LEARNING MATERIAL

COURSE: B.PHARMACY, 6th Sem, Medicinal Chemistry, BP -601T

Module 02: Antibiotics

Unit 2.1 Macrolides

2.2 Prodrug

2.3 Anti malarials

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MACROLIDE

Objectives:

1. Understand the chemistry of drug with respect to their biological activity.
2. Know the Importance of SAR of Drugs
3. Know the metabolism, Adverse Effect and therapeutic value of drugs.
4. Understand the importance of Drug design.

Learning Outcomes:

1. Students will Learn about the structures and Medicinal uses of Drugs.
2. Students will learn about relation of structure with its activity.
3. Students will Learn about the designing of drugs.

Macrolides

The macrolides are a group of antibiotics produced by various strains of Streptomyces and having a macrolide ring structure linked to one or more sugars. They act by inhibiting protein synthesis, specifically by blocking the 50S ribosomal subunit. They are broad spectrum antibiotics.

Examples: Erythromycin, Azithromycin, Clarithromycin, Roxithromycin etc.....

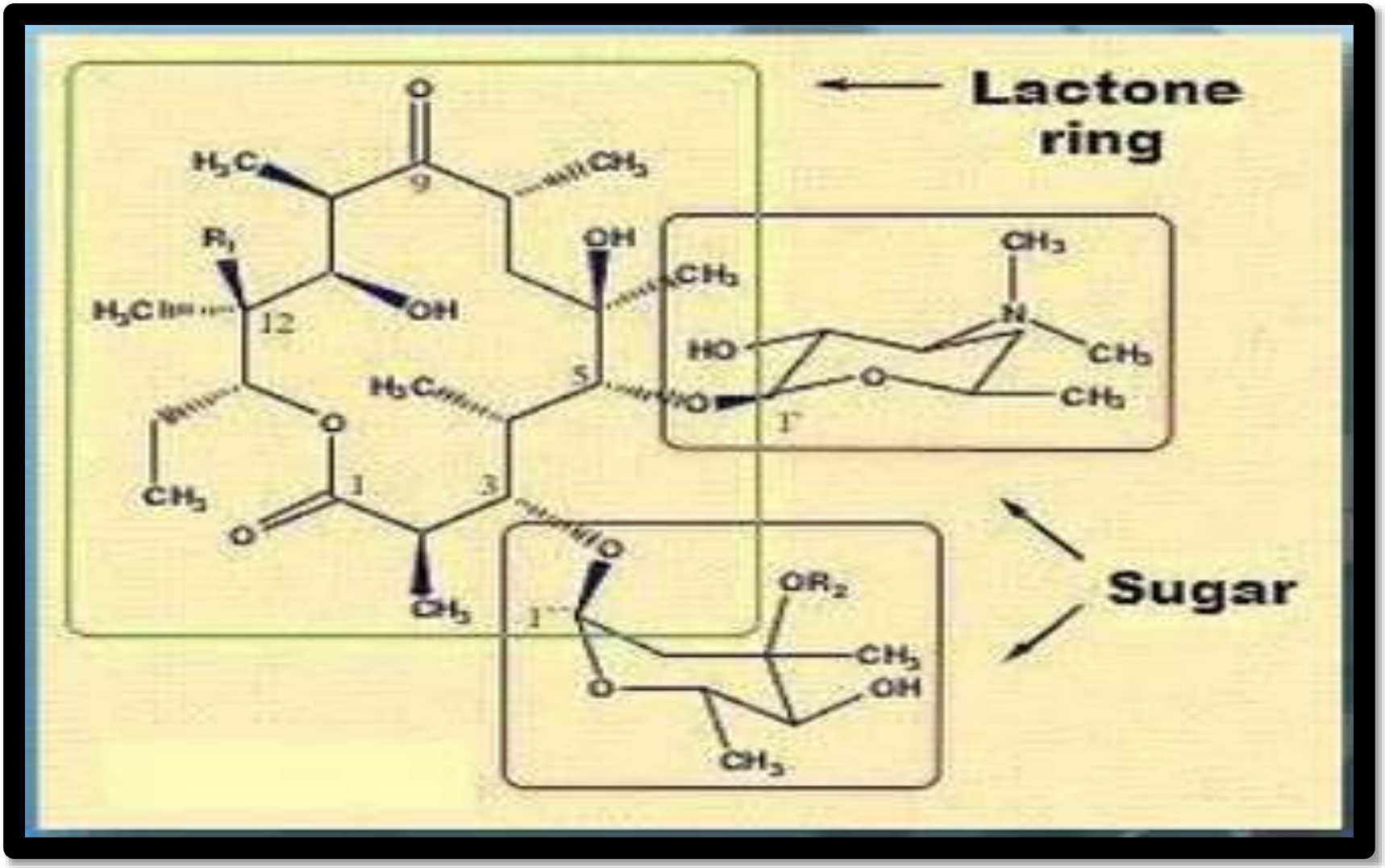
SOURCE:

These Are Produced By Streptomyces species.

CHEMISTRY:

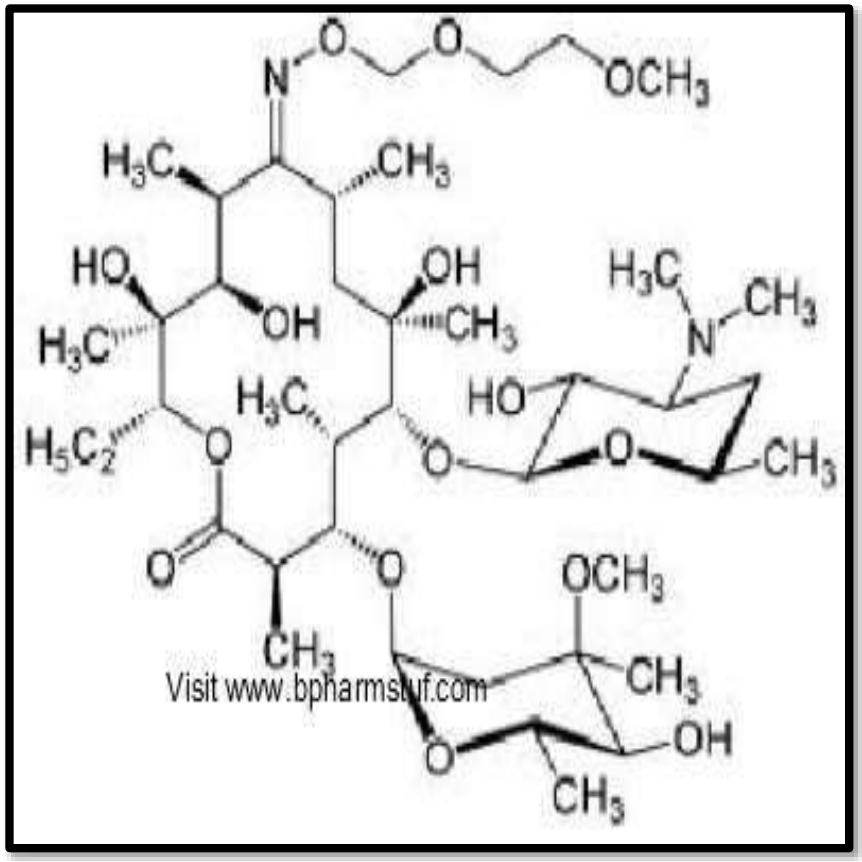
- A macro cyclic lactone, usually having 12 to 17 atoms.
- A ketone group.
- One or two amino sugars linked to the nucleus.
- A neutral sugar linked either to amino sugar or to lactone ring.
- The presence of the dimethyl amino moiety on the sugar residue, which explains the basicity of these compounds and consequently formation salts.

General structure of macrolide



Structure Activity Relationship

- As macrolide are unstable in acidic pH, a no. of strategies have been utilized to improve the acidic stability of erythromycin.
- The addition of hydroxylamine to the ketone to formoxime e.g. roxithromycin
- Alteration of c-6 hydroxyl group: nucleophilic functionality which initiates erythromycin degradation.
- The azalides (azithromycin)are semi- synthetic 15 -membered congeners in which a nitrogen atom has been introduced to expand a 14-membered precursor-leads to an extended spectrum of action.



Physical & Chemical properties

- Water insoluble molecules.
- Occurs as crystalline powders.
- Stable in aqueous solutions at or bellow room temperature.
- Unstable in acidic conditions and forms internal cyclic ketal.

Mechanism of action of macrolide

Macrolide is a protein synthesis inhibitor:

