soluble prodrugs of such agents. E.g. 2-phosphate ester of clindamycin

- Enhancement of drug solubility and dissolution rate (hydrophilicity of drug)
- Enhancement of chemical stability of drug.

Ex: Formaldehyde is used as prodrug ((methenamine)) in the form of enteric coated to prevent hydrolysis in the stomach. ((urinary tract antiseptic)).

Prodrug

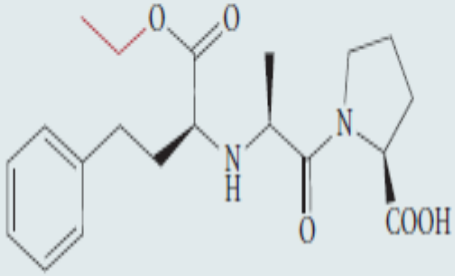
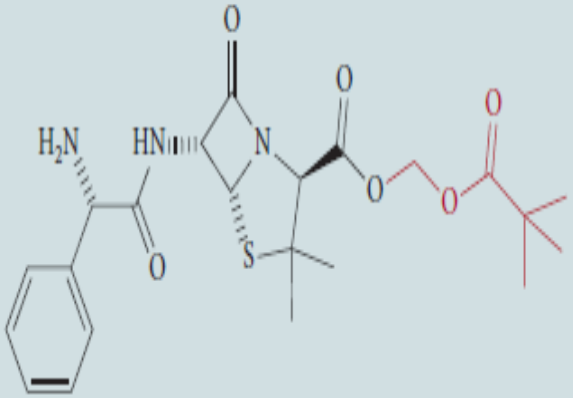
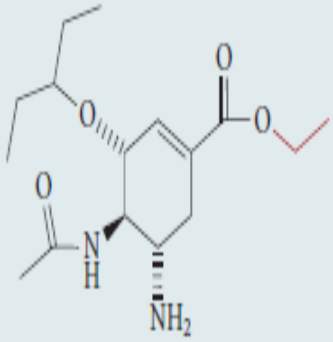
(b) PHARMACOKINETIC APPLICATIONS

- Enhancement of bioavailability (lipophilicity).
- Prevention of presystemic metabolism.
- Prolongation of duration of action.
- Reduction of toxicity.
- site-specific drug delivery (drug targeting).

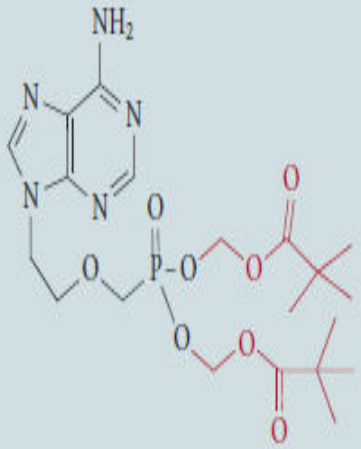
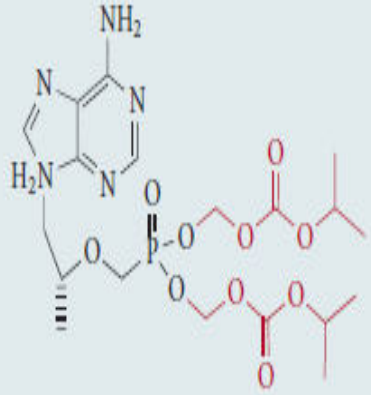
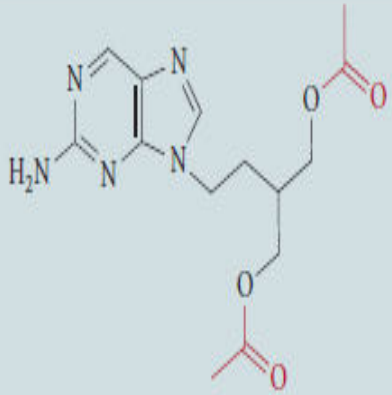
Examples of Prodrugs for improved lipophilicity or permeability

