Prodrugs and Bioprecursors

History

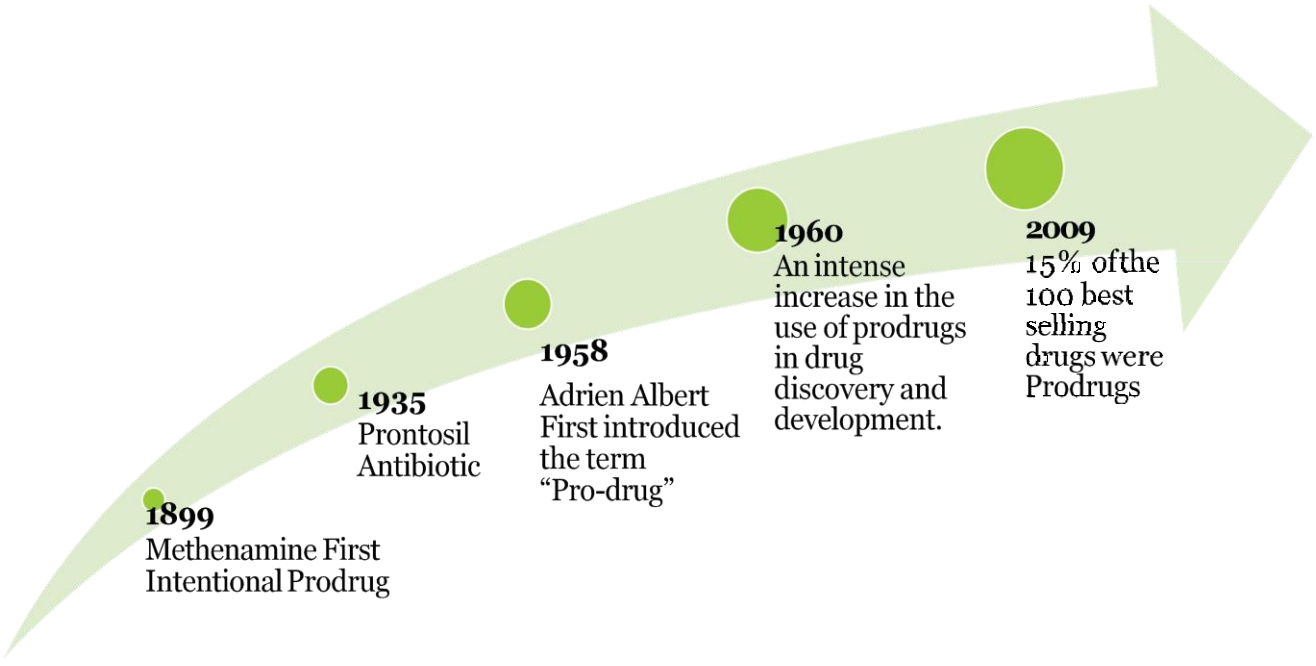
The term prodrug, introduced in **1958 by Adrien Albert**, relates to "Biologically inert derivatives of drug molecules that undergo an enzymatic and/or chemical conversion in vivo to release the pharmacologically active parent drug."

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound.

The first compound fulfilling the classical criteria of a prodrug was **acetanilide**. This is an **antipyretic** agent. Acetanilide is hydroxylated to biologically active **acetaminophen**.

Another historical prodrug is **Aspirin** (acetylsalicylic acid), synthesized in **1897 by Felix Hoffman (Bayer, Germany),** and introduced into medicine by **Dreser in 1899**. Formaldehyde could not be used as urinary tract antibacterial until it was formulated as enteric coated tablet of hexamine.

The prodrug concept was intentionally used for the first time by the Parke-Davis company for modification of **chloramphenicol** structure in order to improve the antibiotic's bitter taste and poor solubility in water. Two prodrug forms of chloramphenicol were synthesized: **chloramphenicol sodium succinate** with a good water solubility, and **chloramphenicol palmitate** used in the form of suspension in children.



Most of the drugs possess some undesirable physicochemical and biological properties.

Therapeutic efficacy of such drugs can be improved by minimizing or removing undesirable properties like pharmacokinetic, pharmaceutical, pharmacodynamic.

Prodrug has been useful in tackling problems such as acid sensitivity, poor membrane permeability, drug toxicity, bad taste, and short duration of action.

This can be done by following ways

- Design and development of new drug
- Design of hard drug and soft drug
- Prodrug design

Hard Drug

A hard drug is one, which is resistant to biotransformation and therefore has a longer biological half-life. Design of the hard drug involves metabolic stabilization of existing drug by putting certain functional groups, which are stable and does not undergo biotransformation. E.g Chlorpropamide

Soft Drug

A soft drug is one, which undergoes rapid biotransformation in predictable manner into non-toxic compound. This design is possible by introducing a certain functional group over lead compound, which undergo rapid biotransformation. E.g Replacement of alkyl side chain of the drug with an ester group.

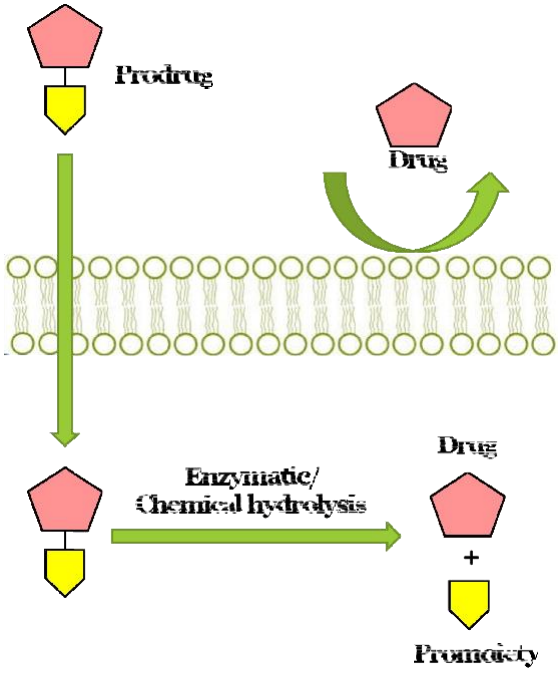
What are Prodrugs?

Also known as proagent

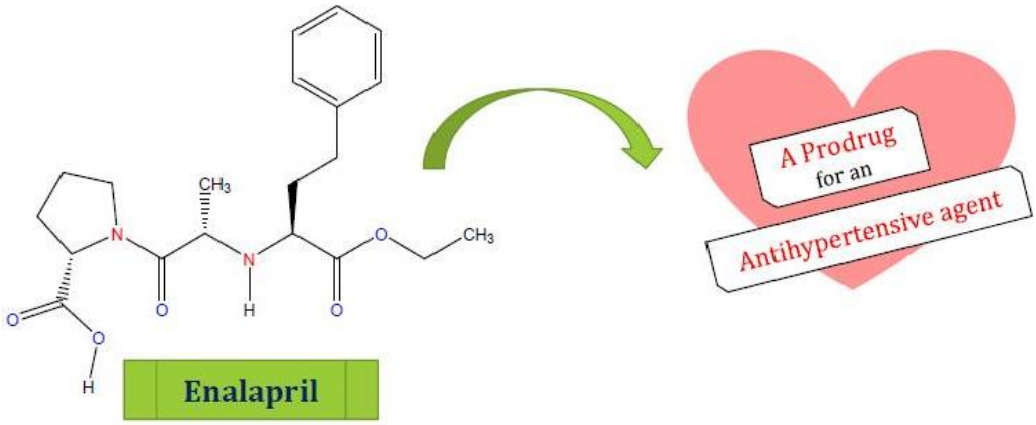
Definition: A pharmacologically inactive chemical entity that when metabolized or chemically transformed by a mammalian system is converted into a pharmacologically active substance.

Drug latentation (Concept added later)

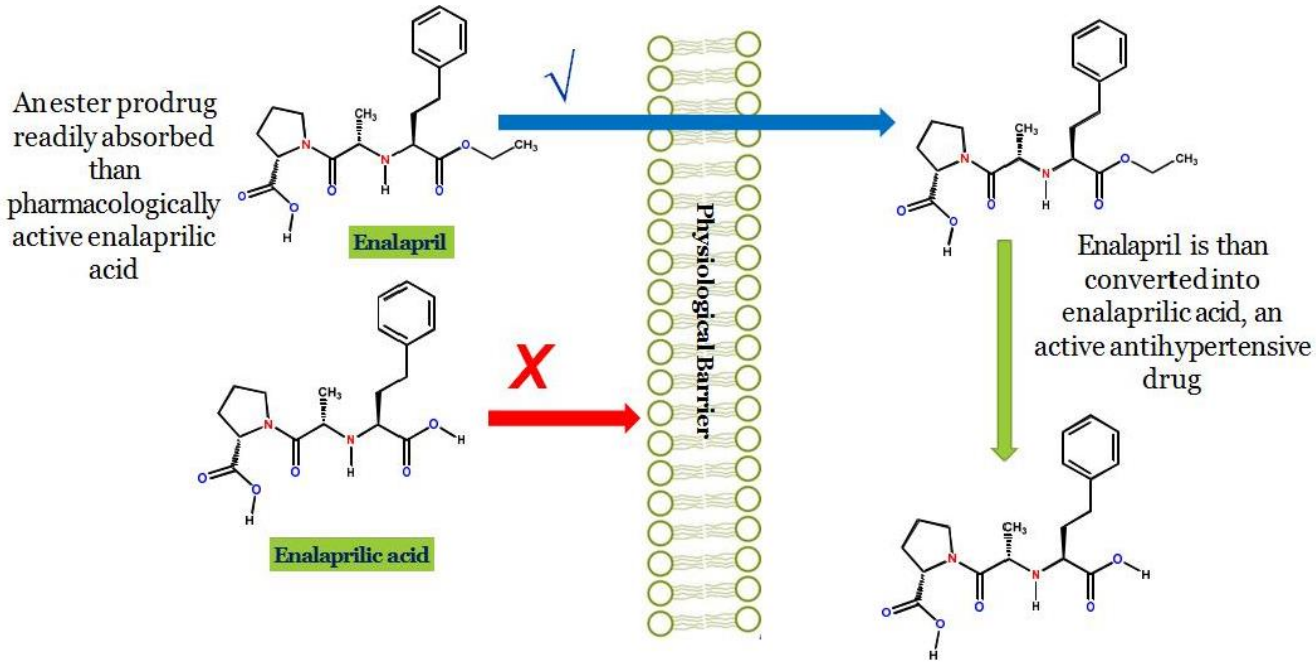
Prodrug is Process of purposely designing and synthesizing a molecule that specifically requires "bio-activation" to a pharmacologically active substance.



To further understand a prodrug take a look at this example



Enalapril is a ethyl ester of enalaprilic acid which is an active inhibitor of angiotensin converting enzyme.



Approximately 7% of prodrugs in the market are Prodrugs.

Why Prodrugs:

- Increasing solubility
- Enhancing lipophilicity
- Enhancing active transport
- Extending the half-life
- Achieving site-specific delivery
- Improve patient compliance

Ideal Prodrug:

- Should undergo biotransformation rapidly via chemical enzymatic process to its active form and a nontoxic moiety within the body
- Must release the active drug and promoiety prior to, during, or after absorption, or in a specific target tissue/organ upon the purpose of which the prodrug has been designed.

Classification of Prodrugs

A) Carrier linked prodrugs

1) Bipartate prodrug
2) Tripartate
3) Mutual

B) Bioprecursor or Metabolic precusrsor

1) Proton activation
2) Elimination activation
3) Oxidative activation
4) Reductive activation
5) Decarboxylation activation

C) Site specific delivery (Chemical delivary system)

A) Carrier linked prodrugs

Carrier-linked prodrugs are those in which **the active drug is covalently linked to an inert carrier or transport moiety**. Such prodrugs have greatly modified lipophilicity due to attached carrier. These are esters or amides. The active drug is released by hydrolytic cleavage, either chemically or enzymatically.

Ideal Characteristics of carrier:

- Carrier should protect the drug until it reaches to the site of action
- Localize the drug at the site of action.
- Allow the release of drug
- Minimize the host toxicity.
- It should be nontoxic
- It should be compatible with drug
- It should be biodegradable
- It should be inert
- It should be readily prepared and should be inexpensive

Classification of Carrier linked prodrug

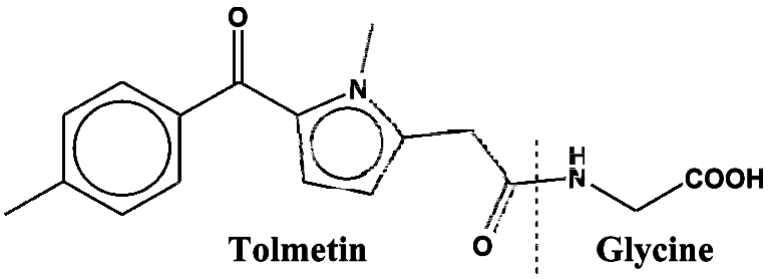
Bipartate: These prodrugs comprised of one carrier attached to the active substance or the drug.

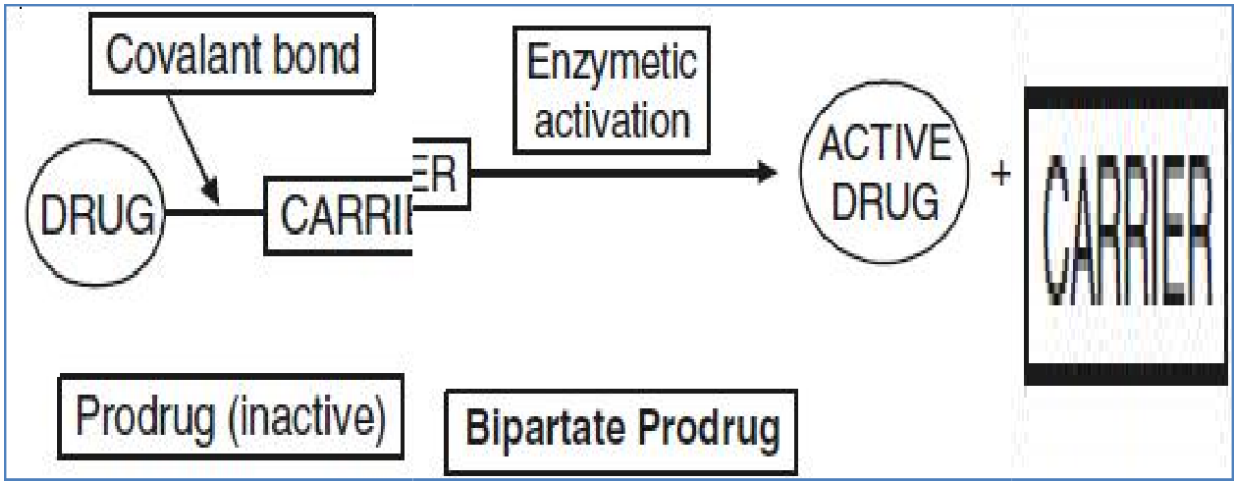
Tripartate: In these prodrugs, the active drug is linked to the carrier moiety through a spacer or connector group.