Macrolide bind to 50S ribosomal subunit

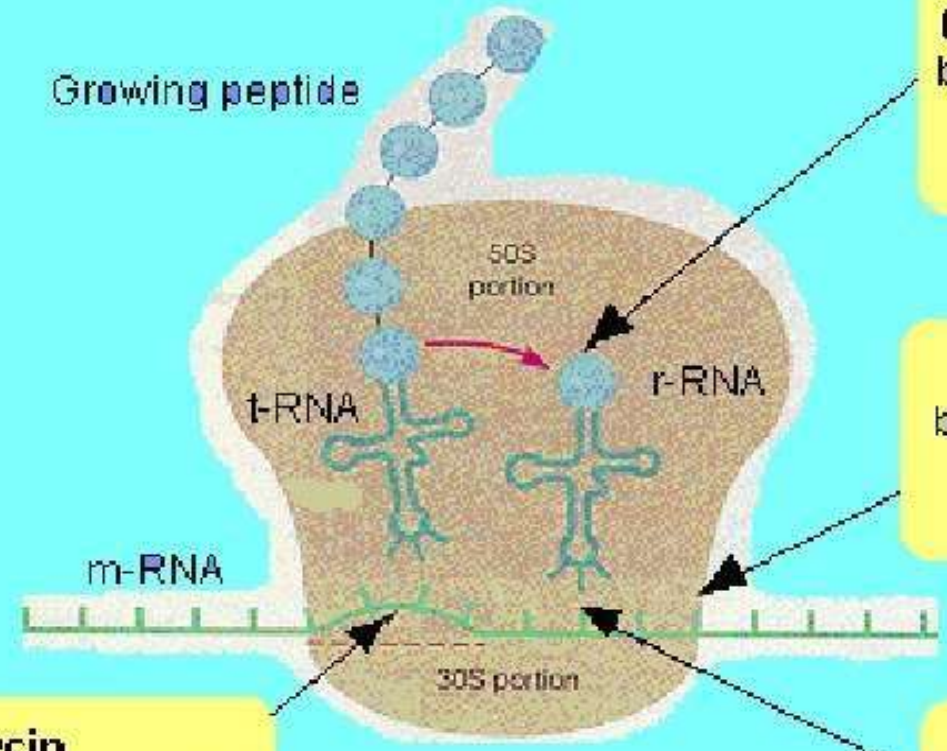
↓

Inhibit polypeptide chain elongation & protein synthesis inhibition

↓

Result in inhibition of growth & multiplication

INHIBITION OF PROTEIN SYNTHESIS



Clarithromycin
binds to 50S r-RNA and inhibits formation of peptide bond

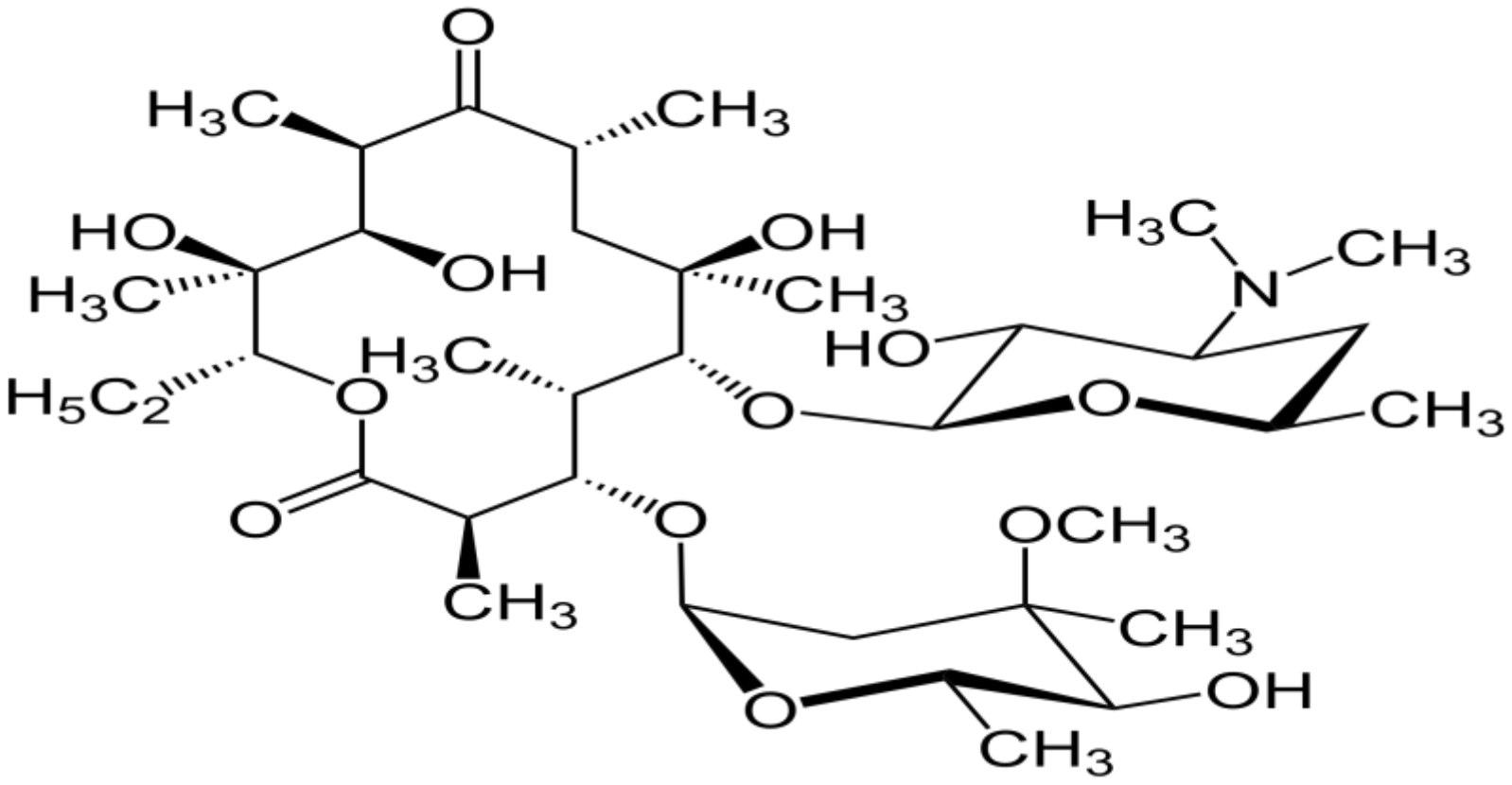
Erythromycin
binds to 50S r-RNA and prevents movement along m-RNA

Roxithromycin
changes shape of 30S r-RNA and causes m-RNA to be read incorrectly

Azithromycin
interfers with the t-RNA anticodon reading of m-RNA codon

Types of macrolide

- **Erythromycin**



Source:

Isolated from *streptomyces erythreus*

Physical properties:

- Yellow to white crystalline powder.
- Soluble in alcohol, slightly soluble in water.
- Stable at neutral pH.

- **Dosage forms:**

- Oral and topical dosage forms.
- Enteric coted and delayed realese dosage forms.

- **Drug interactions:**

- Anticoagulants
- Benzodiazepines

Uses:

It is used in,

- Streptococcal pharyngitis
- Tonsillitis
- Respiratory infection
- Diphtheria
- Tetanus
- Syphilis & gonorrhoea
- Whooping cough

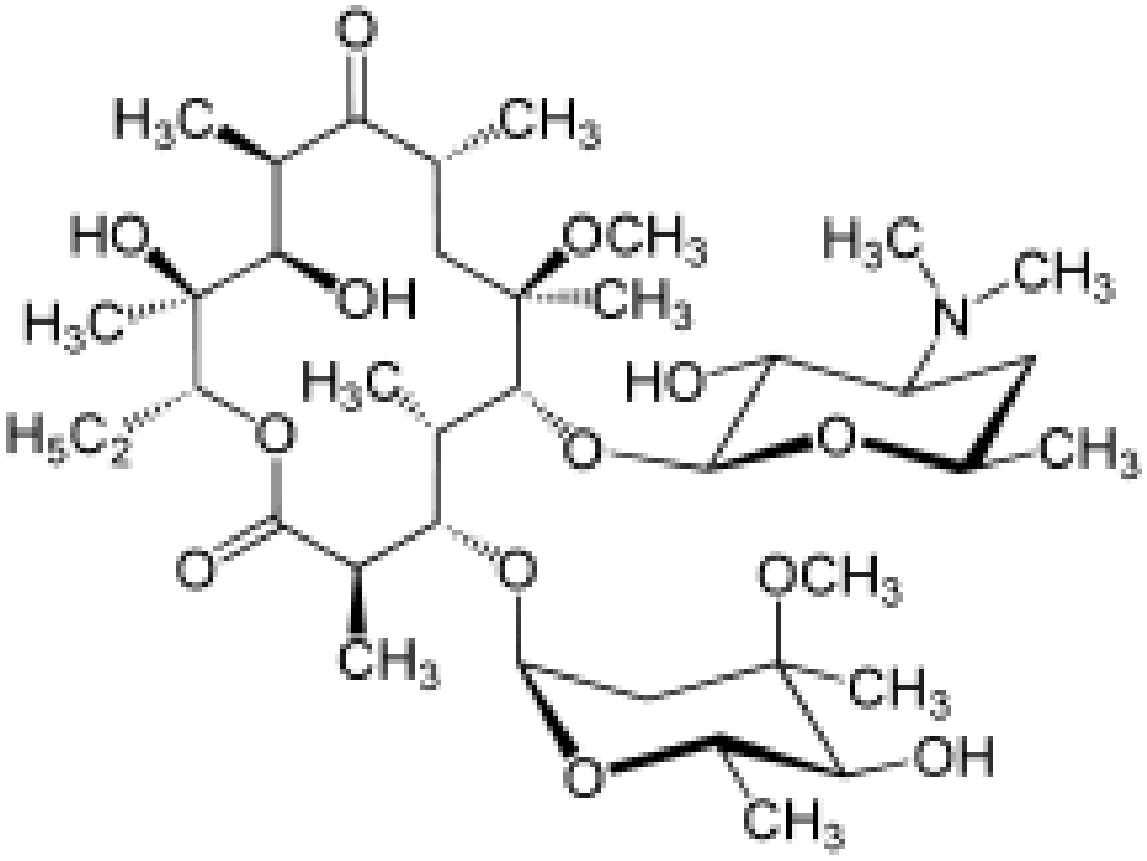
Adverse effects

- Abdominal cramps
- Epigastric distress
- Jaundice
- Transient deafness
- Hypersensitivity rashes
- Hearing impairment

Therapeutic agents of erythromycin

- Erythromycin ethylsuccinate
- Erythromycin estolate
- Erythromycin gluceptate
- Erythromycin lactobionate

❖Clarithromycin



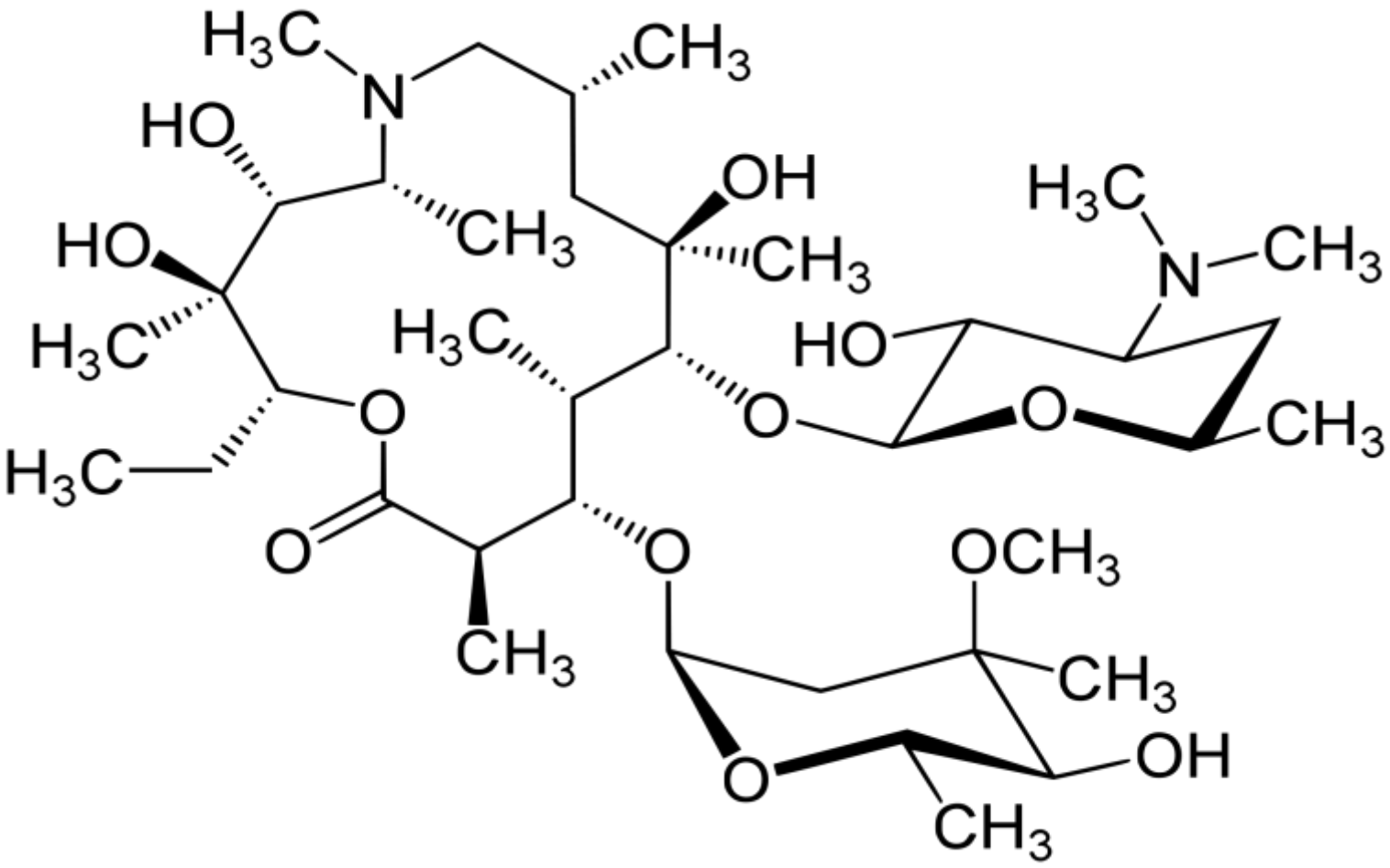
Advantages

- Cannot undergo cyclic ketal formation, so doesn't cause cramp in GI
- Higher blood concentrations.
- More lipophyl.
- Lower doses with less intervals.

Uses:

- Atypical mycobacterial infection
- Resistant leprosy
- Toxoplasmosis
- *H.Pylori* induced peptic ulcers

Azithromycin



❖Properties:

1.Nitrogen containing 15-membered lacton ring macrolides(azalides).

2.Stable under acidic conditions ,because it does not form cyclic ketal.

3.Strongest activity against mycoplasma pneumoniae.

4.More effective on gram-negative bacteria.

5.Well tolarated.

Uses:

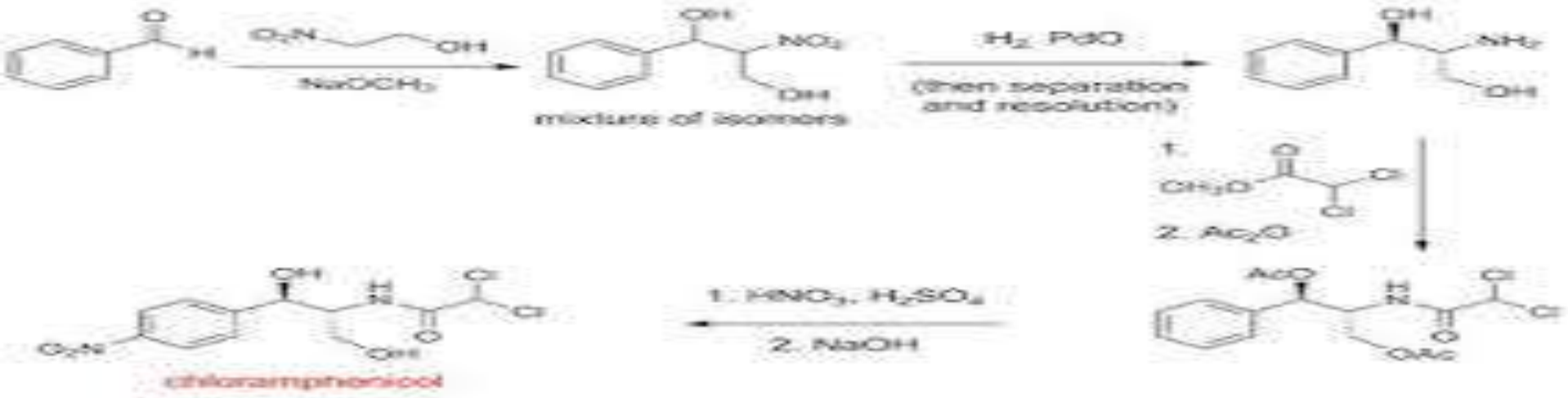
- In the treatment of Urogenital infections caused by *N.gonorrhoeae* and *Chlamydia trachomatis.*

- For the treatment of respiratory tract infections.