Prodrug

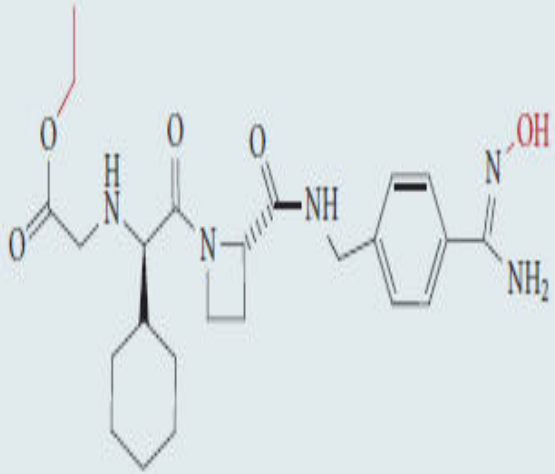
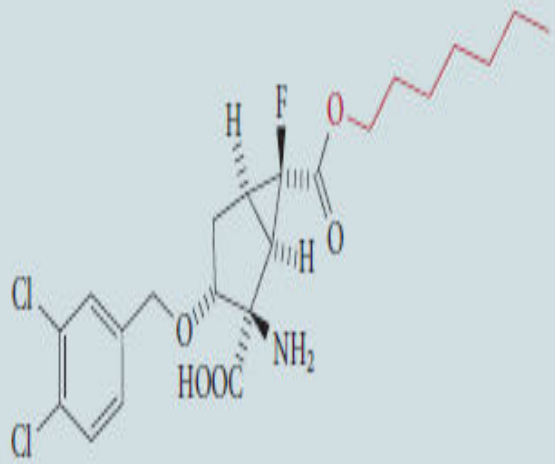
Table 1 | **Prodrugs for improved lipophilicity or permeability**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Enalapril (angiotensin-converting enzyme inhibitor)	Monoethyl ester of enalaprilat		• Bioconversion by esterases • The oral bioavailability of enalaprilat in humans is 36–44% • 53–74% of the administered dose is absorbed[3,172]
Pivampicillin (β-lactam antibiotic)	Pivaloylmethyl ester of ampicillin		• Bioconversion by esterases • The oral bioavailability of 32–55% for ampicillin increased to 87–94% for pivampicillin[173,174]
Oseltamivir (anti-influenza)	Ethyl ester of oseltamivir carboxylate		• Bioconversion by esterases • The oral bioavailability of less than 5% in rat and marmoset for oseltamivir carboxylate increased to 80% for oseltamivir in humans[80–82]

Prodrug

Adefovir dipivoxil (antiviral)	Bis-(pivaloyloxy-methyl) ester of adefovir		• Bioconversion by esterases and phosphodiesterases • The oral bioavailability of ~10% for adefovir increased to 30–45% for adefovir dipivoxil[78,79]
Tenofovir disoproxil (antiviral)	Bis-(isopropyloxy-carbonyloxymethyl) ester of tenofovir		• Bioconversion by esterases and phosphodiesterases • The oral bioavailability of tenofovir from tenofovir disoproxil is 39% in the fed state[74,76,77]
Famciclovir (antiviral)	Dimethyl ester of penciclovir		• Bioconversion by esterases and oxidation from purine to guanide • The oral bioavailability of 4% for penciclovir increased to 75% for famciclovir[175–177]

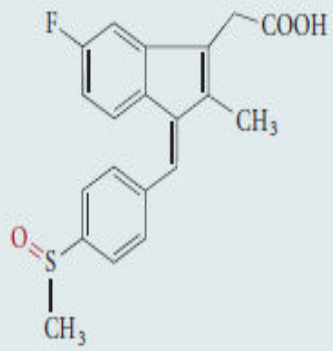
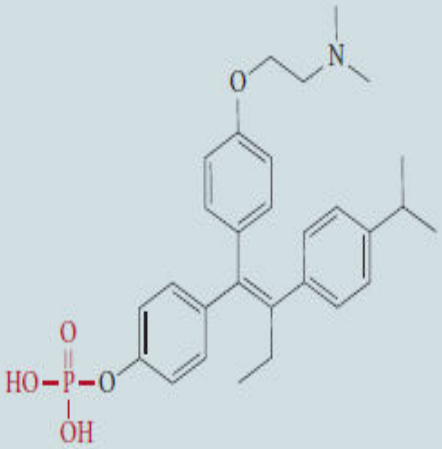
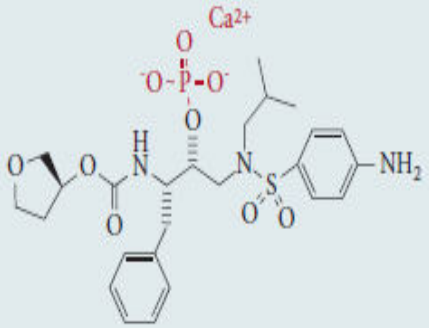
Prodrug

Ximelagatran (anticoagulant)	Hydroxyamidine and ethyl ester of melagatran		• Bioconversion by esterases and reductive enzymes • The oral bioavailability of 3–7% for melagatran increased to 20% for ximelagatran[84,86]
MGS0210 (glutamate receptor (MGLUR2) antagonist)	n-Heptyl ester of MGS0039		• Bioconversion by esterases • The oral bioavailability of less than 13% for MGS0039 in monkeys increased to 44% for MGS0210 in monkeys[41,50]