Mutual: It consists of two pharmacologically active agents, in which one act as a carrier, thus might give synergistic action.

1) Bipartate Prodrug

It is composed of one carrier (group) attached to the drugs. Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically. E.g. Tolmetin-glycine prodrug:

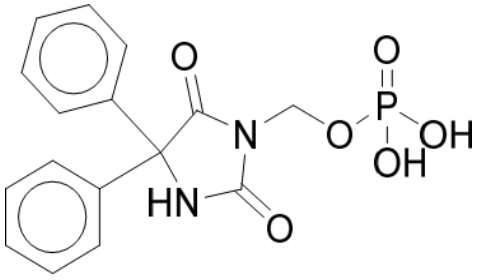




Examples

Conversion of prednisolone to water soluble form i.e., methylprednisolone sodium succinate.

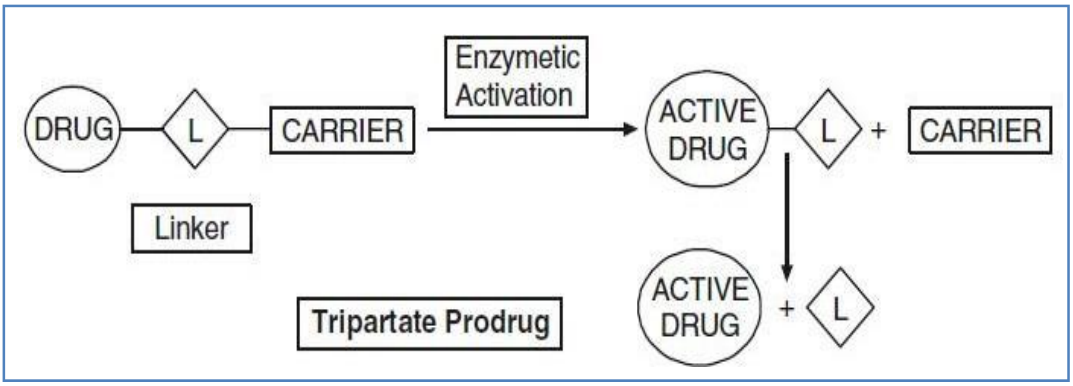
Fosphenytoin is a hydrophilic phosphate prodrug of the anti-convulsant phenytoin and is hydrolyzed by phosphatase. It was designed to enhance the aqueous solubility of phenytoin in IV administration.



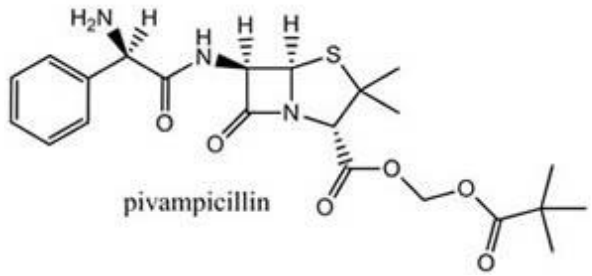
fosphenytoin

2) Tripartite Prodrug

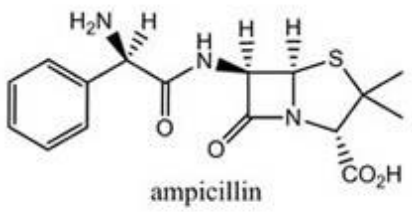
The carrier group is attached via linker/spacer to a drug.



Example: Pivampicillin is a pivaloyloxymethyl ester tripartite prodrug of the β-lactam antibiotic, ampicillin. The prodrug uses a $–CH_2–$ linker to link ampicillin and the pivalic acid carrier. Pivampicillin is thought to have greater biovailability than ampicillin because the ester group grants the compound greater lipophilicity.



pivampicillin

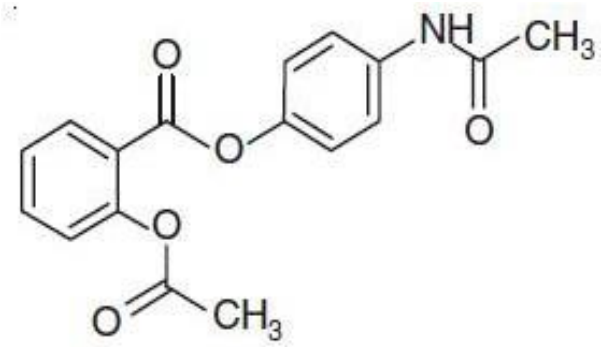


ampicillin

3) Mutual prodrug

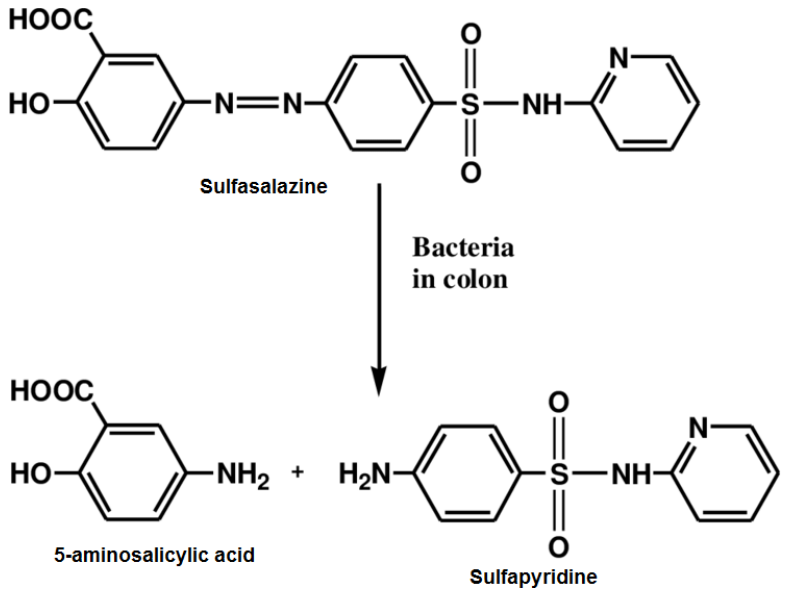
Prodrug of two active compounds are called as mutual prodrug, here two pharmacologically active compounds are coupled together to form a single molecule such that each acts as the carrier for the other.

Example: i) Benorylate is a mutual prodrug of NSAIDs, aspirin and paracetamol.



Benorylate

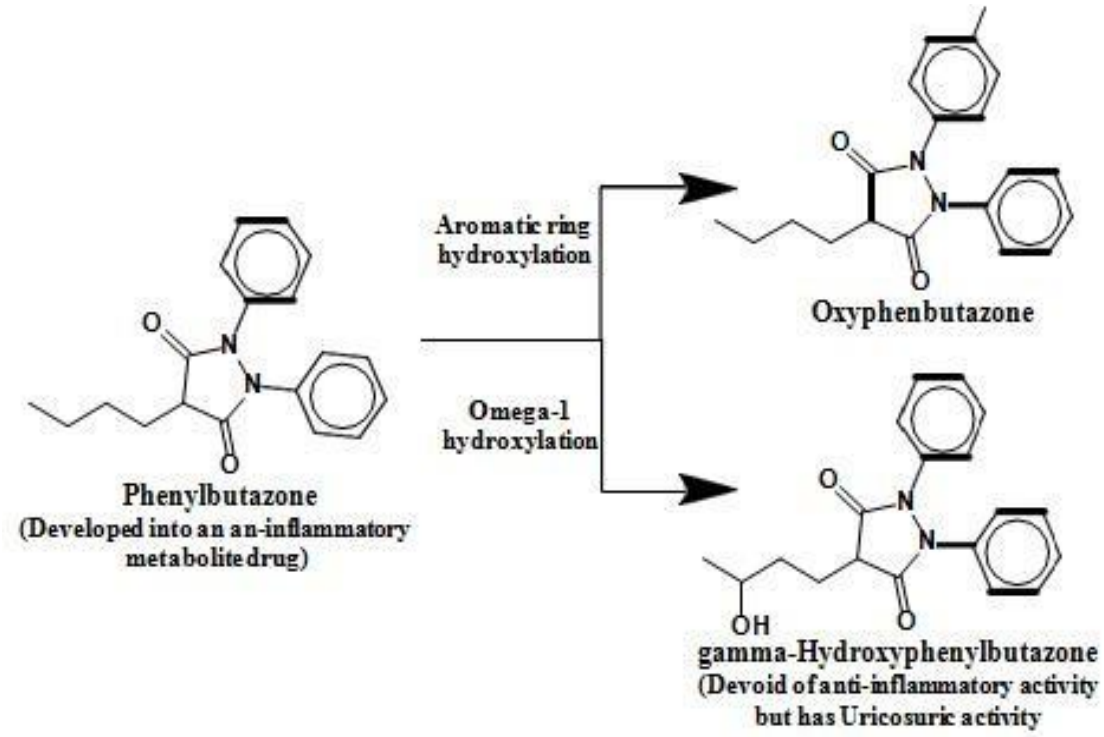
ii) Sulfasalazine is a prodrug composed by a molecule of 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), linked by an azo bond, which has been shown to be effective in the therapy of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease, as well as of rheumatic diseases, such as rheumatoid arthritis and ankylosing spondylitis.



B) Bioprecurssor or Metabolic Prodrug

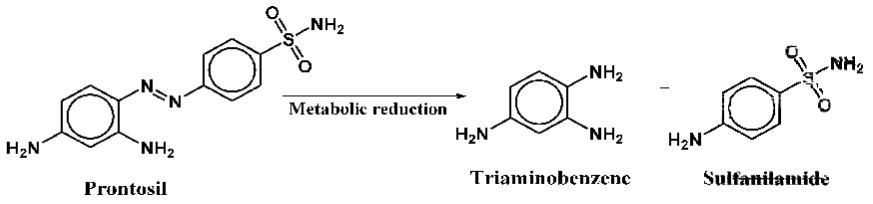
Bioprecursors or metabolic precursors **are inert molecules obtained by chemical modification of the active drug but do not contain a carrier**. Such a moiety has almost the same lipophilicity as the parent drug and is bioactivated generally by redox biotransformation, only enzymatically.

- The bioprecursor does not contain a temporary linkage between the active drug and carrier moiety, but **designed from a molecular modification of an active principle** itself.
- Bioprecursor prodrugs rely on oxidative or reductive activation reactions unlike the hydrolytic activation of carrier-linked prodrugs. e.g. Phenylbutazone. Phenylbutazone gets metabolized to oxyphenbutazone.

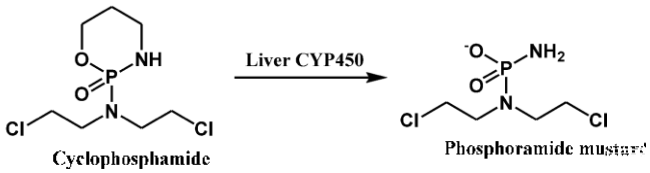


- Upon administration many compounds are metabolized by molecular modification into new compounds that are active in principle or can be metabolized further into the active drugs.

- Eg: Prontosil---Sulfanilamide (Antibacterial)



- Eg: Cyclophosphamide---Phospharamide Mustard (Antineoplastic)

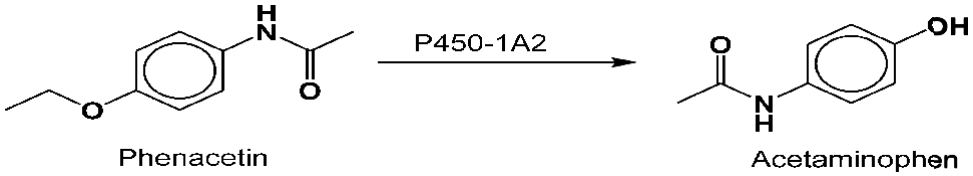


Activation Systems:

- Oxidative activation
- Reductive activation
- Nucleotide activation
- Phosphorylation activation
- Decarboxylation activation
- Proton activation
- Elimination activation

- **Oxidative activation:** Classified as
  - N and O-dealkylation
  - Oxidative deamination
  - Epoxidation

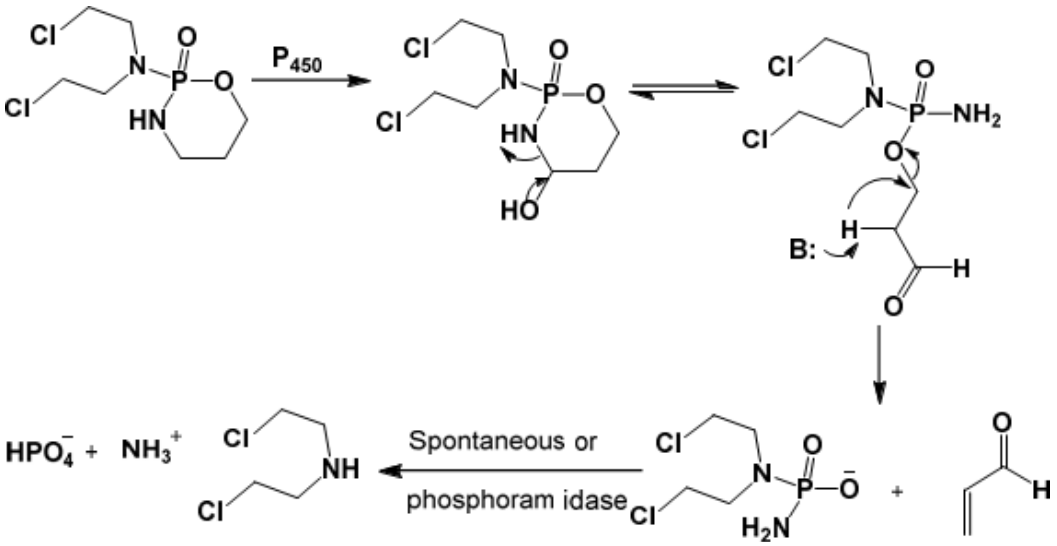
<u>O-dealkylation:</u>



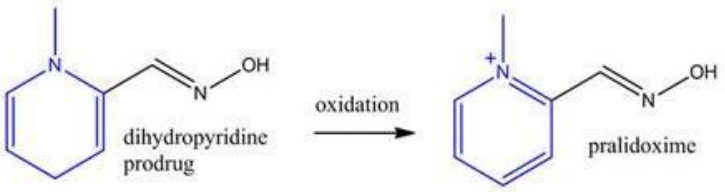
<u>Oxidative deamination:</u>

- Neoplastic cells have a high concentration of phosphoramidase, so hundreds of phosphamide analogs of nitrogen mustards were made for selective activation in these

cells. **Cyclophosphamide** was very effective drug for the treatment of cancer disease. Oxidative deamination leads to ring opening and release of the active nitrogen mustard which alkylates the DNA of cancer cell and inhibit the replication.