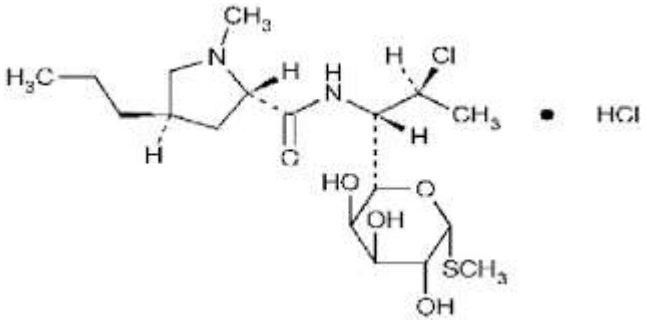
- Pregnant women infected with scrub typhus: Azithromycin can suitable for doxycyclin.

Miscellaneous

Structure and Synthesis of Chloramphenicol



Clindamycin

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PRODRUG

Introduction

- Almost all drugs possess some undesirable physicochemical and biological properties.
- Drug candidates are often discontinued due to issues of poor pharmacokinetic properties or high toxicities
- Their therapeutic efficacy can be improved by eliminating the undesirable properties while retaining the desirable ones.
- This can be achieved through biological, physical or chemical means.

- The **Biological approach** is to alter the route of administration which may or may not be acceptable to patient.

- The **Physical approach** is to modify the design of dosage form such as controlled drug delivery of drug.

- The best approach in enhancing drug selectivity while minimizing toxicity, is the **chemical approach** for design of prodrugs.

Definition

- 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.

History of Prodrugs

- The first compound fulfilling the classical criteria of a prodrug was **acetanilide**, introduced into the medical practice by Cahn and Hepp in 1867 as 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.

- 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 c**hloramphenicol palmitate** used in the form of suspension in children.

Objectives of Prodrug Design

- There are three basic, overlapping objectives in prodrug research:

1. **Pharmaceutical Objectives:**

- To improve solubility, chemical stability, and organoleptic properties
- To decrease irritation and/or pain after local administration,
- To reduce problems related with the pharmaceutical technology of the active agent.

2. Pharmacokinetic Objectives:

- To improve absorption (oral and by non-oral routes).
- To decrease presystemic metabolism to improve time profile.
- To increase organ/ tissue-selective delivery of the active agent.

3. Pharmacodynamic Objectives:

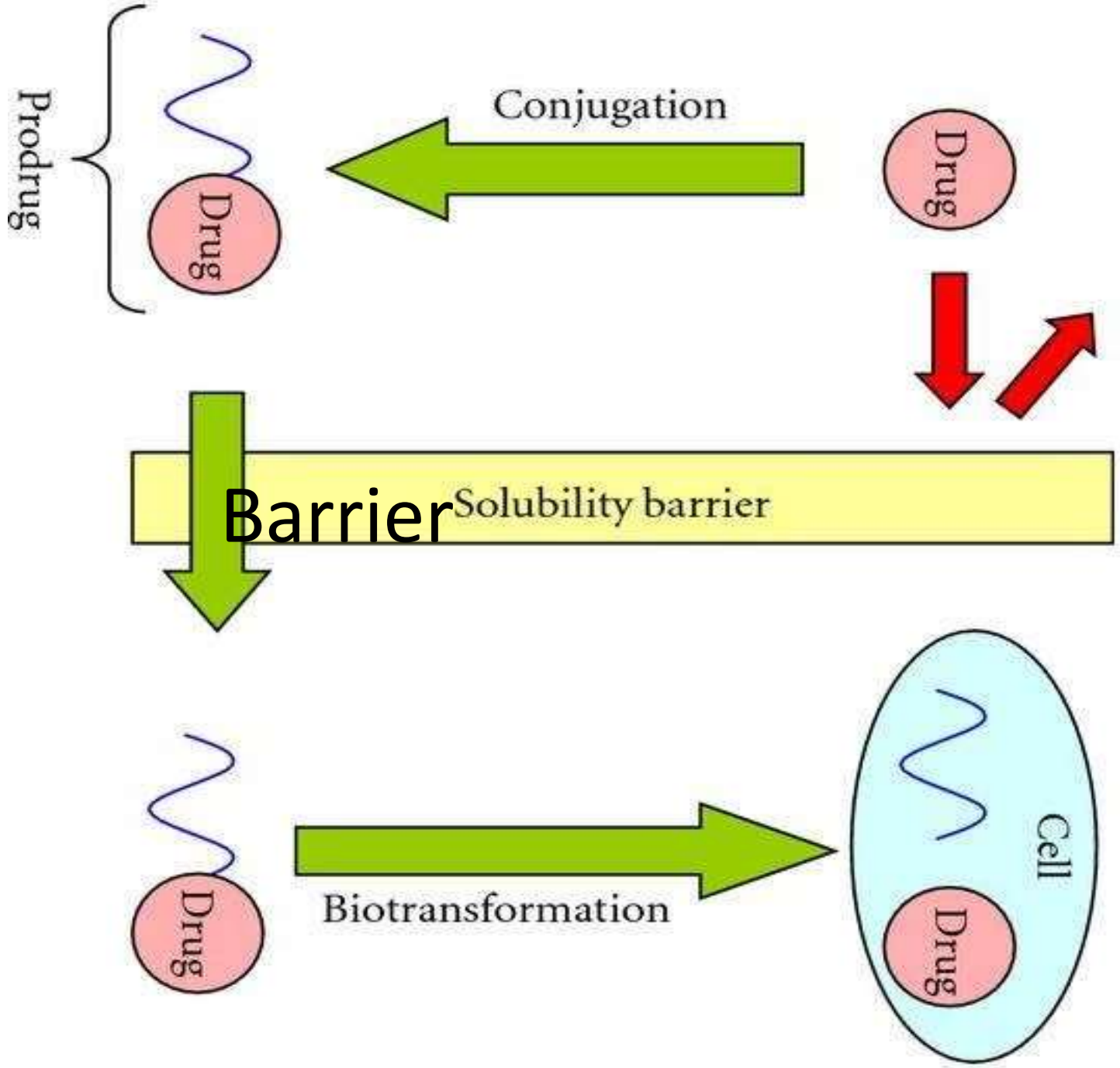
- To decrease toxicity and improve therapeutic index.
- To design single chemical entities combining two drugs (co-drugs strategy.

Prodrug concept

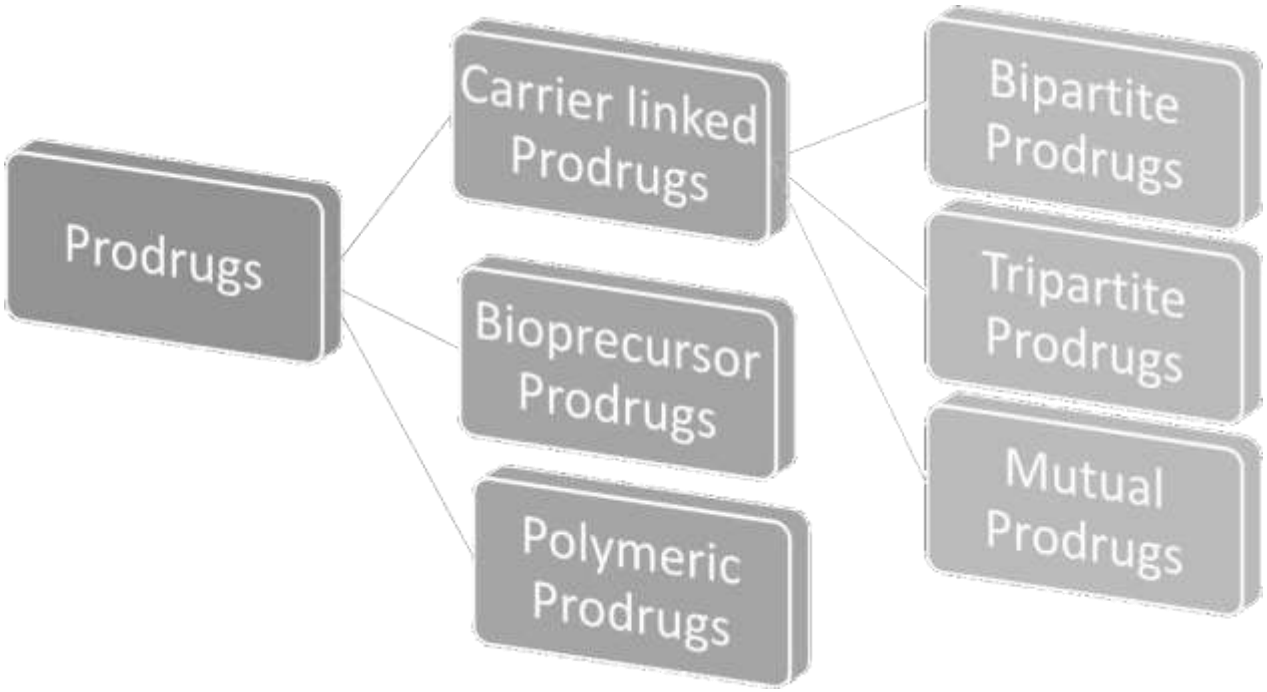
- The awareness that the onset, intensity and duration of drug action are greatly affected by the physicochemical properties of drug has promoted the emergence of various prodrugs.

- Most of the limitations can be overcame by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site.

- The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming various physical, chemical and social barriers is certainly the utilization of the prodrug approach holds great potential.


Prodrug
Drug
Conjugation
Drug
Barrier
Solubility barrier
Drug
Biotransformation
Cell
Drug

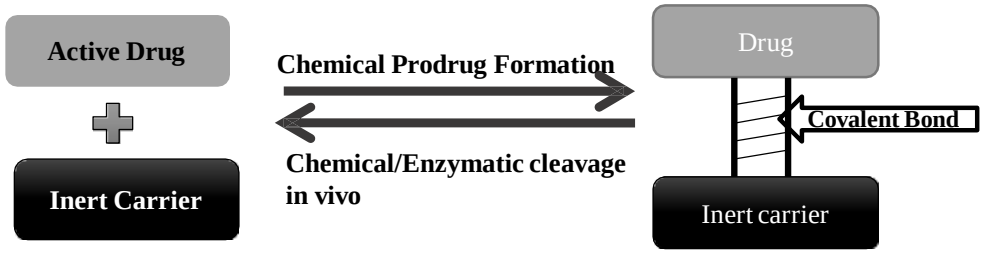
Classification of Prodrugs



Carrier linked prodrug

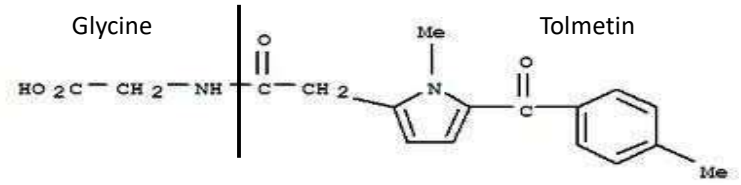
❖Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties.

❖The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety.