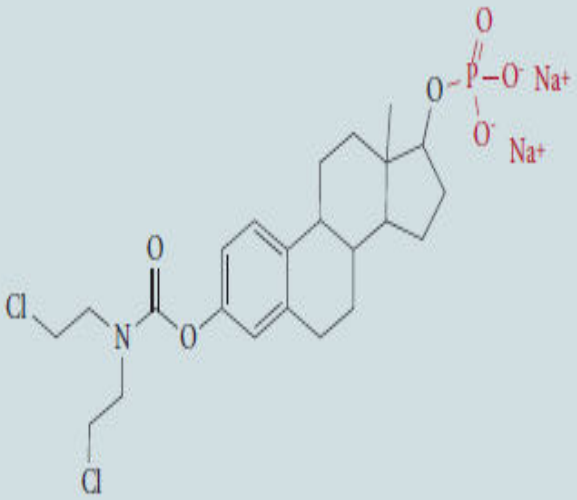
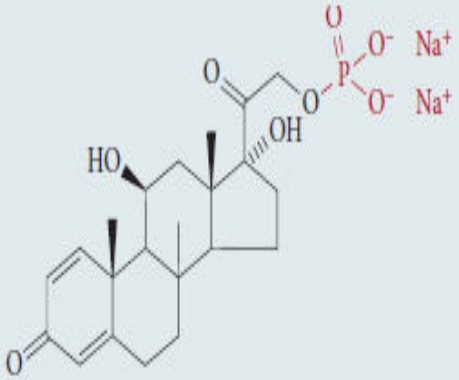
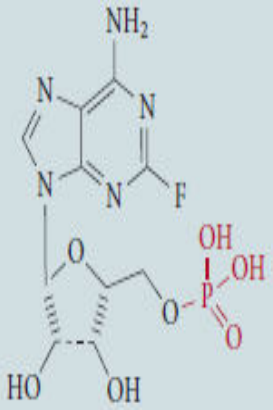
Examples of Prodrugs for improved aqueous solubility

Prodrug

Table 2 | **Prodrugs for improved aqueous solubility**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Sulindac (non-steroidal anti-inflammatory)	Oxide prodrug of sulindac sulphide		• Bioprecursor prodrug that is reduced to the active sulphide form after oral absorption • ~ 100-fold increase in aqueous solubility[62,65]
Miproxifene phosphate, TAT-59 (anticancer)	Phosphate ester of miproxifene/DP-TAT-59		• Bioconversion by alkaline phosphatases • Aqueous solubility at pH 7.4 increased by ~1,000-fold[69] • Enhanced bioavailability to 28.8% in rats and 23.8% in the dog[66] • Dose-linear pharmacokinetics in humans[69]
Fosamprenavir (antiviral)	Phosphate ester of amprenavir		• Bioconversion by alkaline phosphatases • 10-fold increased aqueous solubility • More simplified and patient compliant dosage regimen • Prolonged exclusive patent[70-72]

Prodrug

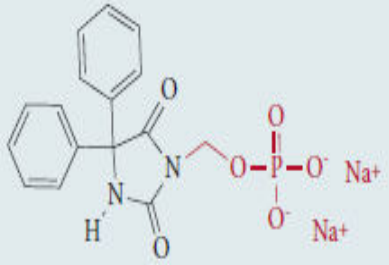
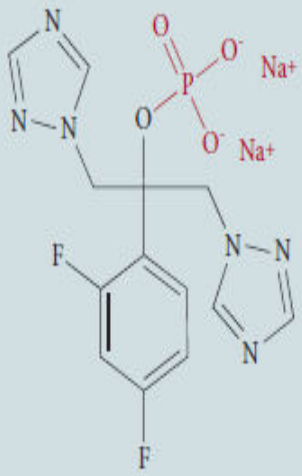
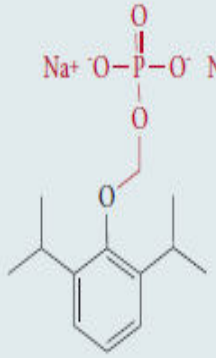
Estramustine phosphate (anticancer)	Phosphate ester of estramustine		• Bioconversion by alkaline phosphatases • Marketed both as injectable and oral formulations for the treatment of prostate carcinoma since the mid-1970s[178,179]
Prednisolone phosphate (glucocorticoid)	Phosphate ester of prednisolone		• Bioconversion by alkaline phosphatases • The prodrug enabled the development of a liquid formulation, and thus, improved childrens' compliance to prednisolone treatment[28,180]
Fludarabine phosphate (antiviral)	Phosphate ester of fludarabine		• Bioconversion by alkaline phosphatases • Until recently, fludarabine phosphate was marketed only for parenteral use[181] • Based on a modest advantage over the parent drug, development of an oral prodrug of fludaribine may have only been as a consequence of the prior existence of a commercial parenteral prodrug[28,181]