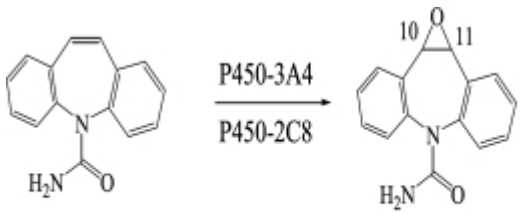


Pralidoxime (Protopam) is used as an antidote to treat poisoning by certain organophosphorus compounds. The antidote basically works by reactivating acetylcholinesterase following inhibition by irreversible AChE inhibitors such as sarin. Pralidoxime itself is too polar to cross the blood brain barrier. Replacing the pyridine with dihydropyridine gives a prodrug. The dihydropyridine group grants the prodrug enough lipophilicity to cross the blood brain barrier, where the dihydropyridine is oxidatively converted to the pyridinium to give the parent drug, pralidoxime.



Epoxidation:

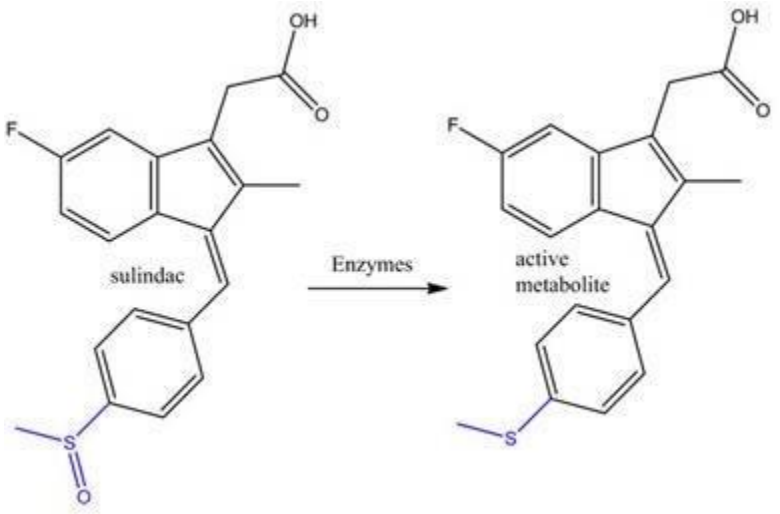
Cabamazepine is an anticonvulsant agent which is metabolically tansformed to the active epoxide derivatives



Carbamazepine Carbamazepine-10,11-epoxide

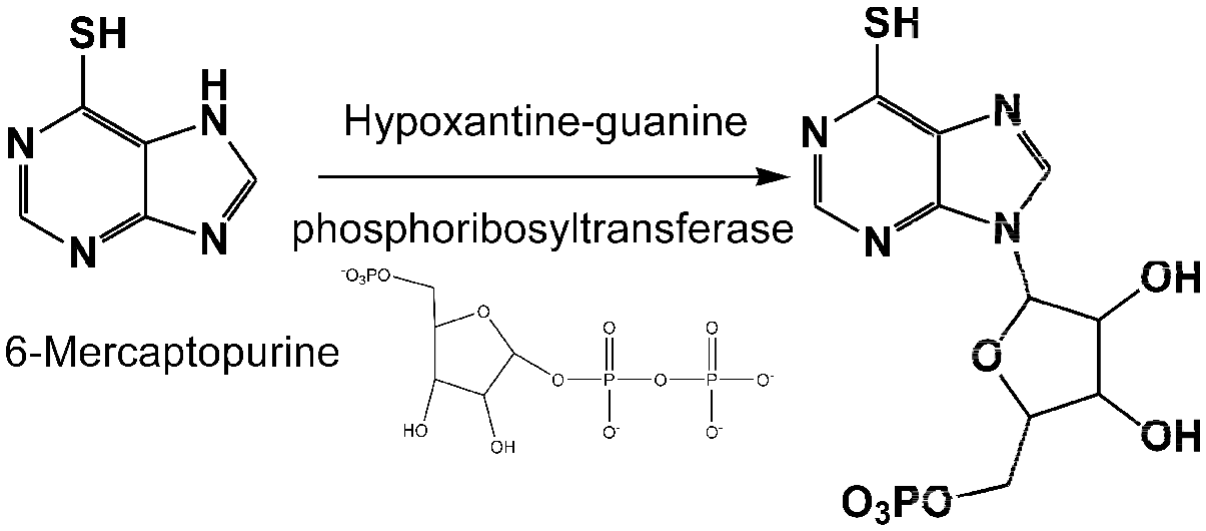
- **Reductive activation:**

  Sulindac is a non-steroidal anti-inflammatory drug (NSAID) used to treat acute and chronic inflammatory conditions. Sulindac is a prodrug that contains a sulfoxide group, and is an example of a prodrug that is activated by reduction. The sulfoxide is converted to a thioether (sometimes referred to as sulfide), giving the active metabolite. The reduction of the sulfoxide is mainly mediated by liver enzymes. Because sulindac is a prodrug, the active metabolite is present in lower concentrations at the gastric mucosa. The incidence of GI side effects is lowered compared to a chemically related NSAID, indomethacin.



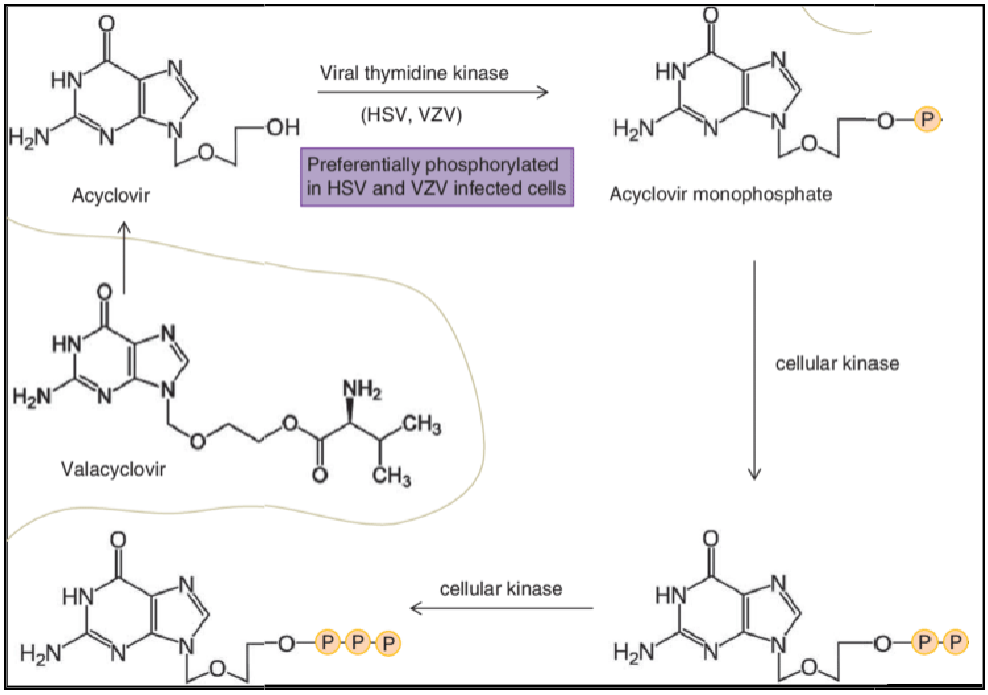
- **Nucleotide Activation:**

  6-mercaptopurine is activated by a hypoxanthine-guanine phosphoribosyltransferase



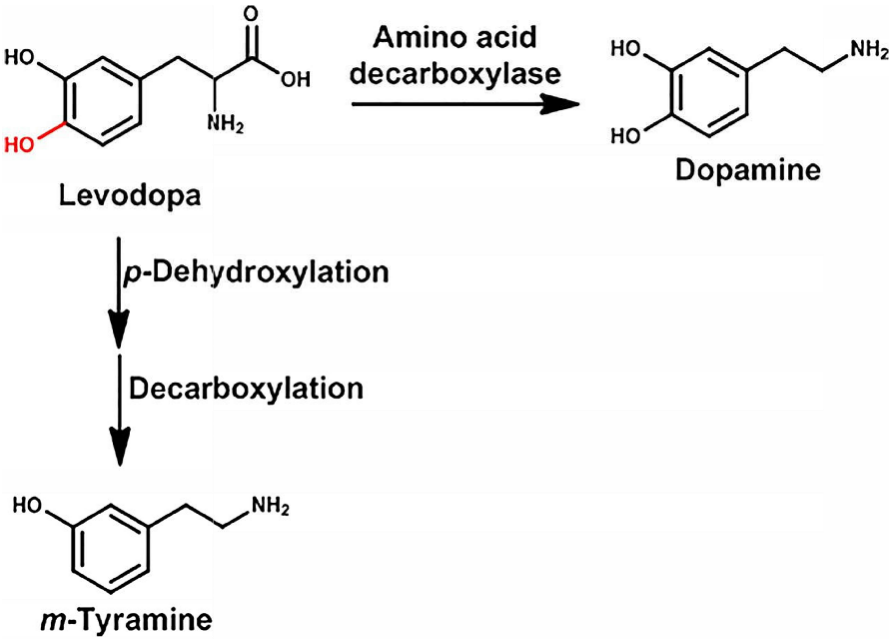
- **Phosphorylation activation:**

  Example: Acylcovir inhibit viral DNA synthesis which requires activation. Acyclovir requires three phosphorylation steps for activation. It will first converted to monophosphate derivative by virus thymidine kinase enzyme and then to di- and tri-phosphate compounds by host cell enzymes.



- **Decarboxylation:**

  Levodopa is converted to dopamine via the action of a naturally occurring enzyme called DOPA decarboxylase. This occurs both in the peripheral circulation and in the central nervous system after levodopa has crossed the blood brain barrier.



Applications of Prodrugs

i) For Reduction of pain at the site of injection

ii) For Masking taste and odour

iii) For Enhancement of Drug Solubility

iv) For Improvement of oral bioavailability

v) For Enhancement of Chemical stability

vi) For site specific drug delivery

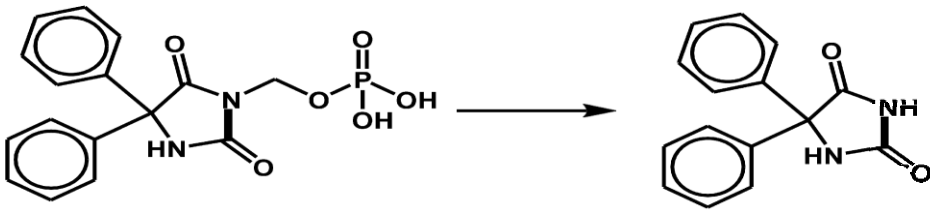
vii) For longer duration of action

viii) For less gastric irritation

i) Reduction in pain at the site of injection

Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs.

E.g., IM injection of phenytoin was found to be painful due to poor solubility. Therefore, the pH in the vehicle for injection is adjusted to 12, which leads to soft tissue injury and pain in the site of administration, due to phenytoin precipitation So, prodrugs are produced like hydantoic ester prodrug of phenytoin (fosphenytoin) an aqueous soluble form of phenytoin.



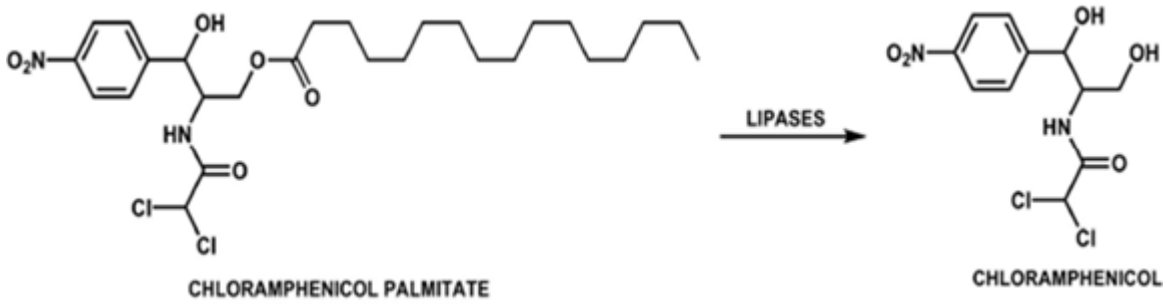
Fosphenytoin **Phenytoin**

ii) Masking Taste and Odour

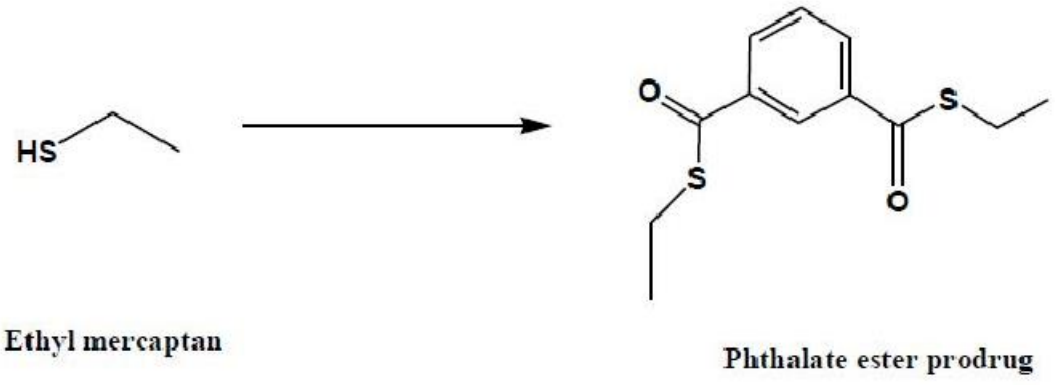
Undesirable taste arises due to adequate solubility and interaction of drug with taste receptors.