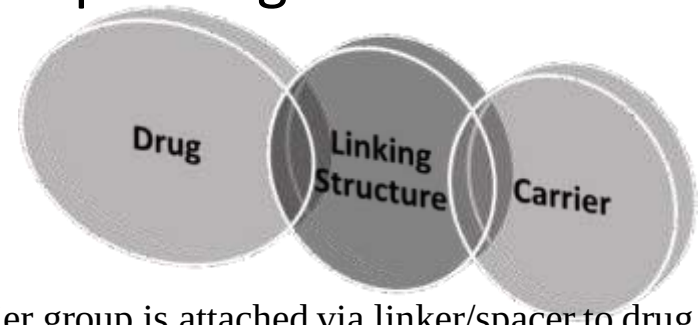


Bipartite prodrug

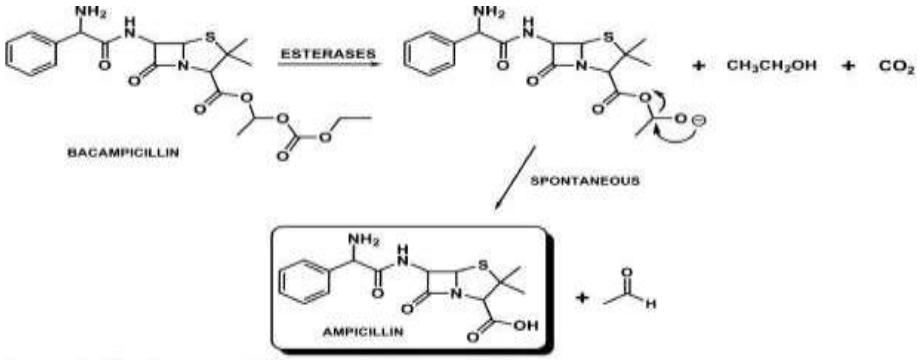
- It is composed of one carrier (group) attached to the drugs.
- Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically.
- E.g. Tolmetin-glycine prodrug.



Tripartite prodrug

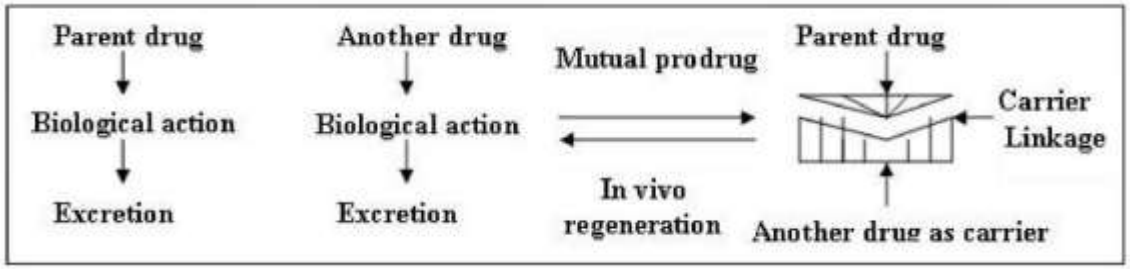


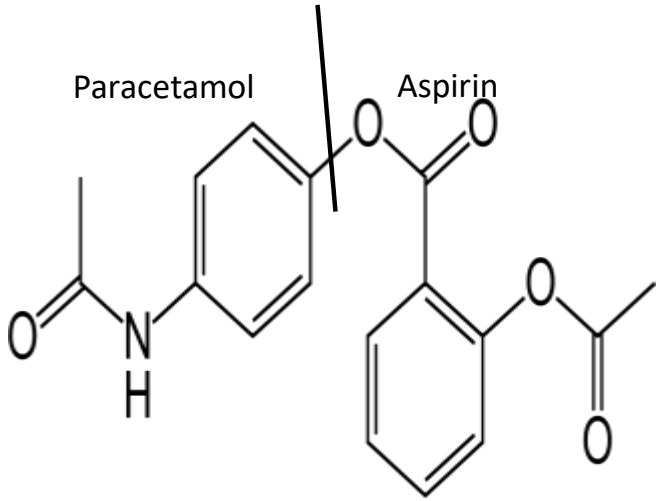
The carrier group is attached via linker/spacer to drug.



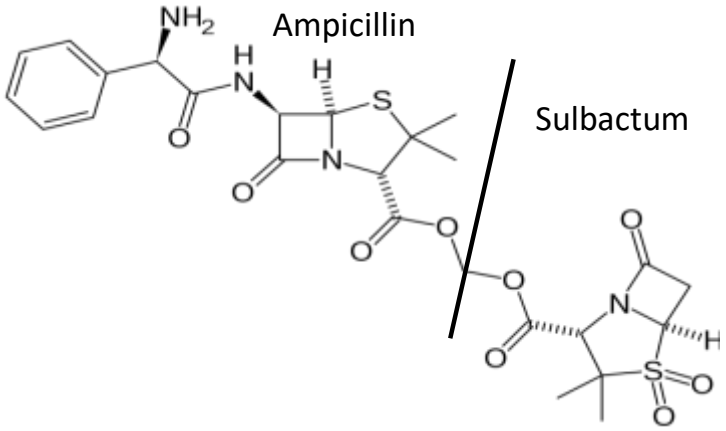
Mutual Prodrugs

- A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa.
- A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked.
- Benorylate is a mutual prodrug aspirin and paracetamol.
- Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum.





Benorylate



Sultamicillin

Bioprecursors

- 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.
- Eg: phenylbutazone. Phenylbutazone gets metabolized to oxyphenbutazone that is responsible for the anti inflammatory activity of the parent drug

• Polymeric Prodrugs

- Also known as macromolecular prodrug, the drug is dispersed or incorporated into the polymer (both naturally occurring and synthetically prepared) system without formation of covalent bond between drug and polymer.
- Eg: p–phenylene diamine mustard is covalently attached to polyamino polymer backbone polyglutamic acid.

Novel Classification

- Type I Prodrugs
- Type II Prodrugs

- Type I prodrugs are bioactivated inside the cells (intracellularly). Examples of these are anti-viral nucleoside analogs that must be phosphorylated and the lipid-lowering statins.

- Type II prodrugs are bioactivated outside cells (extracellularly), especially in digestive fluids or in the body's circulation system,

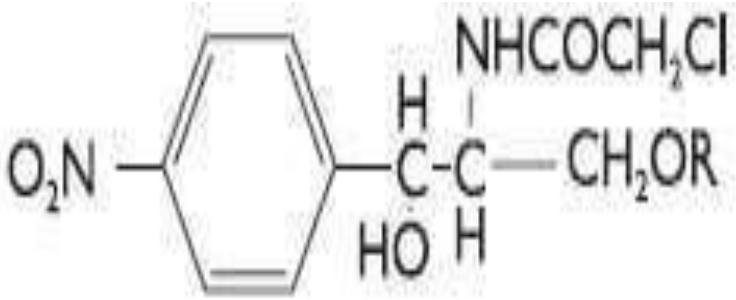
Type	Bioactivation site	Subtype	Tissue location of bioactivation	Examples
Type I	Intracellular	Type IA	Therapeutic target tissues/cells	Aciclovir, fluorouracil, cyclophosphamide, diethylstilbestrol diphosphate, L-DOPA,mercaptopurine, mitomycin, zidovudine
		Type IB	Metabolic tissues (liver, GI mucosal cell, lung etc.)	Carbamazepine, captopril, carisoprodol, heroin, molsidomine, leflunomide, paliperidone,phenacetin, primidone, psilocybin, sulindac, fursultiamine, codeine
Type II	Extracellular	Type IIA	GI fluids	Loperamide oxide, oxyphenisatin, sulfasalazine
		Type IIB	Systemic circulation and other extracellular fluid compartments	Acetylsalicylate, bacampicillin, bambuterol, chloramphenicol succinate, dipivefrin, fosphenytoin,lisdexamfetamine, pralidoxime
		Type IIC	Therapeutic target tissues/cells	ADEPTs, GDEPs, VDEPs

Applications of Prodrugs

Pharmaceutical applications

❑ Masking Taste or 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.
- Eg: 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 hydrolysed to active chloramphenicol by the action of pancreatic lipase.
- Eg:Ethyl mercaptan has a boiling point of 25ºC and a strong disagreeable odour. But diethyl dithio isophthalate, prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless.

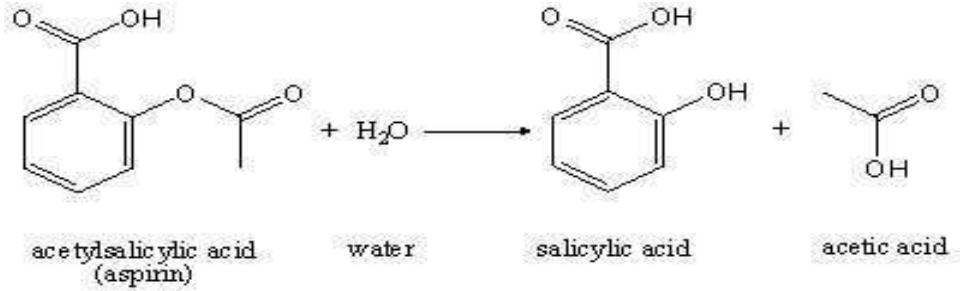


Chloramphenicol, R=H

Chloramphenicol palmitate, R= $CO(CH_2)_{14}CH_3$

❑ Reduction of gastric irritation

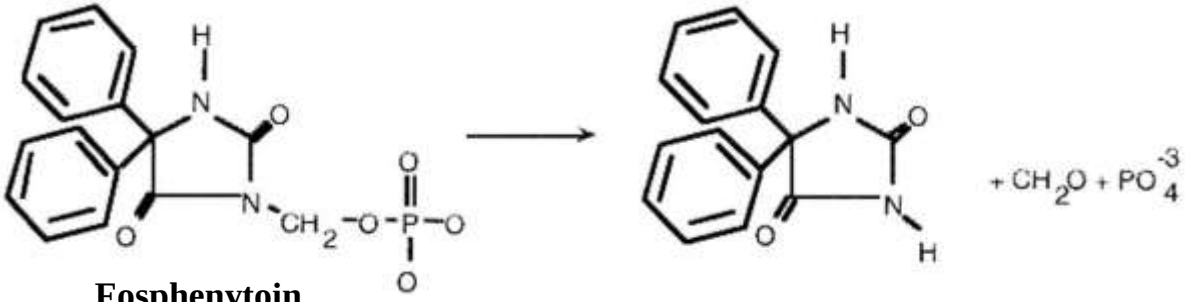
Eg: Aspirin is a prodrug of salicylic acid is designed to reduce gastric irritation



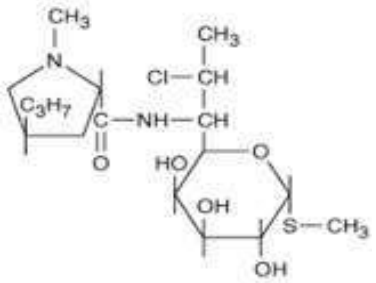
Drug	Prodrug
Salicylic acid	Aspirin
Diethyl stilbestrol	Fosfestrol
Kanamycin	Kanamycin pamoate
Phenylbutazone	N-methyl piperazine salt
Nicotinic acid	Nicotinic acid hydrazide
Oleandrin	oleandrin acetate

❑ Reduction in Pain at Site of Injection

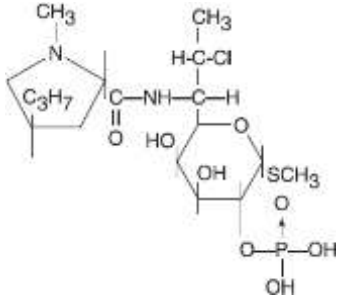
- Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs.
- Eg: IM injection of antibiotics like clindamycin and anti convulsant like phenytoin was found to be painful due to poor solubility. So, prodrugs are produced like 2'phosphate ester of clindamycin and hydantoic ester prodrug of phenytoin (fosphenytoin) an aqueous soluble form of phenytoin respectively.