Prodrug

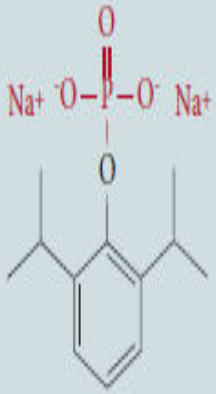
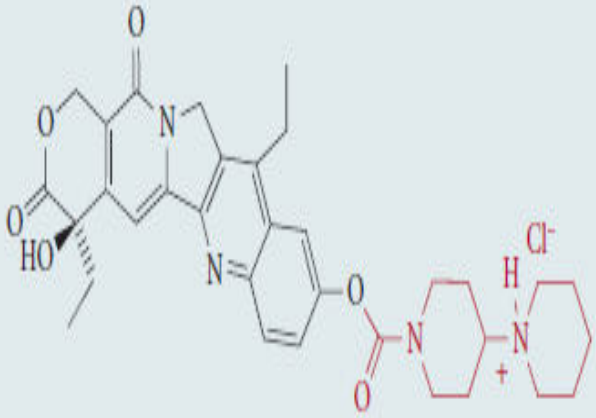
Examples of Prodrugs for improved parenteral administration

Prodrug

Table 3 | **Prodrugs for improved parenteral administration**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Fosphenytoin (anticonvulsant)	Phosphonooxymethyl amine of phenytoin		• Rapidly converted to phenytoin by alkaline phosphatases (half-lives 7-15 min)[101,102] • Increased aqueous solubility from 20–25 µg per ml of phenytoin to 140 mg per ml of fosphenytoin
Fosfluconazole (antifungal)	Phosphate ester of fluconazole		• Bioconversion by alkaline phosphatases[106] • Allows a low-volume bolus and higher dose product for intravenous administration • Increased aqueous solubility of fosfluconazole (over 300 mg per ml)
Phosphonooxymethyl propofol (anaesthetic)	Phosphonooxymethyl ether of propofol		• Is rapidly converted to propofol after intravenous administration by alkaline phosphatases[106,185] • Significantly increased the aqueous solubility of propofol from 150 µg per ml to ~500 mg per ml

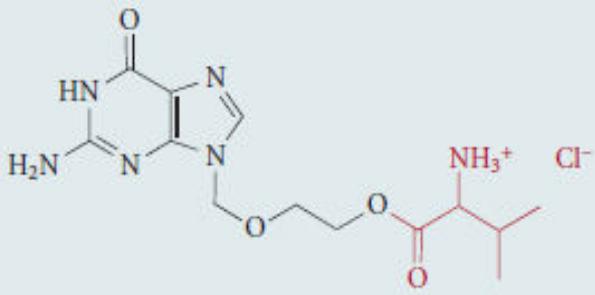
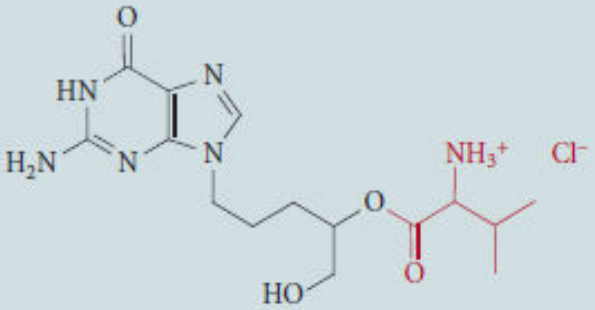
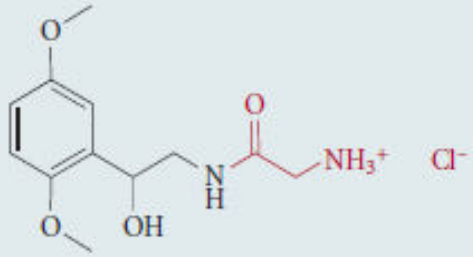
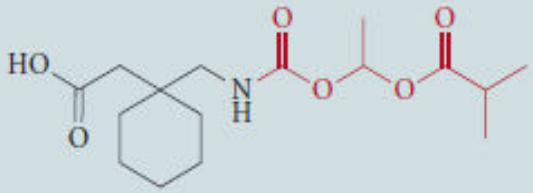
Prodrug

Propofol phosphate (anaesthetic)	Phosphate ester of propofol		• Significantly increased the aqueous solubility of propofol (150 µg per ml) • But bioconversion to propofol after intravenous administration is significantly slower when compared with phosphonooxymethyl propofol[107]
Irinotecan (anticancer)	Dipiperidino carbamate of camptothecin		• Increased aqueous solubility from 2–3 µg per ml (in water) of camptothecin to 20 mg per ml (at pH 3–4) of irinotecan • Undergoes rapid, pH-dependent equilibrium with closed and open forms of the lactone ring • Only the lactone form is active[112,115]