It can be solved by lowering the solubility of drug or prodrug in saliva.

E.g., chloramphenicol palmitate is the sparingly soluble of prodrug of chloramphenicol, which is practically tasteless due to its low aqueous solubility, as well as it is hydrolyzed to active chloramphenicol by the action of pancreatic lipase.



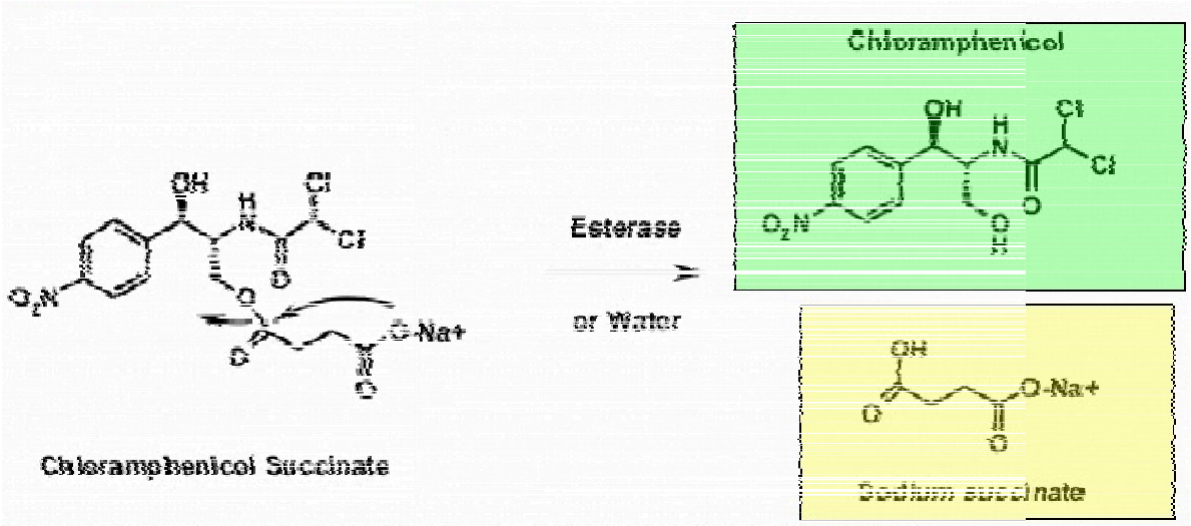
Odor is an aesthetic concern for drugs with high vapor pressure or low boiling point, which makes them difficult to be formulated. For example, ethyl mercaptan a tuberculostatic agent used for the treatment of leprosy has unpleasant smell because of low boiling point 25°C. The most attractive derivative prodrugs were its ethyl thiol esters; diethyl dithiolisophthalate prodrug of ethyl mercaptan was developed; this prodrug was found to be highly active and odorless.



iii) Enhancement of Drug Solubility

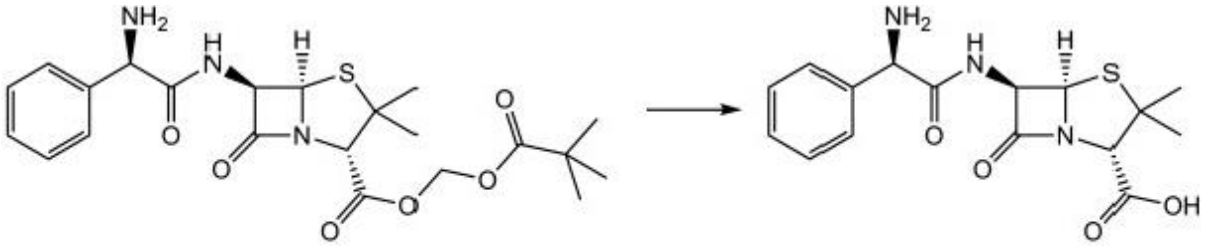
The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use.

E.g., chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively. On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration.



iv) Improvement of oral bioavailability

Chemical modification of drugs is used to improve physicochemical properties solubility, stability, and lipophilicity. Oral drug bioavailability is critical for the development of new drugs, because low oral absorption leads to inter- and intra-patient variability. One of the strategies developed to improve oral bioavailability is prodrugs. Oral bioavailability of lipophilic drugs depends on the dissolution in the gastrointestinal fluids, and polar drug's bioavailability depends on the transport across gastrointestinal mucosa. Therefore, prodrugs are designed to increase or decrease lipophilicity.



Pivampicillin
clogP = 1.77

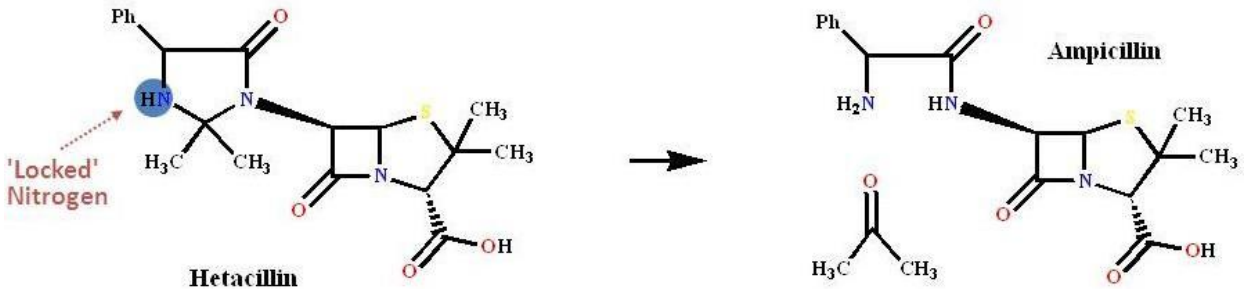
Ampicillin
clogP = –2.30

v) Enhancement of Chemical stability

Chemical stability is an utmost necessary parameter for every therapeutic agent. The prodrug approach is based on the modification of the functional group responsible for the instability or by

changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable.

E. g., Inhibiting the auto-aminolysis, which occur due to capability of NH_2 group of side chain to attach β lactam ring of other molecule, Ampicillin is chemically unstable in solution due to the α-amino group attacking the β-lactam ring. By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin "ties-up" the amine group and thus inhibits auto-aminolysis.



vi) For site specific drug delivery

Prodrugs are applied for targeting drugs to a specific organ or tissue; they are widely used in chemotherapy. Targeted prodrugs are used to increase absorption and decrease toxicity, they are targeted to an enzyme or membrane transporter.

Tumor targeted Drug delivery:

Cancer chemotherapeutics are toxic and nonselective which limits their use for cancer therapy. Their selectivity depends on the rapidly dividing cells that are more prone to toxic effects. Hence, they are toxic for rapidly proliferating normal tissue such as hair follicles, gut epithelia, bone marrow, and red blood cells. Therefore, in order to improve toxicity and efficacy chemotherapy prodrugs were designed to target tumor cells; this targeting is achieved by binding drugs to ligands having high affinity to specific antigens, receptors, or transporters that are over expressed in tumor cells.

One of the targeting methods is enzyme activated prodrug therapy where the nontoxic prodrug is converted to the active drug in the tumor tissue. The enzyme should be specifically expressed or over expressed in tumor. Plasmin, prostate specific antigen, matrix metalloproteaes, cathepsin B, D, H and L are examples of tumor associated enzymes that are used for prodrug activation in malignant cells. Monoclonal antibodies (mAbs) have a high affinity, hence they are the first

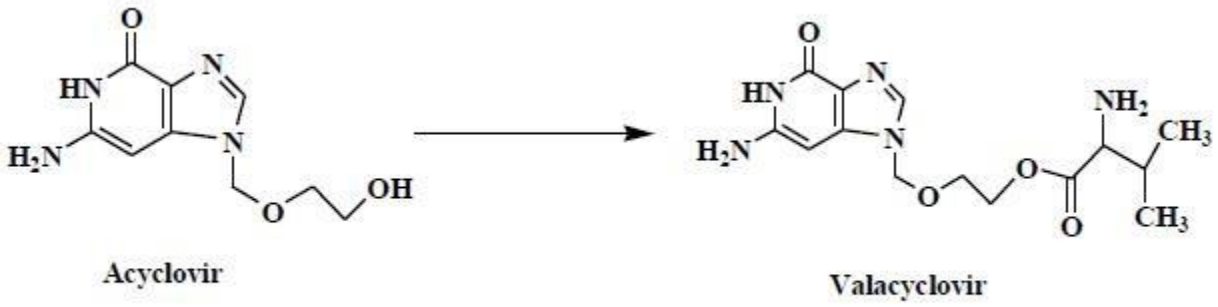
ligands used for tumor targeting. MAbs are designed as drug-antibody conjugate or antibody enzyme conjugate.

Membrane Transporter Prodrug Targeting

Membrane transporters selectively transport peptides, amino acids, phosphates, ascorbic acid, bile acids and others. For example, dipeptides and tripeptides are transported in the intestinal epithelial cells by peptide transporters (PepT1).

Targeting specific transporters, which have an important role in drug absorption, distribution, and elimination, via a prodrug is efficient and selective strategy, in which a prodrug is selectively attached to a molecule that targets a specific membrane transporters; PepT1 is the most promising transporter due to its selectivity and high capacity.

For example, the antiviral drug acyclovir, used to treat herpes simplex virus, by acting as a competitive substrate for DNA polymerase, has low oral bioavailability, because of its hydrophilic nature and poor permeability which limited its efficacy.

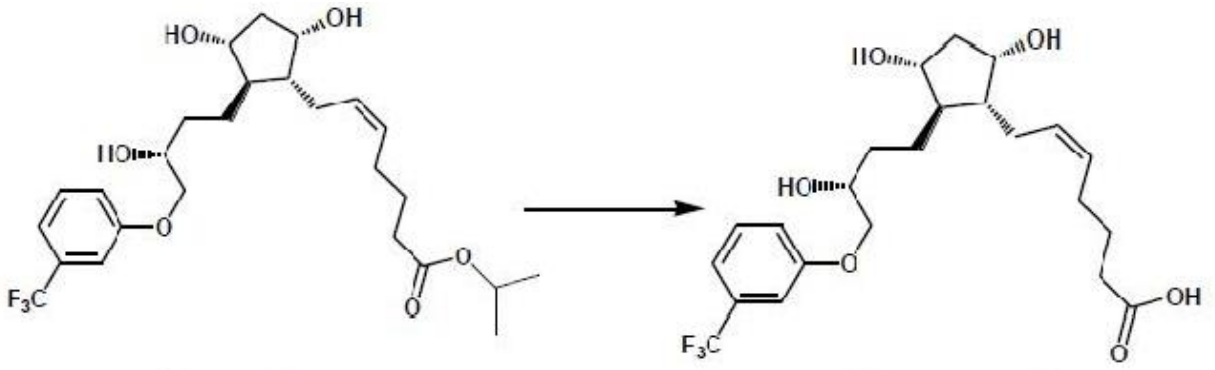


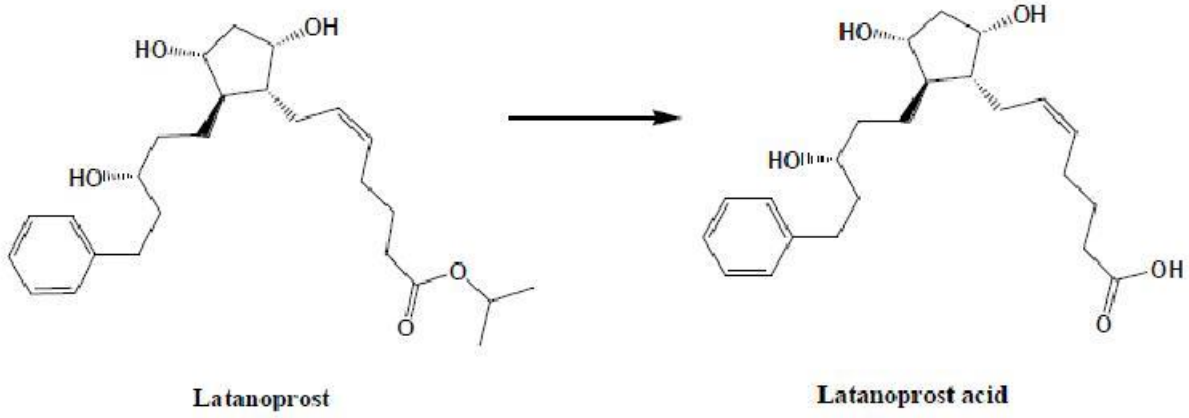
Chemical structures of acyclovir and its valine prodrug, valacyclovir.

To increase the oral bioavailability of acyclovir, L-valine (valacyclovir) prodrug was developed to target PepT transporters in the G.I. This prodrug has a high affinity for PepT transporter, therefore, it is highly absorbed through small intestine and is converted to acyclovir in the gut lumen.

Ophthalmic Drug Delivery

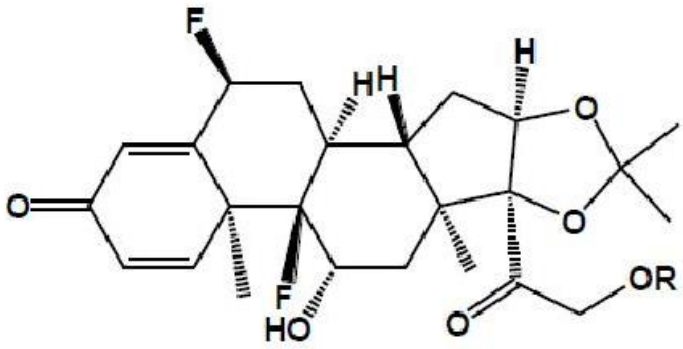
Lipophilic prodrugs are also used to enhance ocular absorption. For example latanoprost and travoprost are isopropyl esters of the parent latanoprost and travoprost carboxylic acids. These ester prodrugs have an increased lipophilicity, which enables them to penetrate the cornium epithelium.





Topical Drug Delivery

Another use of lipophilic prodrugs is to increase transdermal absorption for certain drugs. For example, ester prodrugs with increased lipophilicity allow them to accumulate in the skin leading to higher efficacy and lower side effects. Topical corticosteroids are widely used as anti-inflammatory and immune-suppressants agents for skin problems. However, they may be absorbed systemically and cause side effects [38]. For example, fluocinolone acetonide ester prodrugs (Figure 15) have high membrane retention (in epidermis) and low permeation which is preferred for local application of corticosteroids [39]. The high lipophilicity of the fluocinolone acetonide prodrug makes it more potent than its less lipophilic parent drug, fluocinolone.