Fosphenytoin **Phenytoin**



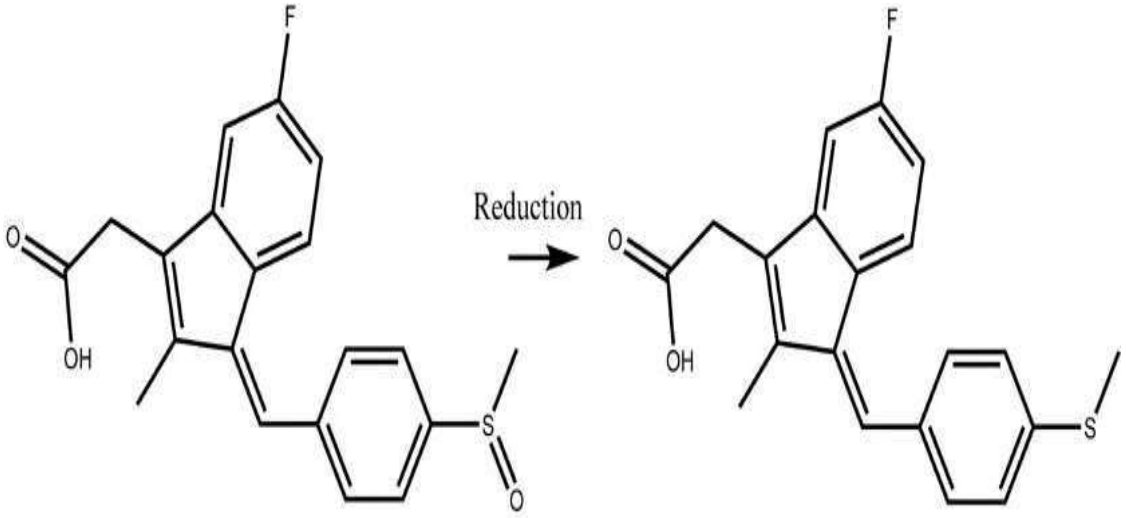
Clindamycin



Clindamycin–2 dihydrogen phosphate

❑ Enhancement of drug solubility and dissolution rate

- The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use.
- Eg: 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.
- The prodrug approach is also made useful for better gastrointestinal absorption.
- Eg: sulindac, a prodrug of sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration
- Testosterone - testosterone phosphate ester
- Tetracycline - tetralysine
- Diazepam - diazepam L-lysine ester



R,S-sulindac prodrug

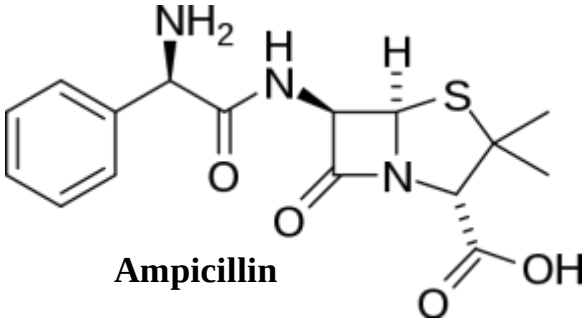
Sulindac sulfide, active NSAID

❑ Enhancement of chemical stability

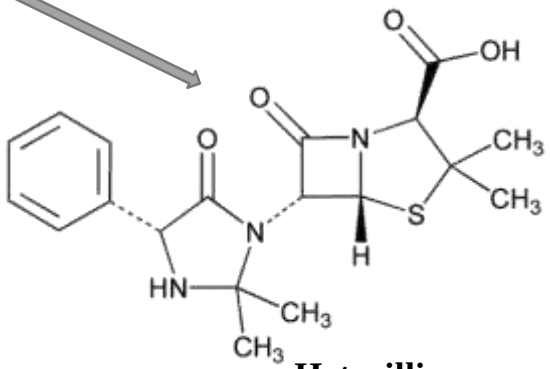
- Chemical stability is an utmost necessary parameter for every therapeutic agent.

- 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.

- Eg: Inhibiting the auto aminolysis, which occur due to capability of NH_2 group of side chain to attach β lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin. 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



Ampicillin



Hetacillin

Pharmacokinetic Applications

❑ Improvement of Bioavailablity

➢ Enhancement of Oral Bioavailablity

- Various therapeutic agents such as water soluble vitamins, structural analogues of natural purine and pyrimidine nucleoside, dopamine, antibiotics like ampicillin and carbenicillin, phenytoin and cardiac glycoside such as gitoxin suffers with poor gastrointestinal absorption.

- The prime cause of the poor absorption of these agents is their highly polar nature, poor lipophilicity and/or metabolism during the absorption process.

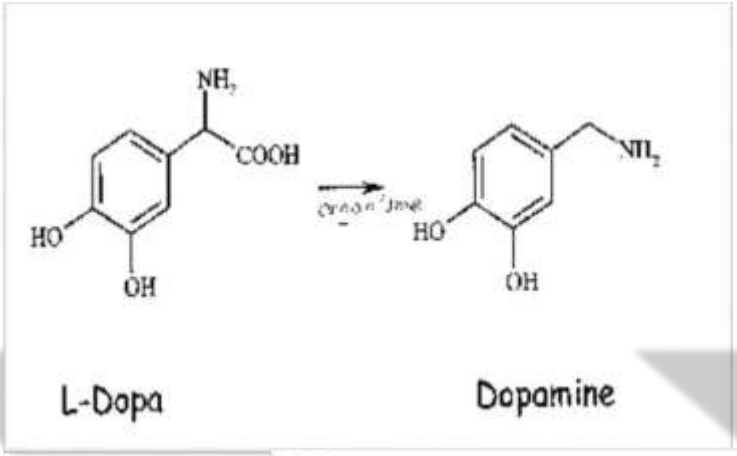
- On contrary gitoxin, a cardiac glycoside has very poor oral bioavailability due to limited aqueous solubility

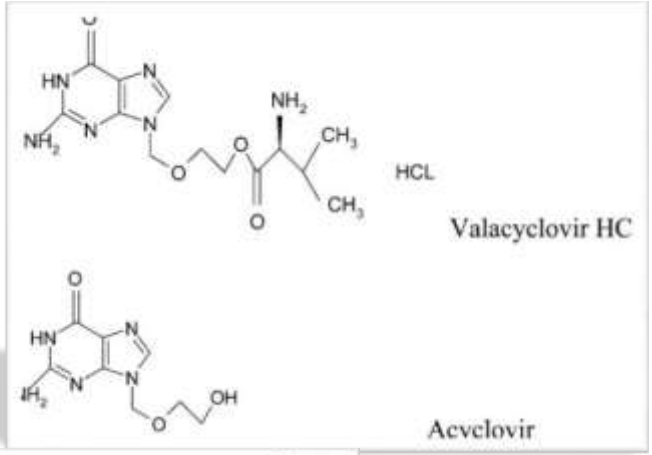
- Absorption of water soluble vitamin was enhanced by derivatization of thiolate ion to form lipid soluble prodrugs .

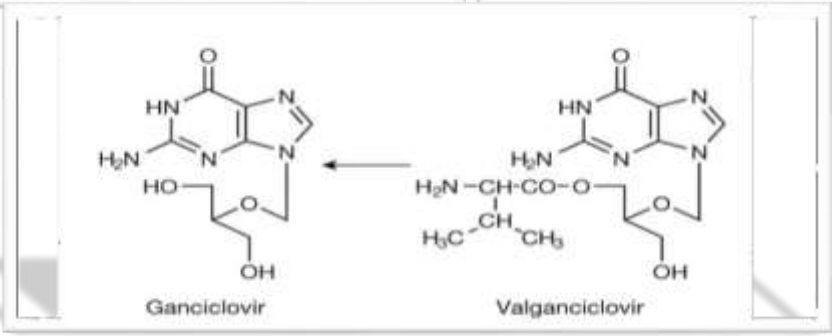
- Dopamine was made useful by making its precursor L-Dopa. Though L-Dopa is highly polar, it is actively transported through specific L–amino acid active transport mechanism and regenerates dopamine by decarboxylation.

- Penta acetyl prodrug of gitoxin has four to five times more aqueous solubility.

- To increase aqueous solubility esterification with amino acids is done. Examples of such prodrugs are valacyclovir and valgancyclovir, which are valine esters of the antiviral drugs acyclovir and gancyclovir, respectively.


L-Dopa
Dopamine


HCL
Valacyclovir HC
Acyclovir


Ganciclovir
Valganciclovir

- **Enhancement of ophthalmic bioavailability**
  - Epinephrine - dipivalyl derivative
  - Latanoprost and travoprost - isopropyl esters of latanoprost acid and travoprost acid

- **Enhancement of percutaneous bioavailability**
  - Mefenide - mefenide hydrochloride/acetate

- **Enhancement of topical administration**
  - Ketolac - Esters of ketolac

❑ Prevention of Presystemic metabolism

- Following oral administration, a drug must pass through two metabolizing organs i.e., liver and gastrointestinal mucosa, before reaching the general circulation.

- Phenolic moiety, oxidative N– and O– dealkylation, ester cleavage and peptide degradation are responsible for the pre-systemic metabolism of various drugs.

- Two types of drugs fall into this category.

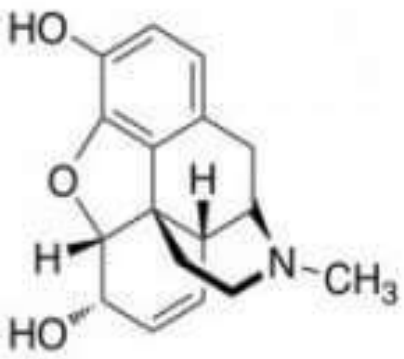
- The first are drugs rapidly degraded by the acid condition of the stomach and the

- Drugs of second category degrade due to enzymes present in the gastrointestinal mucosa and liver.

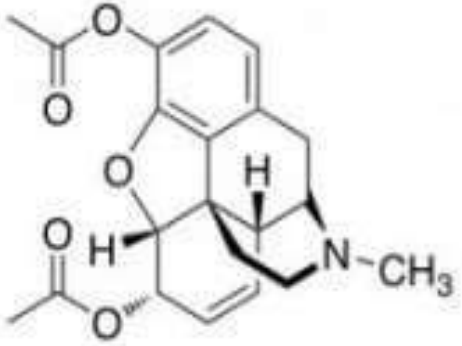
- Prodrugs may protect a drug from presystemic metabolism.

- Naltrexone (treatment of opioid addiction) and is readily absorbed from GIT and hence undergoes Presystemic metabolism. Ester prodrugs such as O-nitrobenzoate and acetylsalicylate increased bioavilablity 45 and 28 fold respectively.

Drug	Prodrug
Propranolol	Propranolol hemisuccinate
Dopamine	L-DOPA
Morphine	Heroin



morphine



heroin

❑ Prolongation of duration of action

- Drugs with short half life require frequent dosing with conventional dosage forms to maintain adequate plasma concentration of the particular drug.
- In plasma level time profile and consequently patient compliance is often poor.
- Prolongation of duration of action of a drug can be accomplished by the prodrug . Prodrug can be formed by two approaches-

❖ Control the release of the drug from complex

❖ Control the conversion of prodrug in to the parent drug.

Drug	Prodrug
Testosterone	Testosterone propionate
Estradiol	Estradiol propionate
Fluphenazine	Fluphenazine deaconate

❑ Reduction Local and Systemic Toxicity of Drugs

- An important objective of drug design is to develop a moiety with high activity and low toxicity.

- Gastric irritation and ulcerogenicity associated with aspirin use due to presence of free carboxylic group. Esterification of aspirin(R = alkyl) and other nonsteroidal anti-inflammatory agents (NSAIDs) greatly suppresses gastric ulcerogenic activity.

- Another example is the bioprecursor Sulindac, as it is a sulphoxide, it doesn't cause any gastric irritation and also better absorbed.

- The prodrug Ibuterol is iisobutyrate ester of Terbutaline (a selective β-agonist useful) in glaucoma. This prodrug, is 100 times more potent, has longer duration of action and is free from both local and systemic toxicity.

❑ Site specific drug delivery

- After its absorption into the systemic circulation, the drug is distributed to the various parts of the body including the target site as well as the non-target tissue.

- These problems can be overcome by targeting the drug specifically to its site of action by prodrug design

- The prodrug is converted into its active form only in the target organ/tissue by utilizing either specific enzymes or a pH value different from the normal pH for activation e.g. 5-amino salicylic acid.

- Tumour cells contain a higher concentration of phosphates and amidases than do normal cells. Consequently a prodrug of cytotoxic agent could be directed to tumour cells if either of these enzymes was important to prodrug activation process. Diethylstilbestrol diphosphate was designedfor site-specific delivery of diethylstilbestrol to prostatic carcinoma tissue.