Examples of Prodrugs to exploit carrier-mediated absorption

Prodrug

Table 4 | **Prodrugs to exploit carrier-mediated absorption**

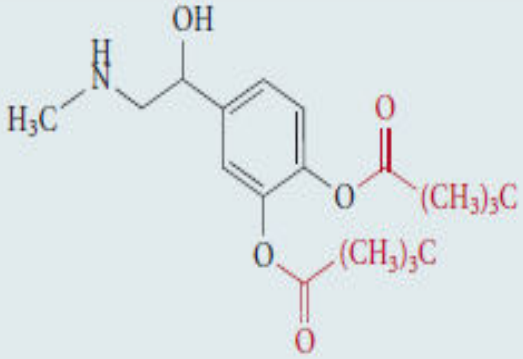
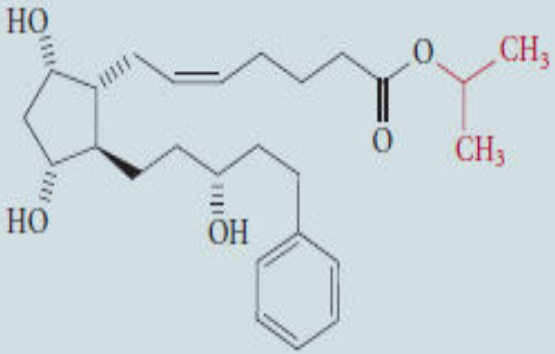
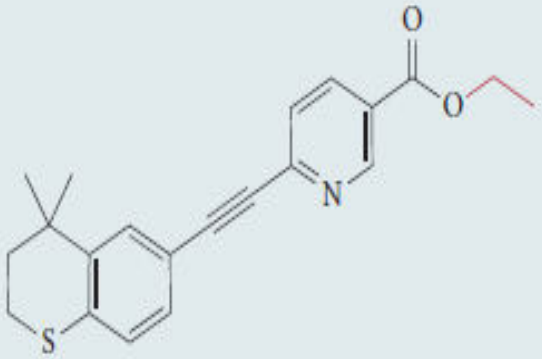
Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
---	---		
Valacyclovir (antiviral)	L-Valyl ester of acyclovir		• Bioconversion by valacyclovir hydrolase (valacyclovirase) • Transported predominantly by hPEPT1 • Oral bioavailability improved from 12–20% (acyclovir) to 54% (valacyclovir)[90–92,182]
Valganciclovir (antiviral)	L-Valyl ester of ganciclovir		• Bioconversion by intestinal and hepatic esterases • Transported predominantly by hPEPT1 • Oral bioavailability improved from 6% (ganciclovir) to 61% (valganciclovir)[183,184]
Midodrine (vasopressor)	Glycyl amide of desglymidodrine		• Bioconversion by unknown peptidase • Transported by hPEPT1 • Oral bioavailability improved from 50% (desglymidodrine) to 93% (midodrine)[94]
XP13512 (restless leg syndrome, neuropathic pain)	Isobutanoyloxy-ethoxy carbamate of gabapentin		• Bioconversion by esterases • Transported by both MCT1 and SMVT • Oral bioavailability improved from 25% (gabapentin) to 84% (XP13512) in monkeys[98,99]

Prodrug

Examples of Prodrugs for improved ophthalmic and dermal delivery

Prodrug

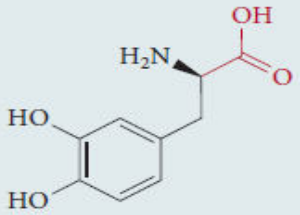
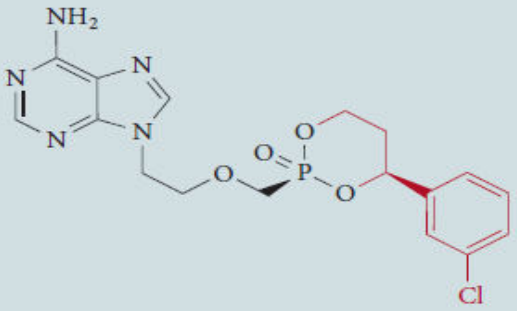
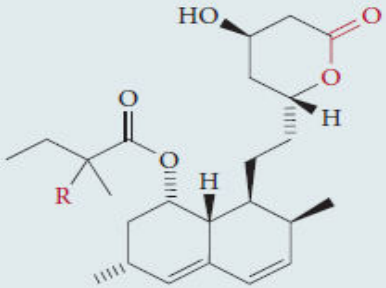
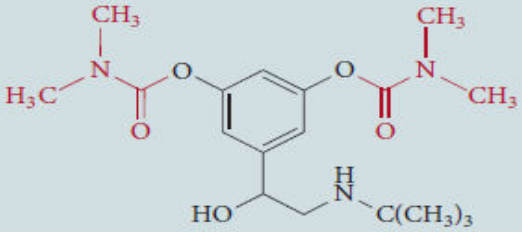
Table 5 | **Prodrugs for improved ophthalmic and dermal delivery**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Dipivefrin (glaucoma)	Dipivalic acid diester of adrenaline		• Bioconversion by esterases • More lipophilic (600-fold) dipivefrin is able to permeate the human cornea 17-times faster than adrenaline[119,120]
Latanoprost (glaucoma)	Isopropyl ester of latanoprost acid		• Bioconversion by esterases • Improved lipophilicity achieves better ocular absorption and safety[124,186]
Tazarotene (topical skin disorders, psoriasis, acne)	Ethyl ester of tazarotenic acid		• Bioconversion by esterases • Is both a prodrug and soft drug (undergoes oxidative deactivation) • Improved lipophilicity and maintained adequate aqueous solubility; resulted in better skin permeation[131,132]