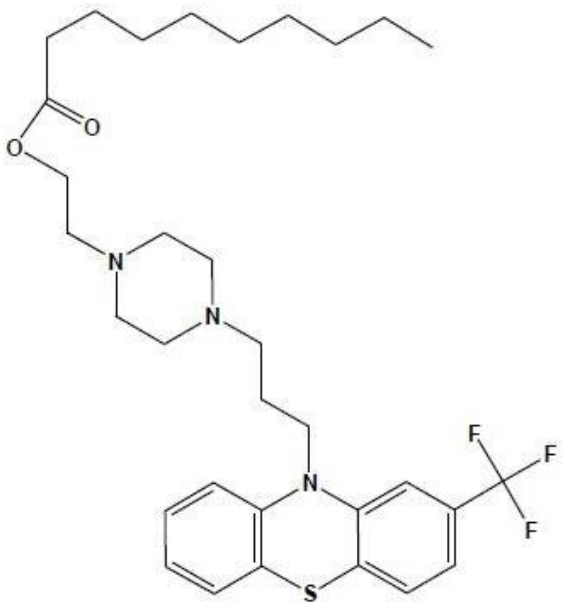


Fluocinolone acetonide (R=$COCH_3$)
Fluocinolone (R=H)

vii) For Longer Duration of Action

Drugs with short half-life require frequent dosing, to maintain blood concentration, which leads to poor patient compliance and fluctuation in the drug concentration. The development of prodrugs with long duration of action can be used to overcome these problems.

Long acting antipsychotic therapy is important to control symptoms and prevent relapse. These long acting agents also improve patient compliance and increase efficacy. For example, fluphenazine decanoate, an ester prodrug of fluphenazine, is used as long acting intramuscular depot injection for the treatment of schizophrenia; this prodrug is administered once every 2 weeks.

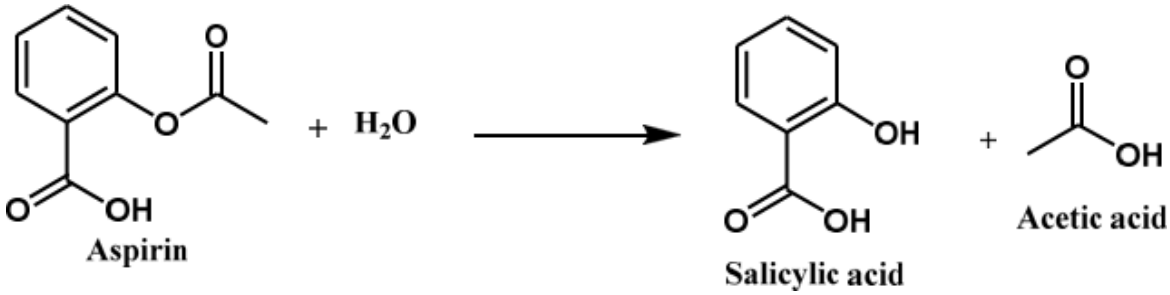


Fluphenazine decanoate

Chemical structure of fluphenazine decanoate prodrug.

viii) Reduction of gastric irritation

E.g., Aspirin is a prodrug of salicylic acid is designed to reduce gastric irritation



Aspirin **Salicylic acid** **Acetic acid**

Antimalarial agents

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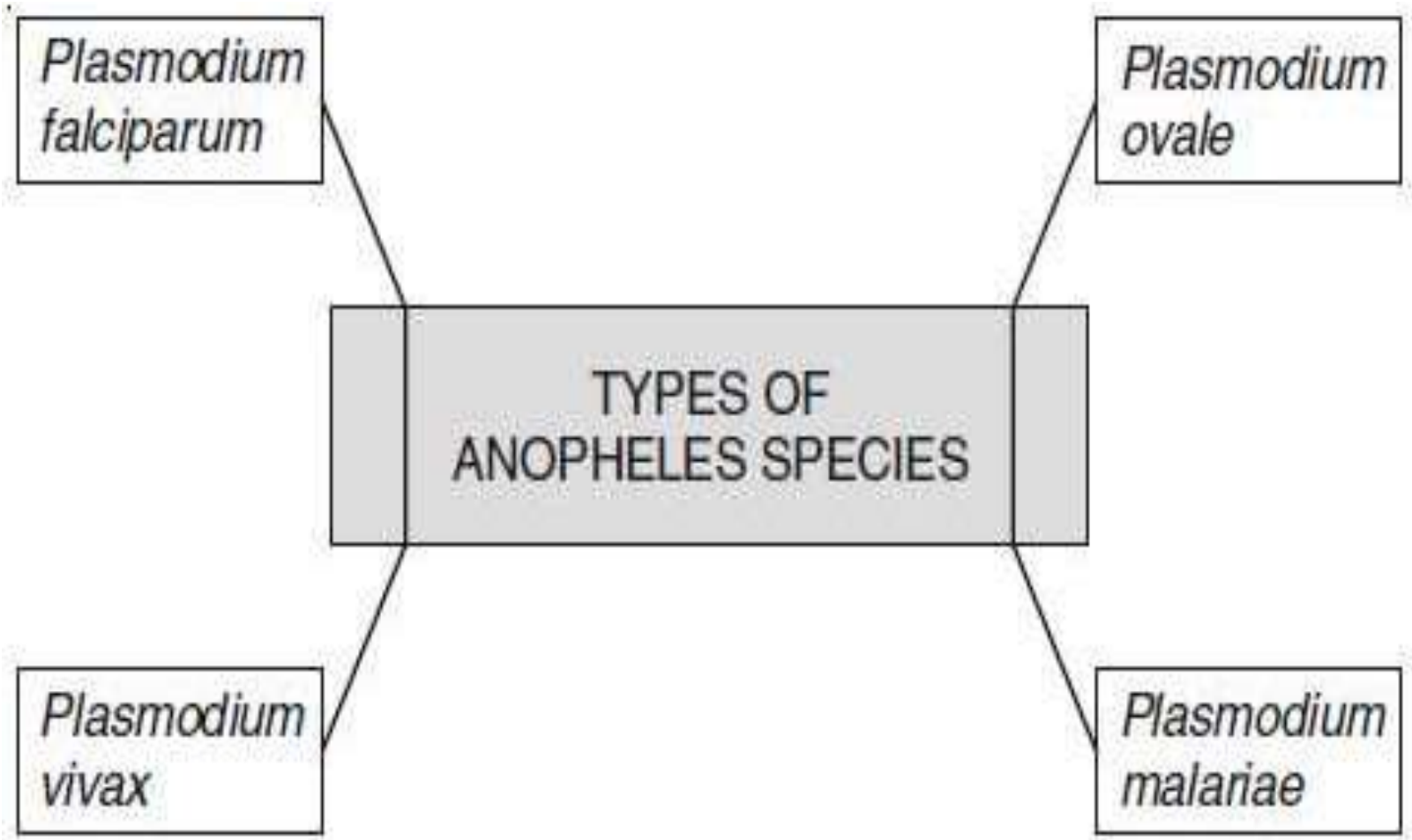
- Malaria is life threatening disease in humans caused by the infection with **protozoan parasites** of the genus, **Plasmodium**.
- These parasites spend an **asexual phase in a man** and a **sexual phase in female Anopheles mosquitos**.
- Out of several hundred known Anopheles species, four species infect man.
- Name is derived from **mala aria or bad air**, and has been called **ague, intermittent fever, marsh fever.**

The adult mosquitoes

Culex

Anopheles

Aedes

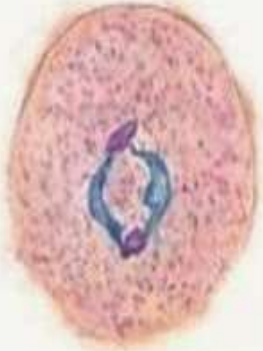
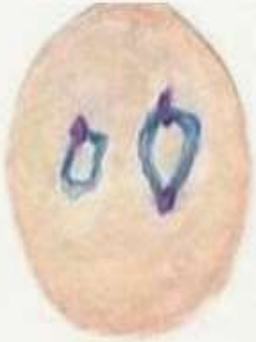

Plasmodium falciparum
Plasmodium ovale
TYPES OF ANOPHELES SPECIES
Plasmodium vivax
Plasmodium malariae

1. **Plasmodium falciparum**: It causes malignant form of malaria, which may cause death by invading the CNS.
2. **Plasmodium vivax**: It causes benign malaria in which fever revisits patient every 48 hours or on the third day.
3. **Plasmodium malariae**: It is responsible for the occurrence of malaria in which fever repeats after every 72 hours.
4. **Plasmodium ovale**: It is responsible for the mild malaria which is most commonly seen in West Africa.

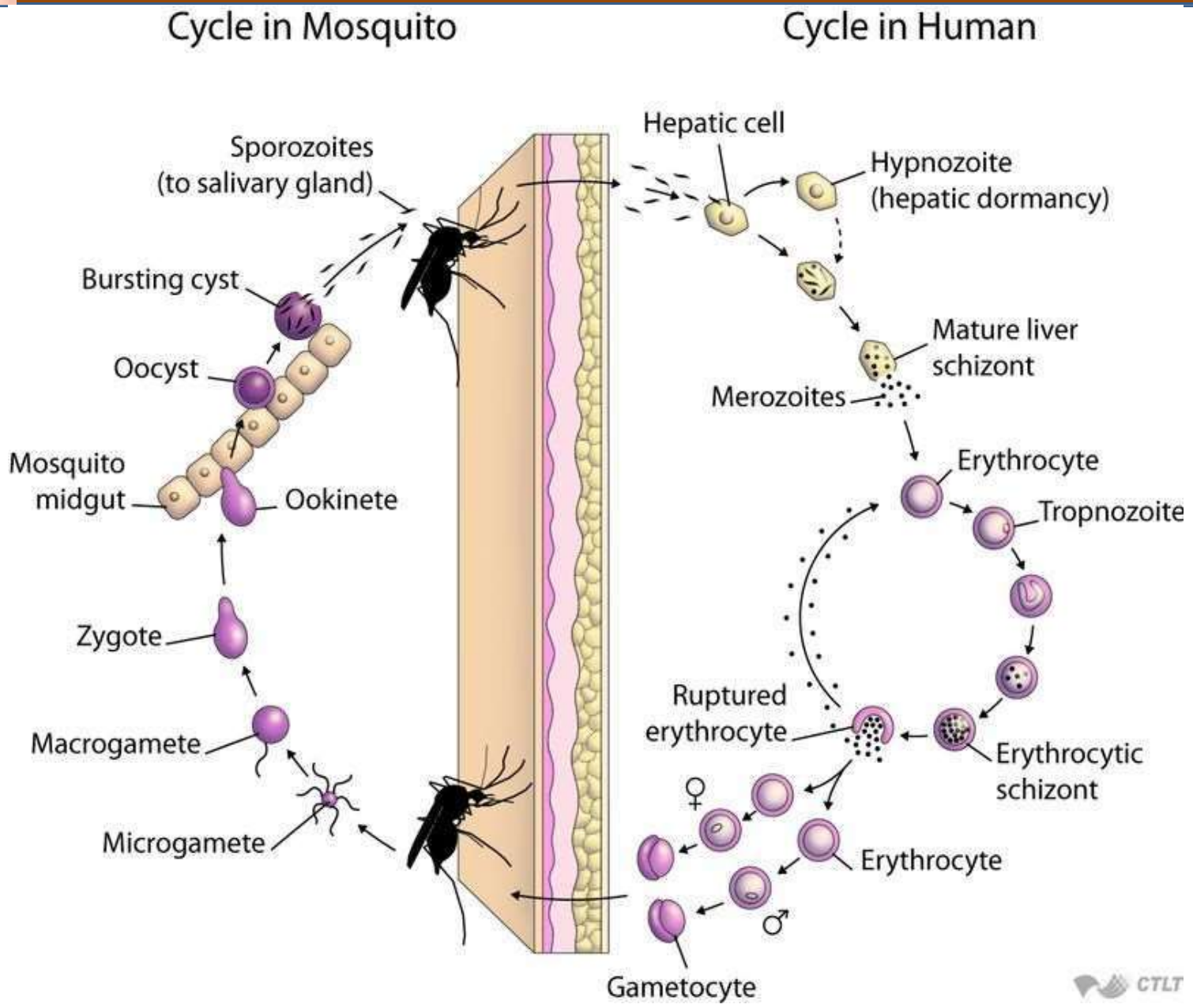
Key Morphological Differences Between Human *Plasmodium* Species in Blood Smears

P. vivax	*P. ovale*	*P. malariae*	*P. falcipar.*
1- enlarged erythrocyte . 2- Schüffner's dots. 3- ameboid trophozoite.	1-elongated oval erythrocyte. 2- Schüffner's dots. 3- compact trophozoite . 4- usually fewer merozoites in schizont .	1- compact trophozoite. 2- merozoites in rosette. 3- Band shape schizont.	1- numerous rings. 2- smaller rings. 3- no trophozoites or schizonts . 4- crescent-shaped gametocytes.

Early Stage Trophozoites

Falciparum	*Malariae/Knowlesi*	*Ovale*	*Vivax*
			
Delicate rings. Double dots (headphones)	Small, thick rings (rare headphones)	Thick ring forms while RBCs contain Shuffer's Dots	Thick ring forms while RBCs contain Shuffer's Dots
			
Multiple infection is common, while RBC size remain unchanged	RBC size remain unchanged	RBC appear enlarged, round/oval	Multiple infection is not as common as falciparum, RBC is enlarged

Malaria Life cycle



Asexual Phase in Human: Pre-erythrocytic Phase

- The female Anopheles mosquito feeds on vertebrate blood.
- Malaria infection is initiated through the bite of infected female
- Anopheles mosquito which releases motile sporozoites into the human bloodstream.
- Within 1–2 hours the sporozoites get entry into the parenchymal cells of the liver.
- Through repeated nuclear divisions sporozoites multiply and develop into schizonts.
- After the period of 10–16 days, liver cells rupture due to multiple repeated divisions of schizonts.
- This results in the release of approximately 20,000 merozoites into circulation.
- This stage is known as pre-erythrocytic or exo-erythrocytic phase of infection.

The entire pre-eryhrocytic phase lasts about 5–16 days depending on the parasite species: on an average 5-6 days for P. falciparum, 8 days for P. vivax, 9 days for P. ovale, 13 days for P. malariae

Erythrocytic Phase

Merozoites now enter into the circulation and invade erythrocytes. Some merozoites invade fresh liver cells and repeat erythrocytic cycle. Erythrocytes are invaded by merozoites for the following reasons.