❑ Site specific Drug Delivery in Chemotherapy

Directed Enzyme Prodrug Therapy (DEPT)

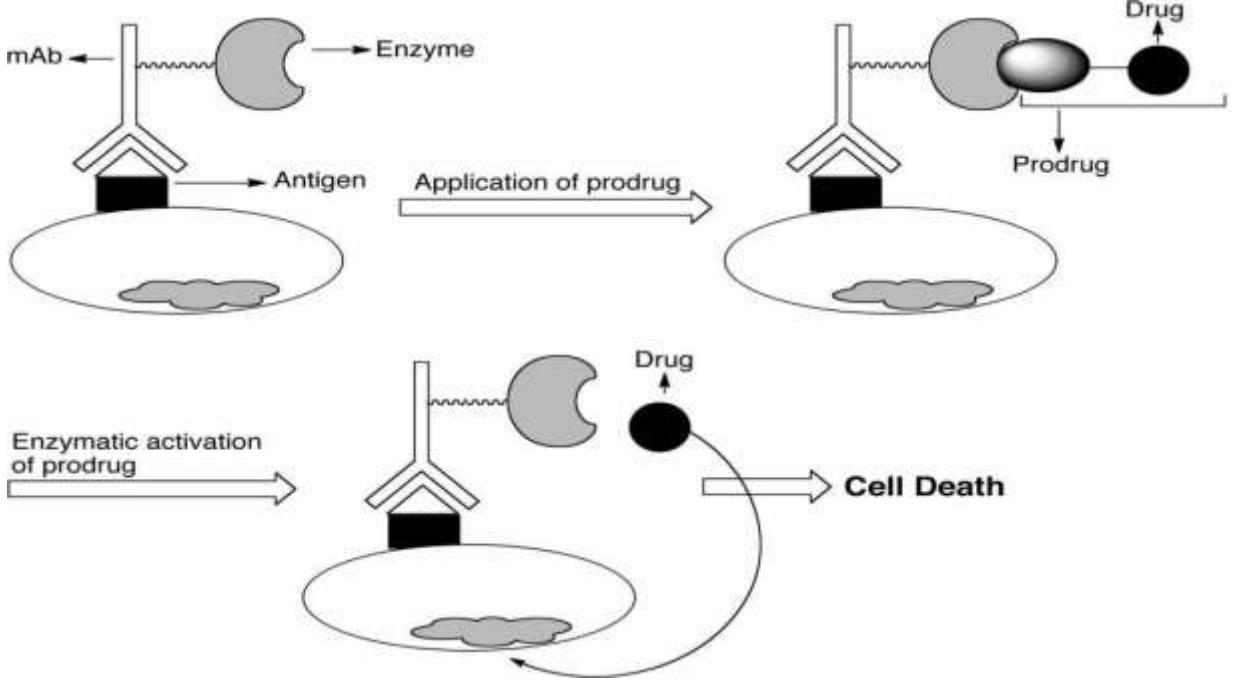
- Many chemotherapy drugs for cancer lack tumour specificity and the doses required to reach therapeutic levels in the tumour are often toxic to other tissues.
- **(DEPT)** uses enzymes artificially introduced into the body to convert Prodrugs, which have no or poor biological activity, to the active form in the desired location within the body.

- DEPT strategies are an experimental method of reducing the systemic toxicity of a drug, by achieving high levels of the active drug only at the desired site.

- ❖ Antibody-directed enzyme prodrug therapy (ADEPT)
- ❖ Gene-directed enzyme prodrug therapy (GDEPT)
- ❖ Virus-directed enzyme prodrug therapy (VDEPT)
- ❖ Polymer-directed enzyme prodrug therapy (PDEPT)
- ❖ Clostridia-directed enzyme prodrug therapy (CDEPT)

❖ Antibody-directed enzyme prodrug therapy (ADEPT)

- **ADEPT** is a strategy to overcome the problems of lack of tumour selectivity.
- An antibody designed/developed against a tumor antigen is linked to an enzyme and injected to the blood, resulting in selective binding of the enzyme in the tumor.
- A prodrug is administrated into the blood circulation, which is converted to an active cytotoxic drug by the enzyme, only within the tumor.
- Selectivity is achieved by the tumor specificity of the antibody and by delaying prodrug administration until there is a large differential between tumor and normal tissue enzyme levels.



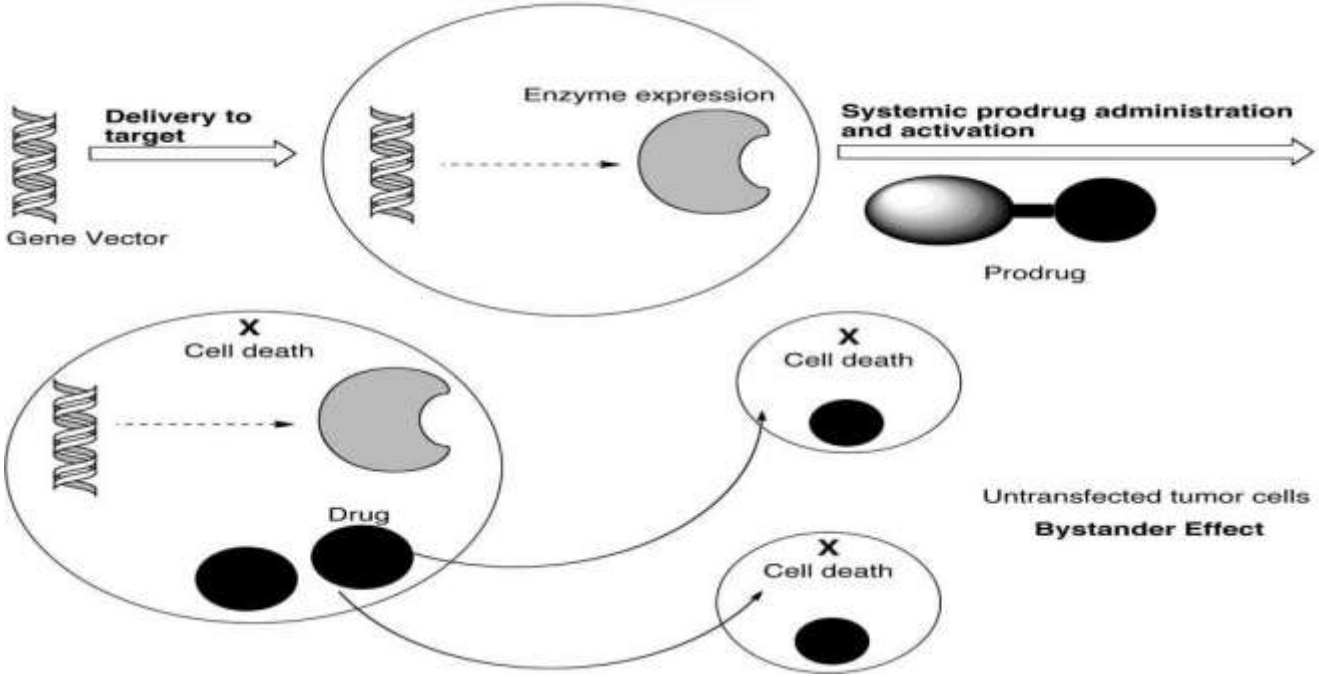
Schematic presentation of antibody-directed enzyme prodrug therapy (ADEPT).
mAb-enzyme conjugate is given first, which binds to antigens expressed on tumor surfaces. Prodrug is given next, which is converted to active drug by the pre-targeted enzyme.

Antibody	Prodrug	Drug	Tumor target
L6	Mitomycin C phosphate	Mitomycin C	Lung adenocarcinoma
BW413	Etoposide phosphate	Etoposide	Colon carcinoma
L6	Doxorubicin phosphate	Doxorubicin	Lung adenocarcinoma

❖ Gene-directed enzyme prodrug therapy - GDEPT

- GDEPT, is a two-step process.
- In the first step, the gene for a foreign enzyme is delivered to tumor cells.
- In the second step, a non-toxic agent is administered systematically and converted by the enzyme to its cytotoxic metabolite.

Enzyme	Prodrug	Drug
Cytochrome p450	Cyclophosphamide, ifosfamide	Phosphamide mustard, acrolein
Cytosine deaminase	5-Fluorocytosine 5-Fluorouridine	5-Fluorouracyl
Nitroreductase	5-(Aziridin-1-yl)-2,4-dinitrobenzamide	5-(Aziridin-1-yl)-4-hydroxylamino-2-nitrobenzamide



Schematic presentation of gene-directed enzyme prodrug therapy (GDEPT).
Gene for foreign enzyme is transfected to tumor cells, which express the enzyme to activate the systemically administered prodrug

❖ **Virus-directed enzyme prodrug therapy (VDEPT)**

VDEPT is the term given to the use of a virus to deliver the gene for GDEPT. VDEPT can potentially be used to enhance the therapeutic potential of oncolytic viruses.

❖ **Polymer-directed enzyme prodrug therapy (PDEPT)**

PDEPT uses polymer-drug conjugates, drugs contained within a polymer 'shell' such as pHPMA and designed to be released only by a specific enzyme.

❖ Clostridia-directed enzyme prodrug therapy (CDEPT)

- **CDEPT** is the use of Clostridia to convert prodrugs into active drug agents. CDEPT exploits the hypoxic environment of solid tumors to target drugs to tumors using anaerobic bacteria resident in the tumour to convert the pro-drug to the active form.

- Solid tumours, in contrast to normal tissues, grow rapidly. As a result, the cancerous tissues may suffer from inadequate blood and oxygen supply. Therefore, clostridia can grow in tumor and destroy it specifically.

- In CDEPT, a prodrug-converting enzyme expressed by a clostridial expression plasmid converts a prodrug into an active drug form within the tumor.

- While the prodrug is the inactive form and can be administrated to the blood, the products of the prodrug cleavage are highly cytotoxic and show their effect only in the vicinity of tumor cells.

CONCLUSION

Prodrug design is a part of the general drug discovery process, in which a unique combination of therapeutically active substances is observed to have desirable pharmacological effects.

In human therapy prodrug designing has given successful results in overcoming undesirable properties like absorption, nonspecificity, and poor bioavailability and GI toxicity.

Thus, prodrug approach offers a wide range of options in drug design and delivery for improving the clinical and therapeutic effectiveness of drug.

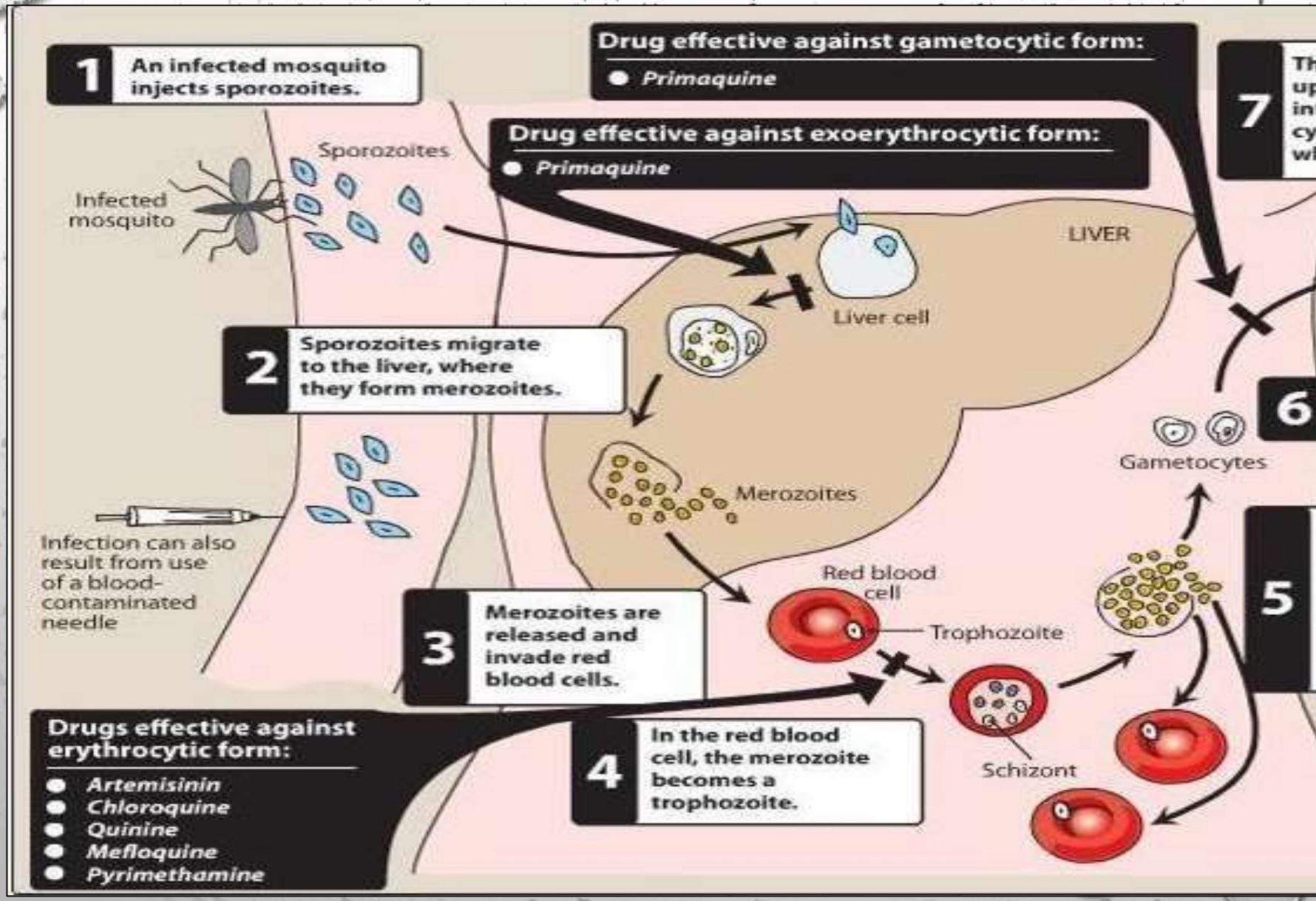

THANK YOU!