Examples of Prodrugs for other purposes

Prodrug

Table 6 | **Prodrugs for other purposes**

Prodrug name (therapeutic area)	Functional group	Structure	Prodrug strategy
Levodopa (Parkinson's disease)	Carboxylic acid of dopamine		• Crosses the blood–brain barrier and enters the brain by using LAT1 • Is decarboxylated to dopamine by aromatic amino-acid decarboxylase[136,137]
Pradefovir mesylate (antiviral)	2-(3-chlorophenyl)-[1,3,2]dioxaphosphinane of adefovir		• Undergoes cytochrome P450-catalyzed oxidation to adefovir predominantly in the liver[154,155,187]
Simvastatin, R= CH_3; lovastatin, R=H (hypercholesterolaemia)	Inactive lactone forms		• Bioprecursor prodrugs that are converted into the active hydroxyl acid forms in the liver[156,157,188]
Bambuterol (asthma)	Bisdimethylcarbamate of terbutaline		• Prolongs duration of drug action • Undergoes cascade of hydrolysis and oxidation reactions to terbutaline[163,165]

LAT1, type 1 L-type amino-acid transporter.

Prodrug

Prodrug Therapies ((cancer therapies))

For selective activation of prodrugs in tumor cells Two steps

I. incorporate a prodrug-activating enzyme into a target tumor cell.
II. administer a nontoxic prodrug which is a substrate for the exogenous enzyme incorporated.

Criteria for Success with Enzyme-Prodrug Therapies

I. The prodrug-activating enzyme is either nonhuman or a human protein expressed poorly
II. The prodrug-activating enzyme must have high catalytic activity
III. The prodrug must be a good substrate for the incorporated enzyme and not for other endogenous enzymes
IV. The prodrug must be able to cross tumor cell membranes
V. The prodrug should have low cytotoxicity and the drug high cytotoxicity
VI. The activated drug should be highly diffusable to kill neighboring nonexpressing cells (bystander killing effect)
VII. The half-life of the active drug is long enough for bystander killing effect but short enough to avoid leaking out of tumor cells

Prodrug

(a) Antibody Directed Enzyme Prodrug Therapy (ADEPT)

An approach for site-specific delivery of cancer drugs.

I. Phase One:

An antibody-enzyme conjugate is administered which binds to the surface of the tumor cells.The antibody used has been targeted for the particular tumor cell.

The enzyme chosen for the conjugate is one that will be used to cleave the carrier group off of the prod rug administered in the next phase.

2 .Phase Two:

After the .antibody-enzyme has accumulated on the tumor cell and the excess conjugate is cleared from the blood and normal tissues, the prodrug is administered.

The enzyme conjugated with the antibody at the tumor cell surface catalyzes the conversion of the prodrug to the drug when it reaches the tumor cell.