1.The plasma constituents and hemoglobin serve as a source of several amino acids necessary for the survival of the parasite.

2.For rapid multiplication of merozoites, the purine bases (i.e. adenine and guanine) are obtained from erythrocytes which are then utilized to synthesize parasitic DNA and RNA molecules.

Schizogony Phase

- Inside erythrocytes, the merozoites continue to grow. In erythrocytes, the merozoites undergo asexual “multiplication, which results into formation of daughter cells, schizonts.
- Due to the repeated multiplication of the latter, erythrocyte ruptures and releases about 6–24 merozoites into the circulation.
- Each merozoites again invades fresh erythrocyte and the cycle of asexual multiplication is repeated again.
- This stage is known as schizogony phase of infection. It continues for 48–72 hours.

Sexual Phase

- After schizogony phase, some of the erythrocytic merozoites develop into male and female gametocytes.
- Such infected blood when ingested by female mosquito, the sexual forms (i.e. gametocytes) undergoes sexual reproduction within the gut of the insect.
- The resulting zygote, through various stages of development gives rise to the infective sporozoites.
- The latter gets localized in the salivary glands of the insect and enters the host blood circulation when the infected mosquito bites a healthy person.

Classification : **On the basis of chemical groups**

1. Quinolines

    A) Cinchona alkaloids: Quinine

    B) 4-aminoquinolines: Chloroquine, Mefloquine

    C) 8-aminoquinolines: Primaquine

2. Artemisinin family: Artemisinin, Artemether, Artesunate
3. Polycyclics: Halofantrine, Lumefantrine
4. 2,4-Diamopyrimidines: Pyrimethamine
5. Biguandes: cycloguanil
6. Sulphonamides: Sulfodoxine, Sulfadiazine, Sulfalene

On the basis of anti malarial activity:

- *Tissue schizonticides*

  e.g. Pyrimethamine and Primaquine

- *Blood schizonticides*

  e.g. chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines

- *Gametocytocides:*

  e.g. Chloroquine and quinine

- *Sporontocides:*

  e.g. Primaquine and chloroguanide

On the basis of anti malarial activity:

Tissue schizonticides for causal prophylaxis: These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrimethamine and Primaquine have this activity. However since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.

Tissue schizonticides for preventing relapse: These drugs act on the hypnozoites of P. vivax and P. ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

Blood schizonticides: These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines

Gametocytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal activity against all plasmodia, including P. falciparum.

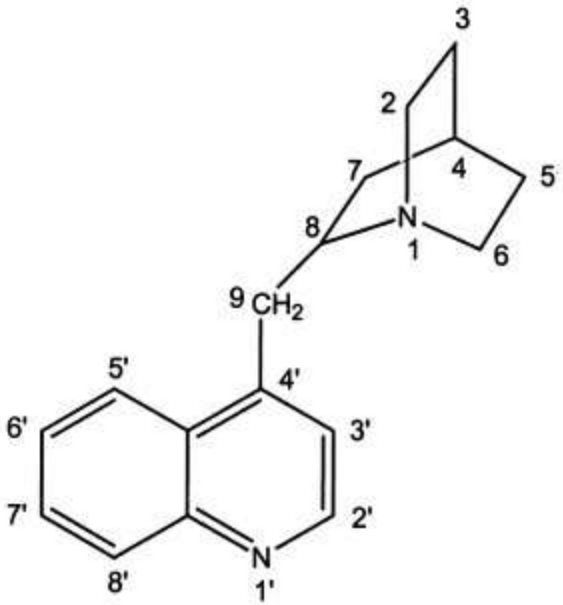
Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

Cinchona Alkaloids

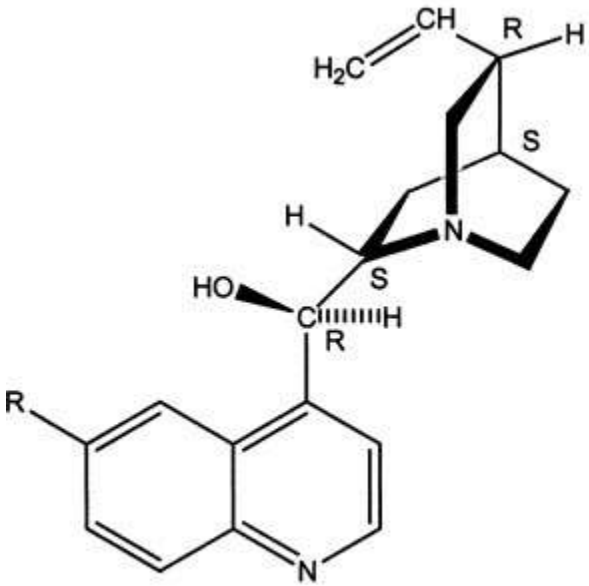
Cinhona tree produces four alkaloids.

These alkaloids are **4-quinolinemethanol derivatives** bearing a substituted **quinuclidine ring**.

These are **enantiomeric pair quinine and quinidine** and their **desmethoxy analogs cinchonidine for quinine** and **cinchonine for quinidine.** Their numbering system is based in **rubane.**

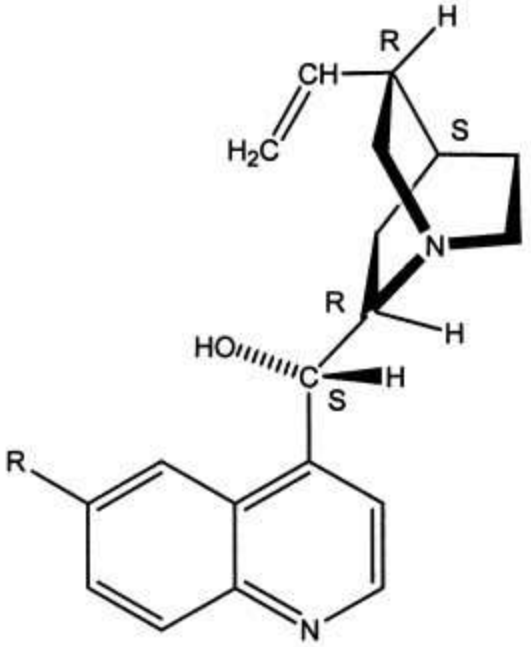


Rubane



Quinine R = OCH_3

Cinchonidine R = H



Quinidine R = OCH_3

Cinchonine R = H

Four stereochemical centers exist in the molecule (at C-3, C-4, C-8, and C-9). Differs at positions 8 and 9

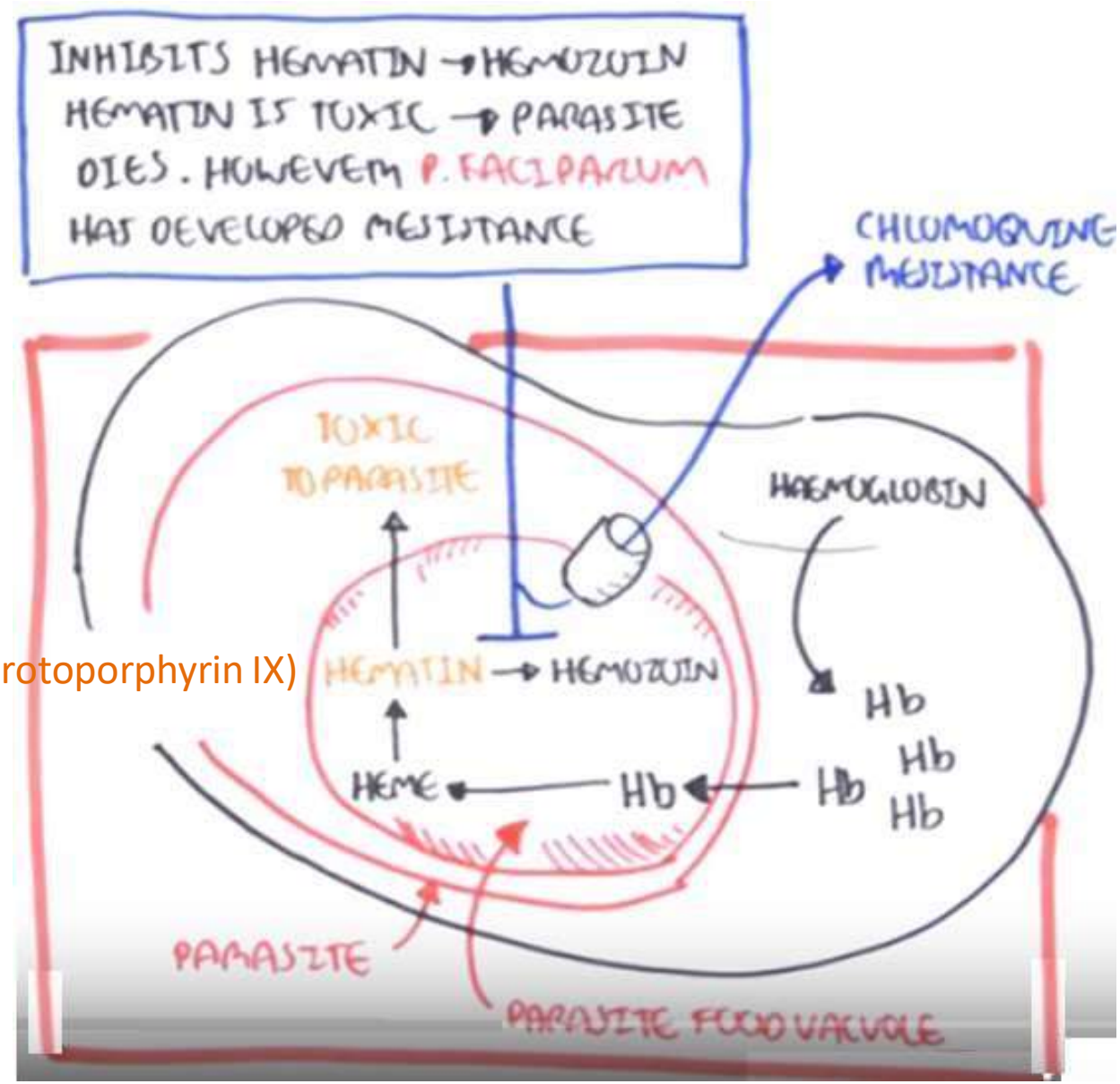
Quinine (absolute configuration of 3R:4S:8S:9R),
Quinidine (absolute configuration of 3R:4S:8R:9S), and their optical isomers all have antimalarial activity. Whereas their C-9 epimers (i.e., the epi-series having either 3R:4S:8R:9R or 3R:4S:8S:9S configurations) are inactive.

Quinine is use for malaria while quinidine is antiarrythmic agents

SAR

- None of the alterations to quinine have improved its action against the parasites.
- The methoxy group of the quinoline ring and the vinyl group of quinuclidine are not required for antimalarial activity.
- Saturation of Vinyl group result in formation of dihydroquinidine which slightly more potent than quinine.
- The secondary alcohol group is essential for activity. Reduction of the alcohol group increases toxicity as well as mitigating antimalarial activity.
- Quinidine (8R, 9S)
- Quinine (8S, 9R)
- The stereoisomer, quinidine, is a more potent antimalarial.

MOA of Quinine, Chloroquine, Amodiaquine, Lumefantrine

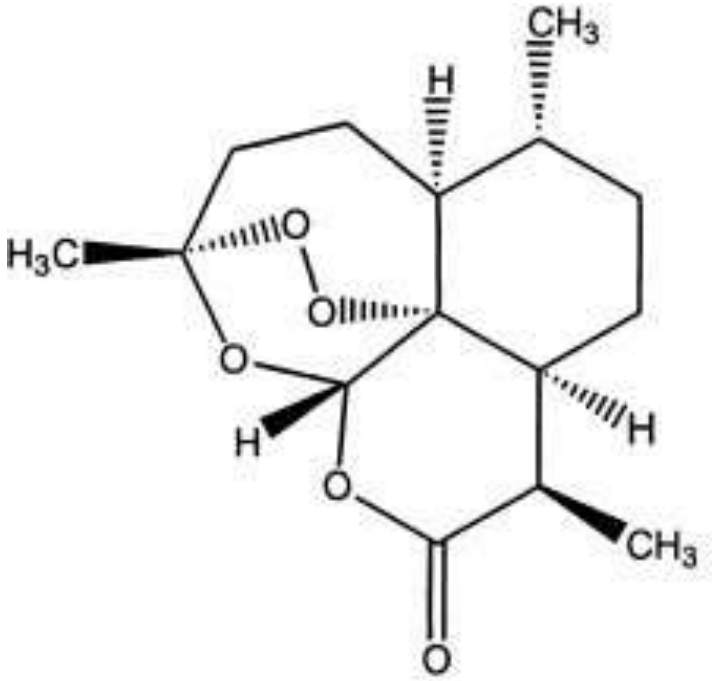


(Ferriprotoporphyrin IX)