ANTIMALARIAL AGENT

INTRODUCTION

- Malaria, one of the most widespread diseases, is caused
  parasite and is transmitted to humans by the female *an*
  Plasmodium belongs to the class of protozoa known as sporoz
- Mainly four species of plasmodium typically cause hu
  plasmodium falciparum, p. Vivax, P. Malariae and P. Ovale .
- A 5th species, *P. Knowlesi,* is primarily a pathogen of monkeys
  been recognized to cause illness, including severe disease, in h
- Although all species may cause significant illness, *p. Falciparu*
  for the majority of serious complications and death.

LIFE CYCLE OF THE MALARIAL PARASITE



- An anopheles mosquito inoculates plasmodium sporozoites infection. Circulating sporozoites rapidly invade liver cells, a stage tissue schizonts mature in the liver. Merozoites are su from the liver and invade erythrocytes.
- Only erythrocytic parasites cause clinical illness. Sexual stag develop in erythrocytes before being taken up by mosquitoes, into infective sporozoites.

THERAPEUTIC CLASSIFICAT

1. Causal prophylaxis: (primary tissue schizonticides)

- Drugs prevent the maturation of or destroy the sporozoites hepatic cell– thus prevent erythrocytic invasion
- Primaquine, proguanil
- Primaquine – for all species of malaria but not used due to i
- Proguanil– primarily for *P. Falciparum* and not effective aga activity), rapid development of resistance

2. Supressives prophylaxis:

- Supress the erythrocytic phase and thus attack of malarial fe prophylactics
- Chloroquine, proguanil, mefloquine, doxycycline

3. Clinical cure: Erythrocytic Schizonticides

- Erythrocytic schizontocides are used to terminate episodes o
- **Fast acting high efficacy drugs:**
  - Chloroquine, quinine, mefloquine, halofantrine, artemicin
  - Used singly to treat malaria fever
  - Faster acting, preferably used in falciparum malaria where may lead to death even if parasites are clear from blood
- **Slow acting low efficacy drugs:**
  - Proguanil, pyrimethamine, sulfonamides, tetracyclines
  - Used only in combination

4. Radical curatives:

- Drug attack exoerythrocytic stage (hypnozoites) given with c
  the total eradication of the parasite from the patient's body
- Radical cure of the *P. Falciparum* malaria can be achieved by
- For radical cure of *P. Vivax* infection, primaquine and progu

5. Gametocidal:

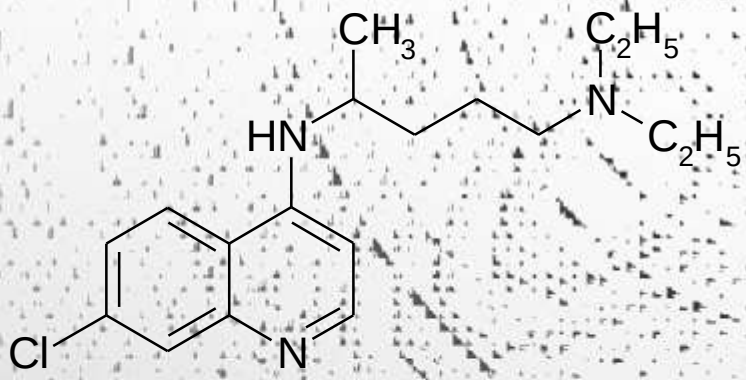
- Removal of male and female gametes of plasmodia form
  blood
- It has no benefit for treated patient
- Primaquine and artemisinins are highly effective against
  species

CHEMICAL CLASSIFICATIO

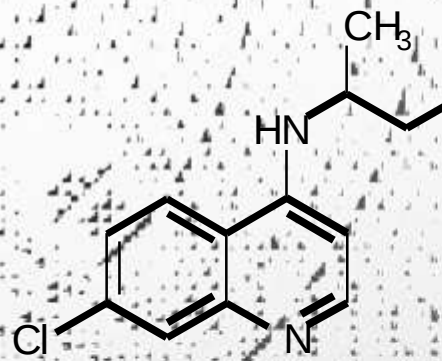
Classes	Drugs
1. 4-aminoquinolines	Chloroquine (CQ), amodiaquin Piperaquine
2. Quinoline-methanol	Mefloquine
3. Cinchona alkaloid	Quinine, quinidine
4. Biguanide	Proguanil (chloroguanide)
5. Diaminopyrimidine	Pyrimethamine
6. 8-aminoquinoline	Primaquine, tafenoquine
7. Sulfonamides and sulfone	Sulfadoxine, sulfamethopyrazi dapsone
8. Amino alcohols	Halofantrine, lumefantrine
9. Sesquiterpine lactones	Artesunate, artemether, arteet

10. Naphthyridine	Pyronaridine
11. Naphthoquinone	Atovaquone
12. Antibiotics	Tetracycline, Doxycycline, Clin

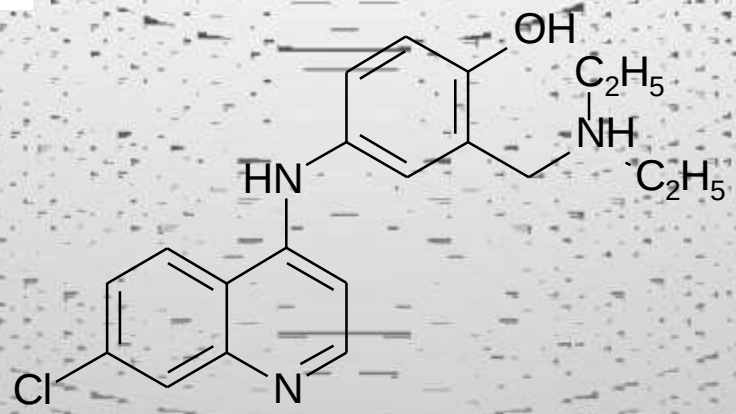
1. 4–AMINOQUINOLINES



Chloroquine



Hydro



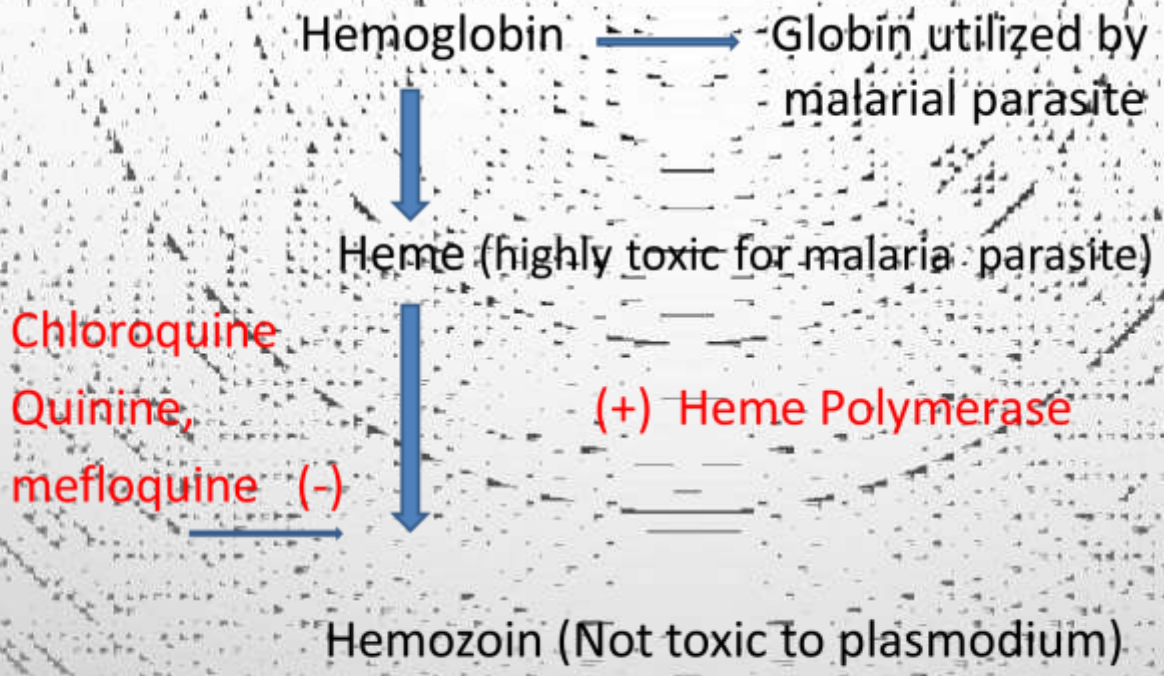
Amodiaquine

CHLOROQUINE:

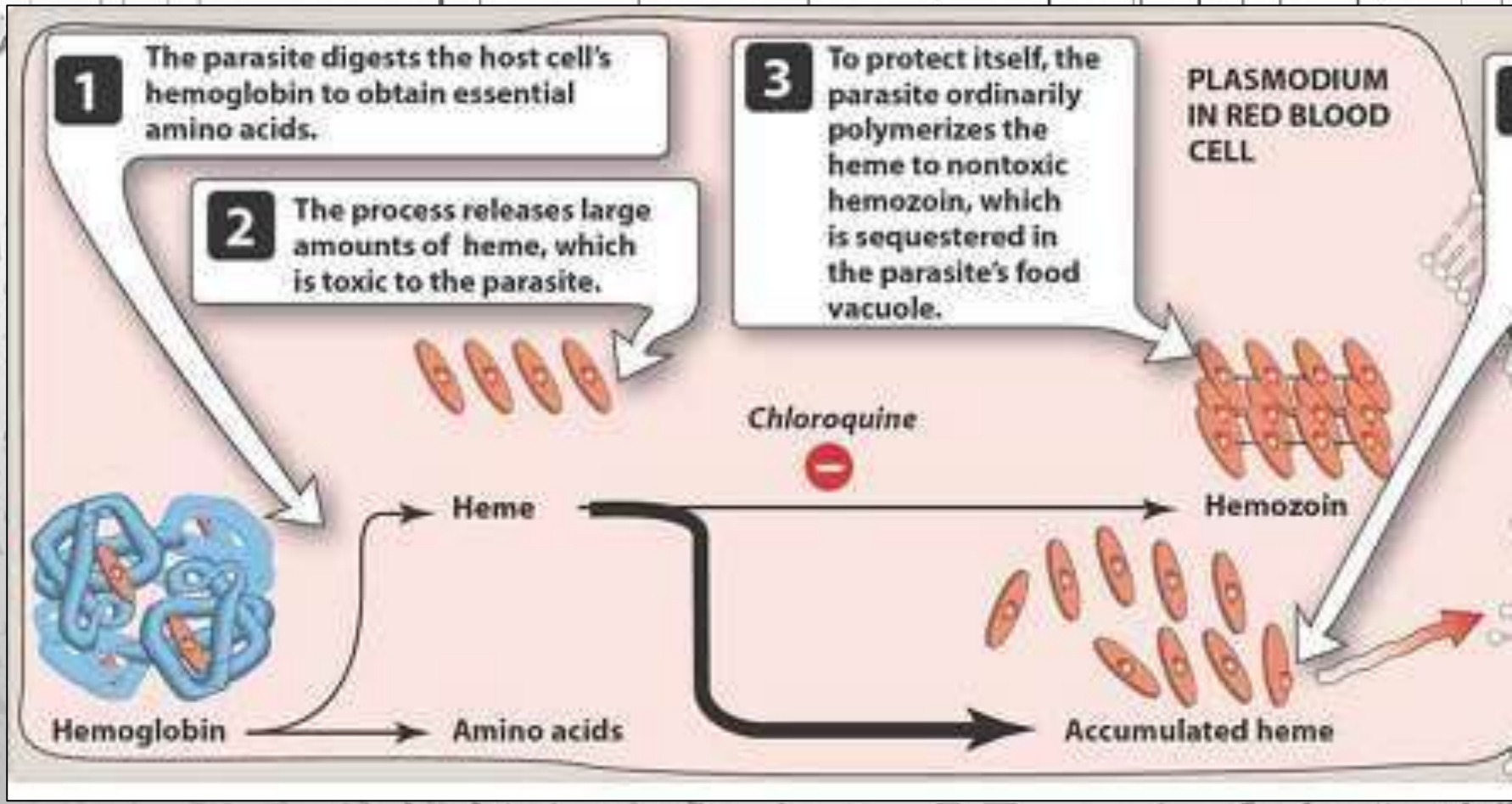
- It has activity against the blood stages of *plasmodium oval* susceptible strains of *P. Vivax and P. Falciparum.*
- Widespread resistance in most malaria-endemic countries has led use for the treatment of p. Falciparum, although it remains effecti *P. Ovale, P. Malariae* and, in most regions, *P. Vivax*.
- **Mechanism of action :**
  - Binds to and inhibits dna and rna polymerase; interferes wi hemoglobin utilization by parasites; inhibits prostaglandin effect
  - The parasite digests the human hemoglobin in order to get a problem here is that the heme part of hb is toxic to the parasite.