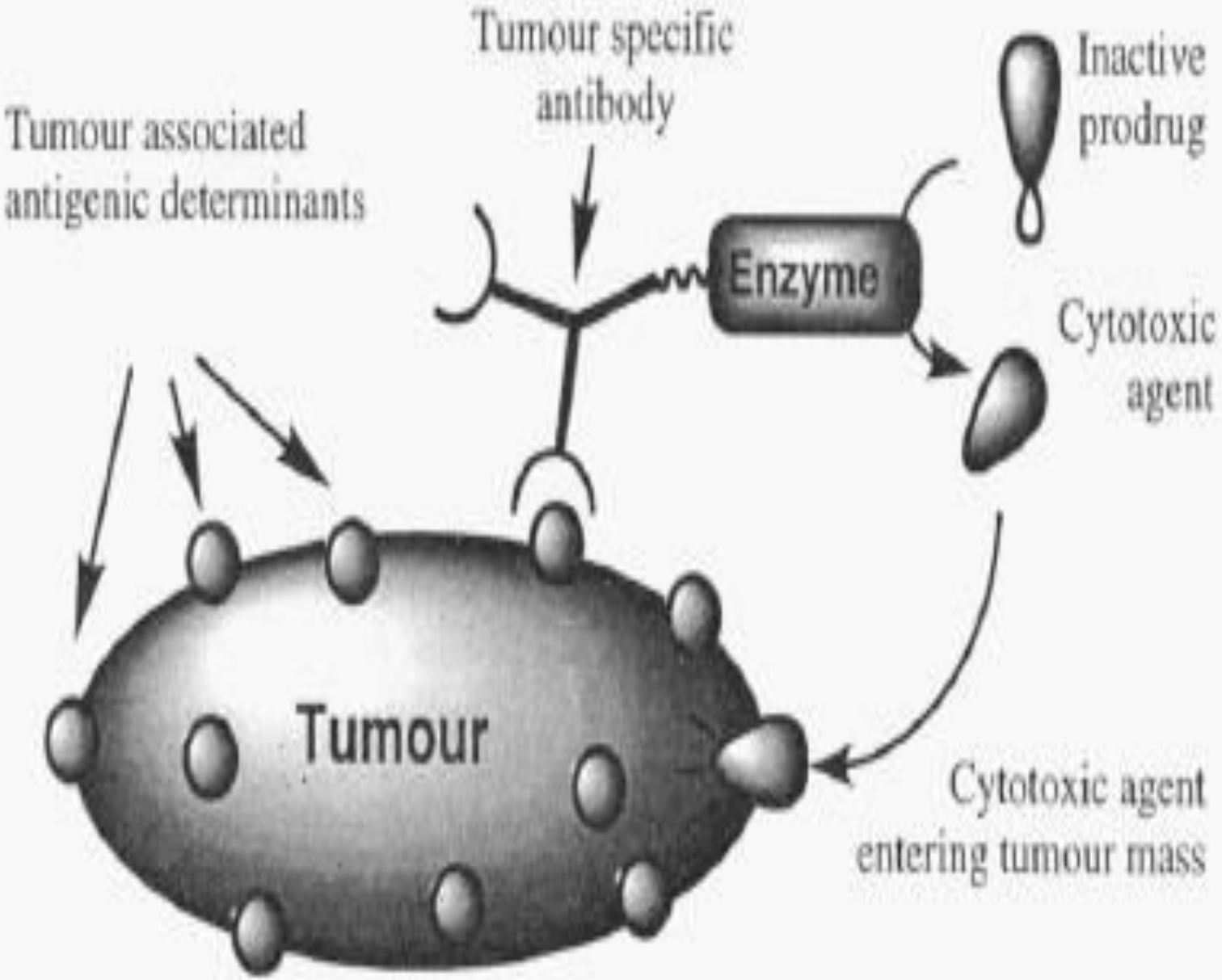
Advantages

1. Increased selectivity for targeted cell.
2. Each enzyme molecule converts many prodrug Molecules.
3. The released drug is at the site of action.
4. Demonstrated to be effective at the clinical level.
5. Concentrates the drug at the site of action.

Disadvantages

1. Immunogenicity and rejection of antibody-enzyme. conjugate
2. Complexity of the two-phase system and i.v administration
3. Potential for leak back of the active drug

Prodrug


Tumour specific
antibody
Inactive
prodrug
Tumour associated
antigenic determinants
Enzyme
Cytotoxic
agent
Tumour
Cytotoxic agent
entering tumour mass

(b) Antibody-Directed Abzyme Prodrug Therapy (ADAPT)

Instead of using a prodrug-activating enzyme, a humanized prodrug¬activating catalytic antibody (abzyme) can be used.

Ideally, the abzyme catalyzes a reaction not known to occur In humans, so the only site where the prodrug could be activated is at the tumor cell where the abzyme is bound.

Antibody 38C2 catalyzes sequential retro-aldol and re tro-Mich ael reactions not catalyzed by any knownsss human enzyme.