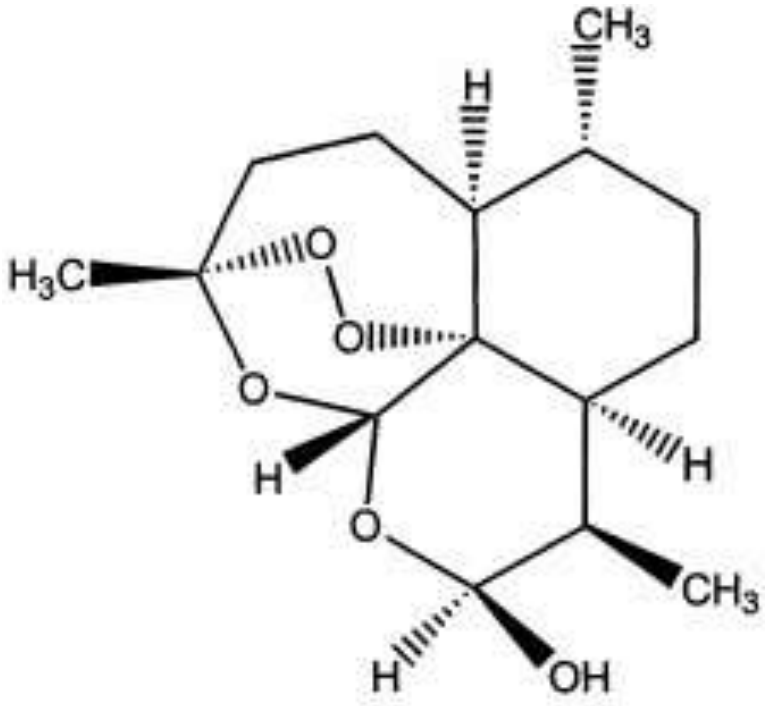
Artemisinin

The artemisinin series are the newest of the antimalarial drugs

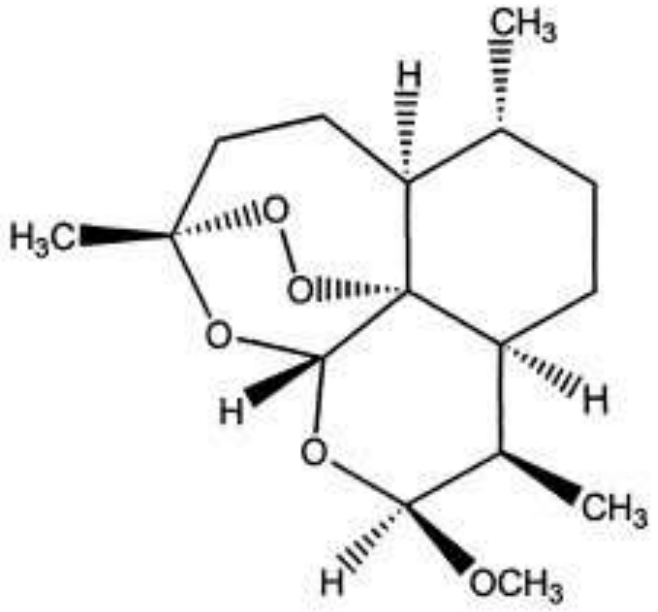
- They are structurally unique
- The parent compound, artemisinin, is a natural product extracted from the dry leaves of ***Artemisia Annua*** *(sweet* wormwood)



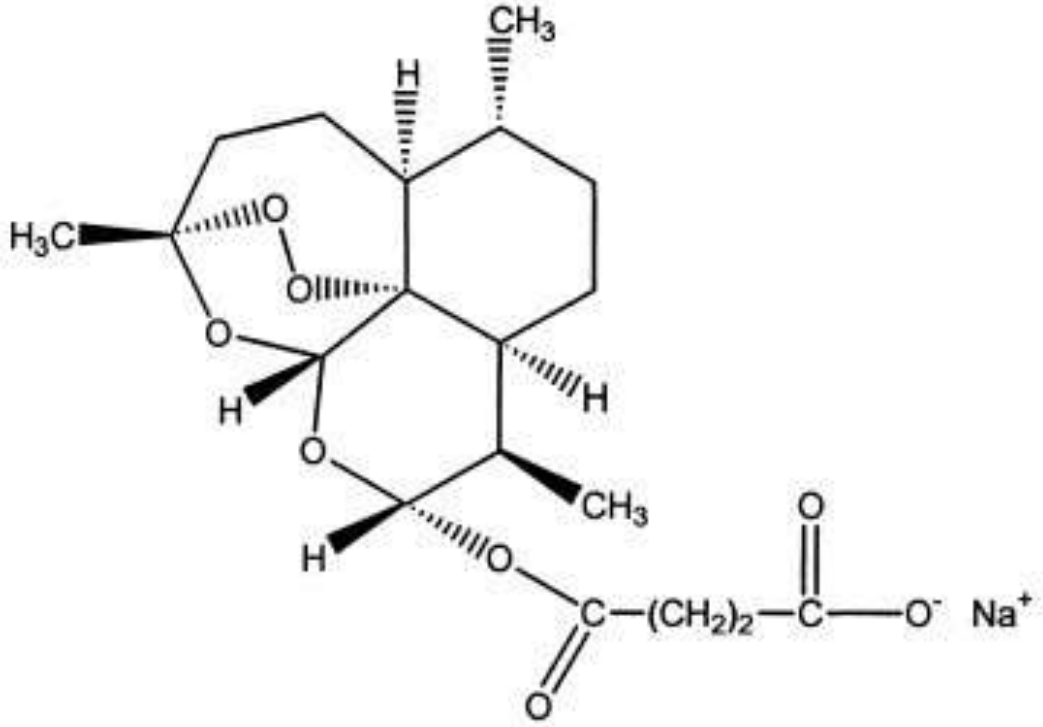
Artemisinin



Dihydroartemisinin



Artemether (oil soluble) R = CH_3
Artemotil (oil soluble) R = CH_2CH_3



Artesunate (water soluble)

All artemisinin compounds are active against the *Plasmodium genera that cause malaria.*

- Artemisinin is *lactone endoperoxide*
- The important structural feature is trioxane consisting of the endoperoxide

MOA

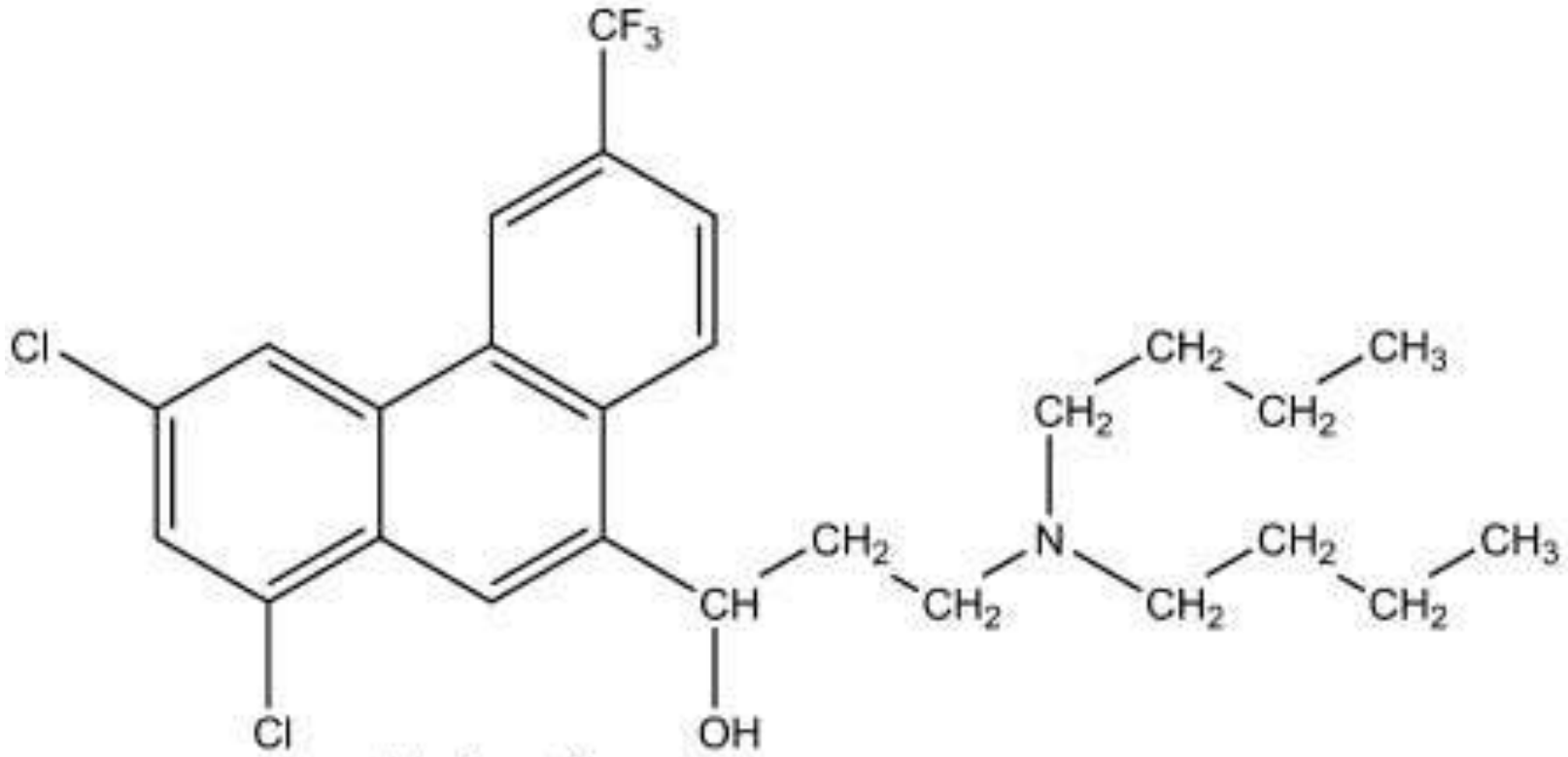
- In erythrocyte, the malaria parasite consumes the hemoglobin consisting of ferrous (Fe+2) iron converting it to toxic hematin containing ferric (Fe+3) and then reduced to heme with its ferrous iron.
- The heme iron reacts with the trioxane moiety releasing reactive oxygen and carbon radicals and the highly reactive Fe-IV O species.
- These species are postulated to be lethal to the parasite.

Polycyclics (Amino alcohols)

Halofantrine (9-phenanthrenemethanol)

- *Structurally, halofantrine differs from all other antimalarial drugs.*
- Halofantrine is a schizonticide (sites 1 and 2) and has no affect on the sporozoite, gametocyte, or hepatic stages
- Specific mechanism of action against the parasite is not known
- Halofantrine can affect nerve conduction in cardiac tissue.

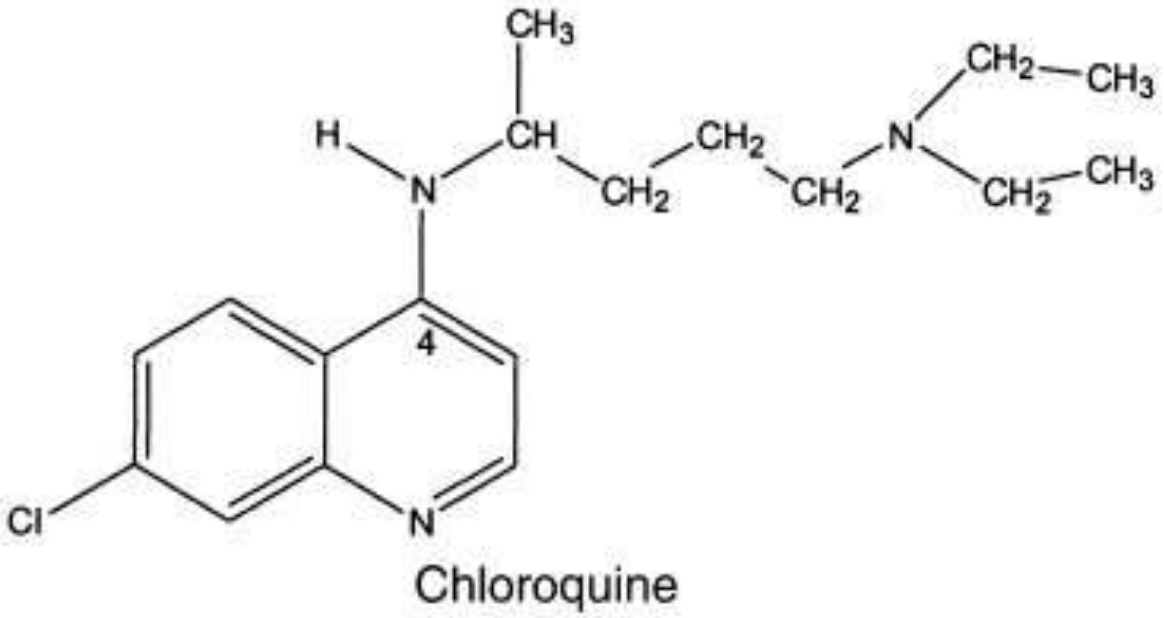
Alternative drug for treatment of chloroquine-sensitive & chloroquine-resistant P. falciparum malaria



Halfantrine

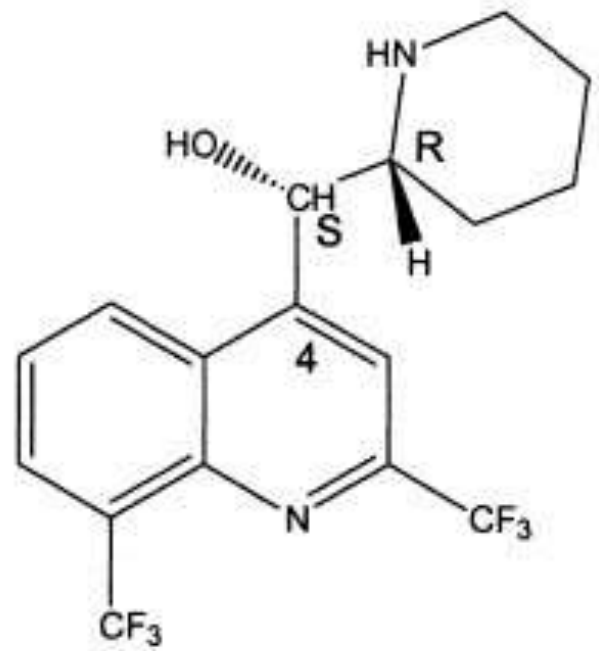
4-Aminoquinolines

- The 4-aminoquinolines antimalarials that are based on the quinine structure.
- This group is substituted at the same position 4 as quinine and have an asymmetric carbon equivalent to quinine's C-9 position



Chloroquine

***(RS)-N'*-(7-chloroquinolin-4-yl)-*N*,*N*-diethyl-pentane-1,4-diamine**



Mefloquine

SAR of 4-aminoquinoline:

A dialkylaminoalkyl side chain, having 2, 5 carbon atoms between the nitrogen atoms is optimal for activity

- tertiary amino group in side chain is very important for antimalarial activity
- Chloro group at 7 & 8 position of quinoline increases activity
- Alkylation at C-3 & C-8 position diminished activity
- Replacement of N-ethyl group with hydroxyethyl group in chloroquine reduces toxicity
- CF3 group in mefloquine block the site of metabolism

Until recently, chloroquine was main antimalarial drug used for both prophylaxis and treatment

- **It is indicated for *P. vivax, P. malariae, P. ovale, and susceptible strains of P. falciparum***

MAO similar to quinine

- 4-aminoquinolines are not effective against exoerythocytic parasites

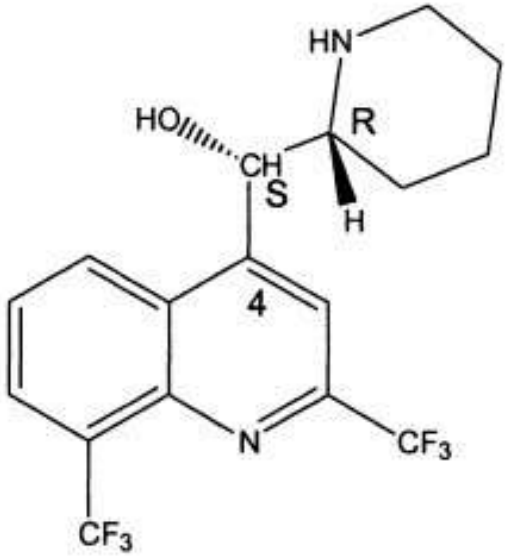
Adverse reactions: retinopathy, hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency , muscular weakness, exacerbation of psoriasis and porphyria, and impaired liver function

Mefloquine

- It is a new 4-aminoquinoline, marketed as *R,S-isomer*
- It differs from the other agents in this class... by having two trifluromethyl groups at positions 2' and 8'.. And no electronegative substituents at positions 6' (quinine) or 7' (chloroquine)
- Mefloquines site of action also differs
- It is schizonticide (site 2)..... acting before the parasite can enter the erythrocyte.

MAO: Interfere with parasite's ability to process heme.

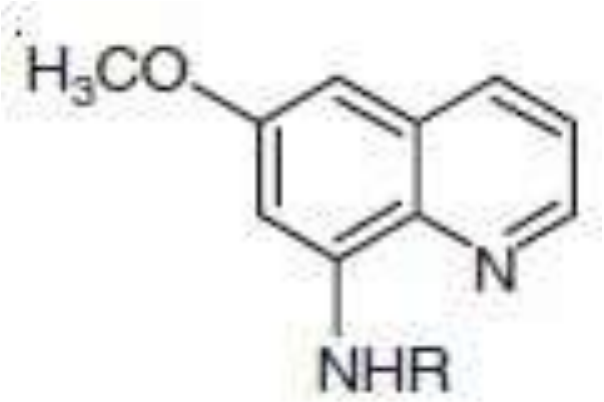
- FDA warning that this drug can cause exacerbate mental disorders

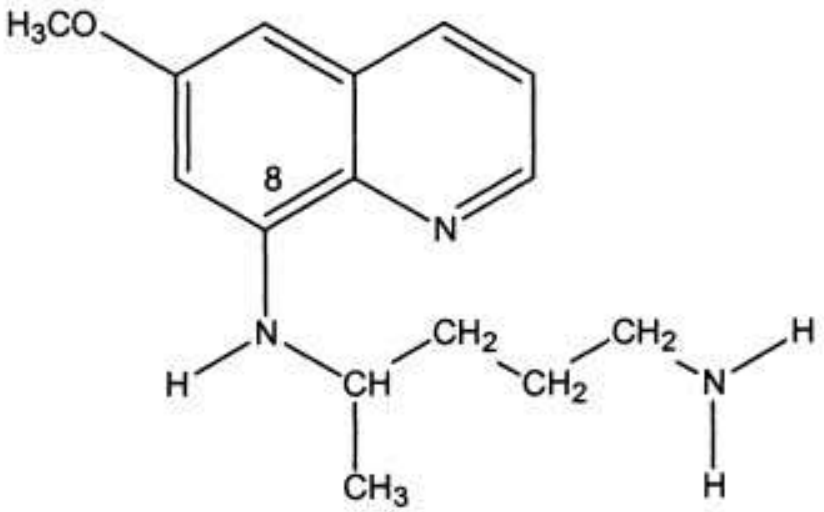


Mefloquine

SAR of 8-aminoquinoline

- ***Primaquine,*** ***Pamaquine, Pentaquine, Isopentaquine***
- little changes in the structure–activity relationships in this series
- All four agents have a 6-methoxy moiety same as quinine
- **Compounds with high chemotherapeutic index had a 6-methoxy group in quinoline nucleus**
- In **8-Aminoquinolines the substituents are on the quinoline are** located at position 8 rather than carbon-4 as found on the cinchona alkaloids





Primaquine

- **Optimal activity was obtained with 2- 6 methylene group between the two nitrogen of the side chain**
- **the terminal aliphatic amino group may be primary, secondary or tertiary.**
- 8-aminoquinolines have one asymmetric carbon
- But there is little difference in antimalarial activity of the stereoisomers
- Any substitution on the quinoline ring will lead to decrease its antimalarial activity.
- Methoxy group at Position 6 is responsible for optimum activity but this group is not essential for antimalarial activity.

Primaquine

•Primaquine is the only 8-aminoquinoline currently in use for the treatment of malaria

• It has narrow spectrum of activity

• being indicated only for exoerythrocytic *P. vivax malaria*

• To treat endoerythrocytic *P. vivax, chloroquine is used with* Primaquine.

MOA of 8-Amino quinoline(Primaquine)

Step-1

- primaquine can generate ROS via an autoxidation of the 8-amino group. The formation of a radical anion at the 8-amino group

Step-2

- As a result, cell -destructive oxidants, such as hydrogen peroxide, superoxide, and hydroxyl radical, can be formed.

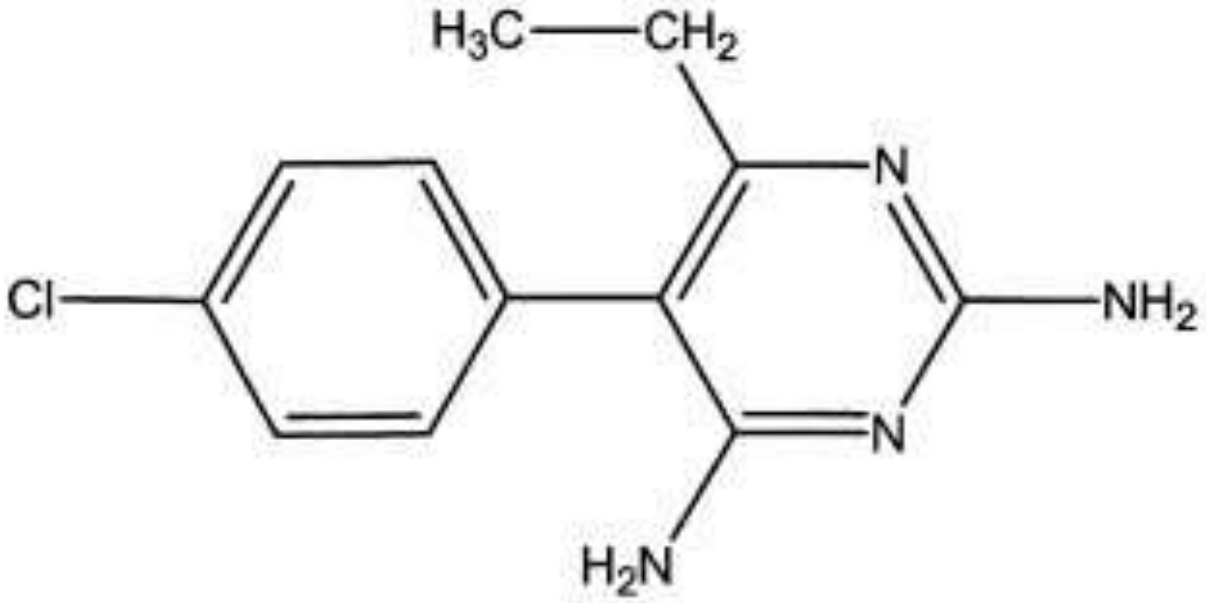
Step-3

- leading to oxidative damage to critical cellular components.

Pyrimethamine (**2, 4-Diaminopyrimidines) DHFR inhibitor**

MAO

- The synthesis of thymidine 5'-monophosphate from deoxyuridine 5'-monophosphate is a universal reaction in all cells forming DNA.
- There are enough differences in this enzyme and dihydrofolate reductase found in mammalian, bacterial, and *Plasmodium cells*
- **Pyrimethamine inhibits the reduction of folic acid and dihydrofolic acid to the active tetrahydrofolate coenzyme form...by inhibiting DHFR**
- **Therefore, dTMP is not synthesized from dUMP**
- **Which inhibit parasite DNA synthesis.**



Pyrimethamine

5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine

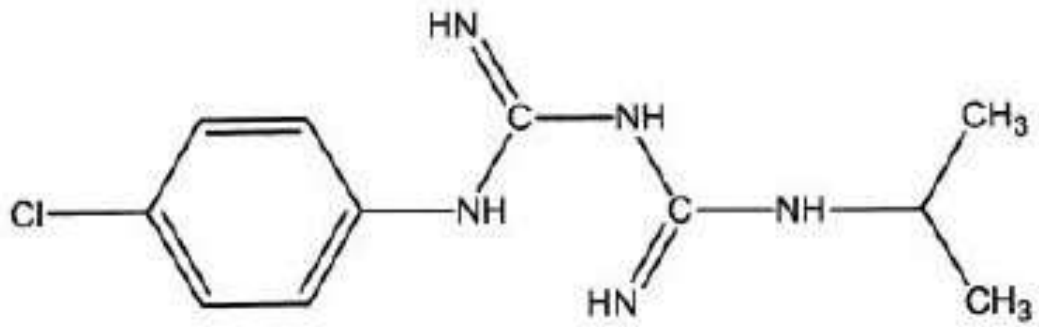
Pyrimethamine acts by inhibiting DHFR at lower concentration

- **It is used in combination with sulphonamides**
- **Combination is used against chloroquine-resistant strains of *P. falciparum***
- The combination is considered to a schizontocide (site 2)
- The sulfonamide, sulfadoxine, interferes with the parasite's ability to synthesize folic acid
- 25 mg Pyrimethamine & 500 mg Sulfadoxine combination is used

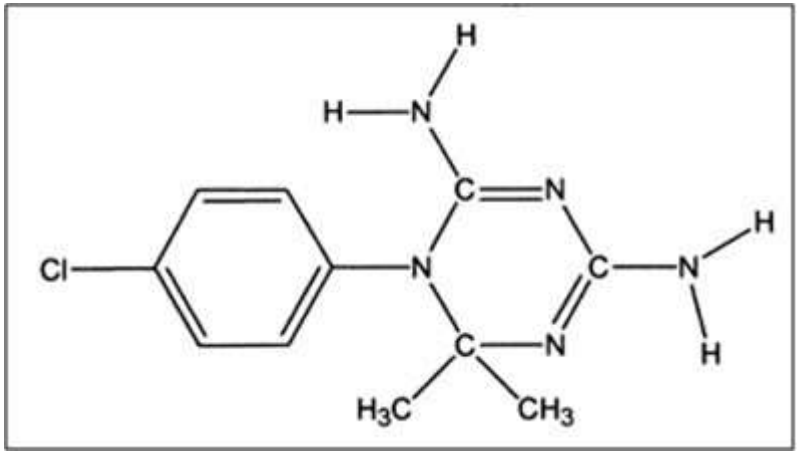
Proguanil (DHFR inhibitor)

•Proguanil (Chloroguanide) is converted to cycloguanil with the help of CYP2C19which interferes with deoxythymidylate synthesis by inhibiting plasmodial dihydrofolate reductase

• Cycloguanil is blood schizontocide



Proguanil



Cycloguanil

Combination Therapy:

Resistance is frequent problem in the prophylaxis and treatment of malaria, therefore combination of drugs having different MOA have been developed.

- The drugs which are included in combination therapy should have:

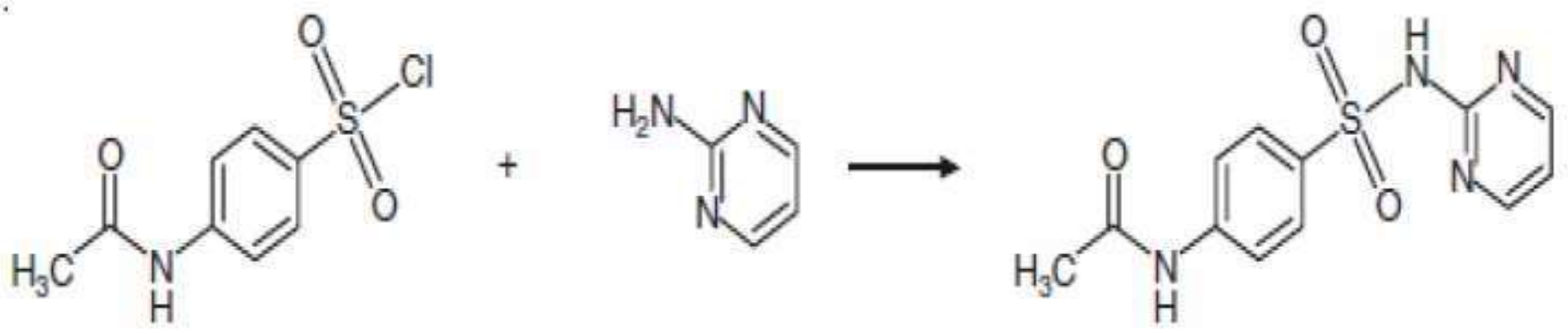
1. Dissimilar modes of action.
2. Different spectra of adverse effects.
3. Additive or synergistic activity.

Examples:

1. Sulfadoxine and Pyrimethamine
2. Atovaquone and Proguanil (Cycloguanil)
3. Artemether and Lumefantrine

- First combination inhibits folic acid synthesis and dihydro folate reductase
- Second combination acts on the parasite's mitochondrial electron transport system and its dihydrofolate reductase.
- Both the drug in third combination act on hematin, but by two different mechanisms.

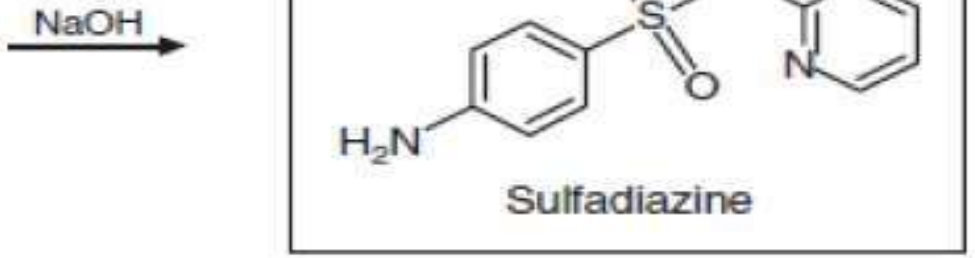
Synthesis of Sulfadiazine



4-acetamidobenzene-sulfonyl chloride

2-amino-pyrimidine

(I)



Sulfadiazine

Synthesis of Pyrimethamine