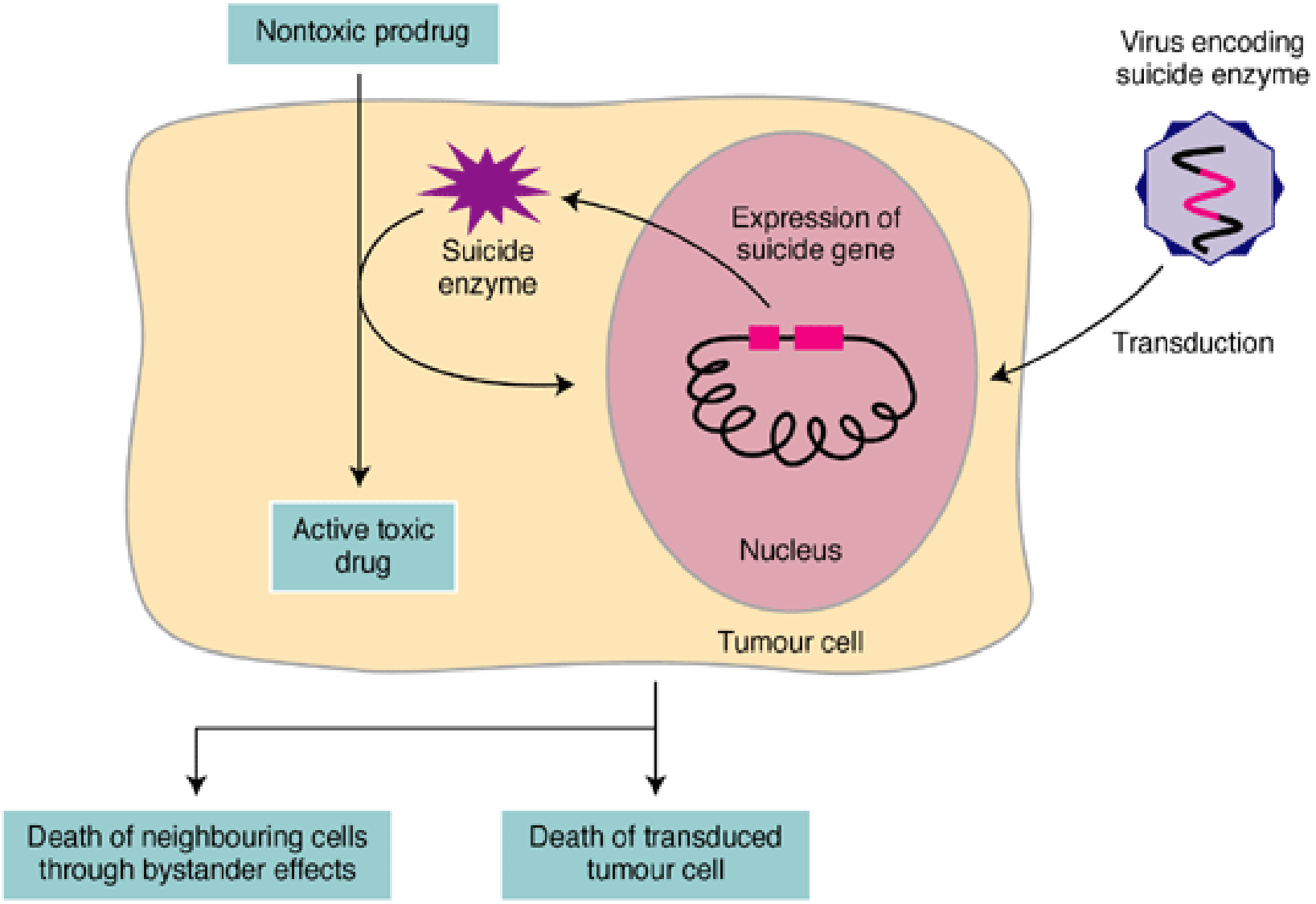
Found to be long-lived in vivo, to activate prodrugs selectively, and to kill colon and prostate cancer cells.

(c) Gene-Directed Enzyme Prodrug Therapy (GDEPT)

¬ A gene encoding the prodrug-activating enzyme is expressed in target cancer cells under the control of tumor-selective promoters or by viral transfection.

These cells activate the prodrug as in DEPT.

Prodrug



Principle of gene-directed enzyme prodrug therapy (GDEPT)

Prodrug

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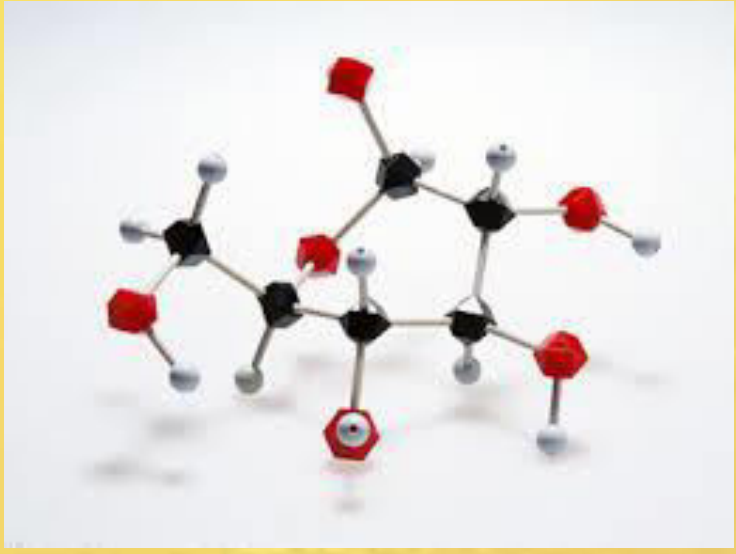

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