- To overcome this obstacle, the parasite has developed an enzy polymerization of heme. To form insoluble crystals called he collected in vacuoles.
- Chloroquine enters parasite cell by simple diffusion. Chloroqu protonated as the digestive vacuole is known to be acidic (pl then cannot leave by diffusion. Chloroquine inhibits polymeriz accumulation of heme.
- Chloroquine binds to heme (or fp) to form what is known as complex, this complex is highly toxic to the cell and disrupts r Action of the toxic compound results in cell lysis and ultim autodigestion.

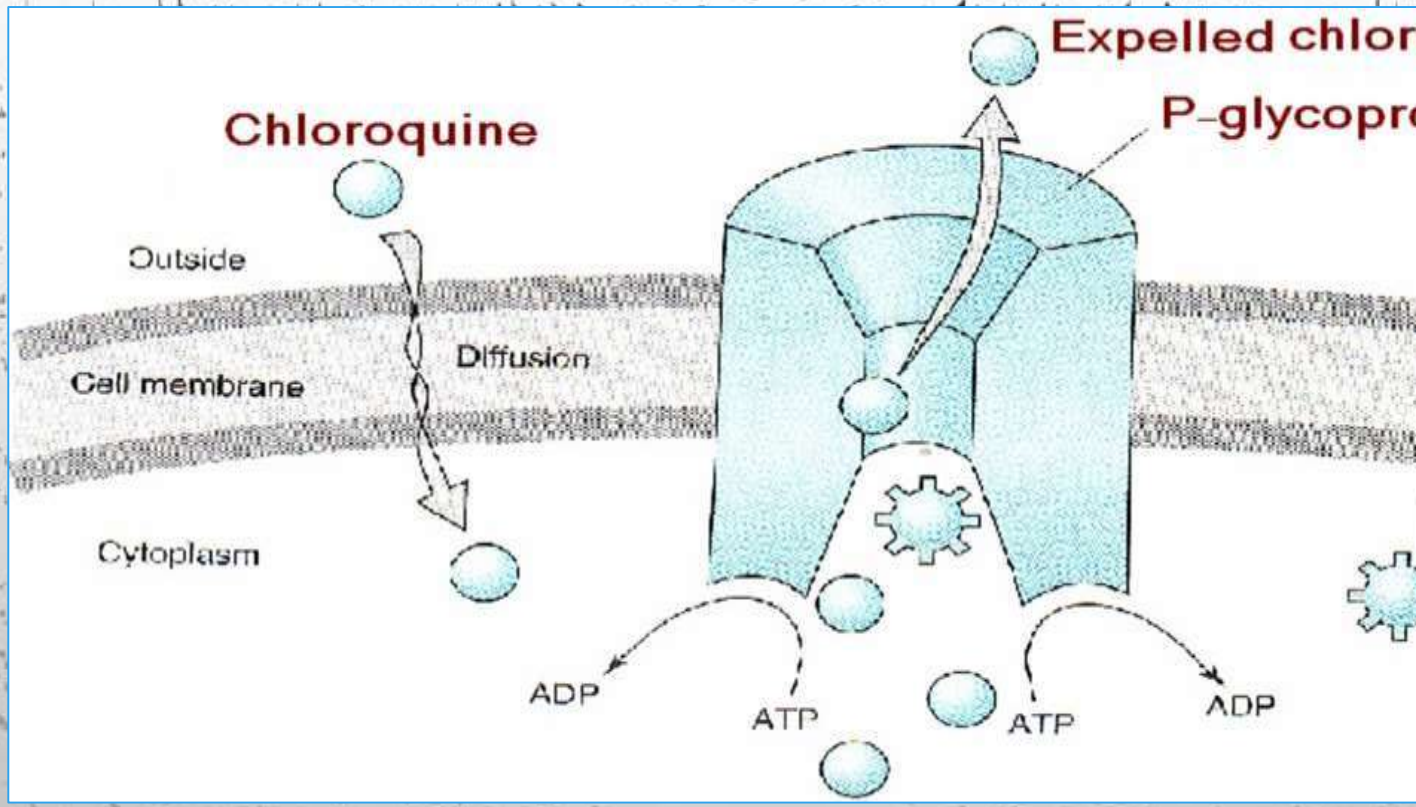
MECHANISM OF ACTION



MECHANISM OF ACTION :



- RESISTANCE RESULTS FROM ENHANCED EFFLUX OF THE EXPRESSION OF THE HUMAN MULTI DRUG RESISTANCE GLYCOPROTEIN.



THERAPEUTIC USES

1. HEPATIC AMOEBIASIS
2. GIARDIASIS
3. CLONORCHIS SINENSIS
4. RHEUMATOID ARTHRITIS
5. DISCOID LUPUS ERYTHEMATOSUS
6. CONTROL MANIFESTATION OF LEPRA REACTION
7. INFECTIOUS MONONUCLEOSIS

- **Hydroxy chloroquine:**
  - Less toxic, properties &uses similar
- **Amodiaquine:**
  - As effective as chloroquine
  - Pharmacological actions similar
  - Chloroquine resistant strains may be effective
  - Adverse events: GIT, headache , photosensitivity, rarely agr
  - Not recommended for prophylaxis

- **Contraindications:**

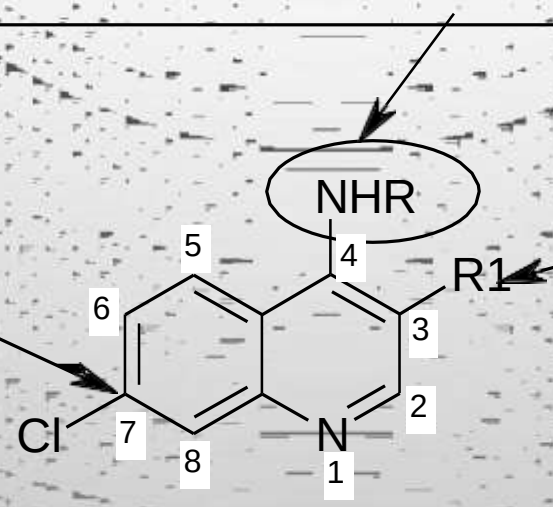
1. Psoriasis or porphyria
2. Visual field abnormalities or myopathy
3. Ca and mg containing antacid interfere with absorption
4. Used with caution in liver disease or neurologic or hemato

SAR of 4–aminoquinolines

Dialkylaminoalkyl side chain

1. 2-5 carbon atoms between the nitrogen atoms,particula
   1-methylbutylamino side chain is optimal for activity as
2. The tertiary amine is important.
3. Introduction of unsaturation in the side chain was not d
4. Substitution of a hydroxy on one of the ethyl groups in te
   (hydroxy quinoline) generally reduces toxicity and increa
   concentration. This is one of the metabolites of chloroqu
5. Incorporation of an aromatic ring in the side chain e.g. ir
   gives a compound with reduced toxicity and toxicity.

Introduction of chloro group at this position is optimal for activity



Introductio
group at th
reduces a

d-Isomer of chloroquine is somewhat less toxic than l-isomer

2. QUINOLINE–METHANOL

- Mefloquine, is marketed as the *R,S–isomer.*
- Mefloquine's effectiveness in the treatment and prophylaxis o malaria is due to the destruction of the asexual blood forms o the malarial pathogens that affect humans, *Plasmodiu falciparum, P. vivax, P. malariae, P. ovale*.
- Used in chloroquine-resistant strains of *P. falciparum* an other species.
- Has strong blood schizonticidal activity against *P. falciparu* and *P. vivax*, it is not active against hepatic stages o gametocytes.

Adverse effects

- ✓ Mefloquine is bitter in taste
- ✓ At high doses: Nausea, vomiting, diarrhea, abdominal pain

CONTRAINDICATIONS

- Hypersensitivity to mefloquine, related compounds (eg, qu
  or any component of the formulation; prophylactic use in p
  of seizures or severe psychiatric disorder (including active
  depression, generalized anxiety disorder, psychosis, or schi

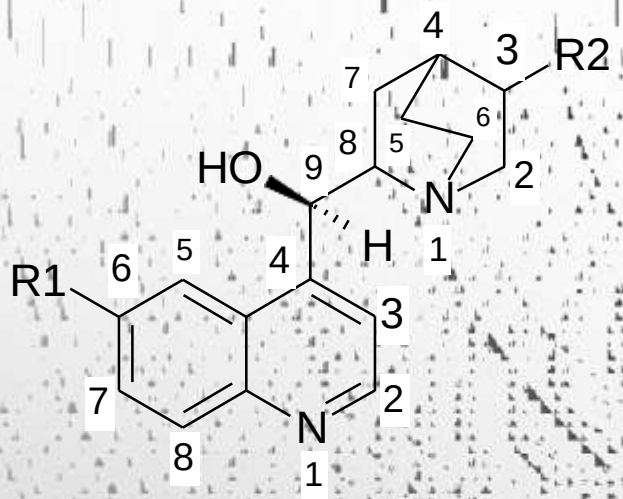
Drug interactions

- Cardiac arrests are possible if mefloquine is taken concur
  quinidine.

Uses

- Effective for multidrug resistant p. Falciparum
- However its use is restricted due to its toxicity, cost and lo

3. CINCHONA ALKALOIDS



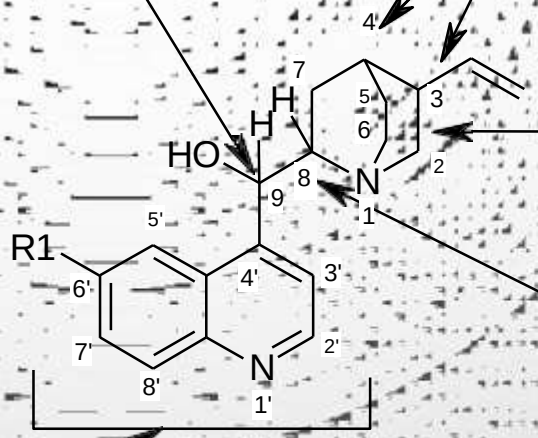
Quinine :	$R_1 = OCH_3 ; R_2 = -CH = CH_2$;
Quinidine :	$R_1 = OCH_3 : R_2 = -CH = CH_2$;
Cinchonine :	$R_1 = H ; R_2 = -CH = CH_2$; (+)
Cinchonidine :	$R_1 = H ; R_2 = -CH = CH_2$; (–)

- Quinine is a *l-isomer* of alkaloid obtained from cinchona bark a (antiarrhythmic) is its *d-isomer.*
- An effective erythrocytic schizontocide as suppressive and u terminate attacks of *vivax, ovale, malariae*, sensitive *falciparum more toxic than chloroquine.*
- Moderately effective against hepatic form (pre-exoerythrocyte and

SAR Of Quinine

1. Modification of the secondary alcohol at C-9, through oxidation, esterification dim inishes activity.
2. The configuration at positions 8 and 9 affects the juxtaposition of the hydroxyl group and the non-arom atic nitrogen atom , a relationship that is associated with antim alarial activity.

Assym metry a
for antim alaria



Quin
for a
am i

Activ
introd
positi

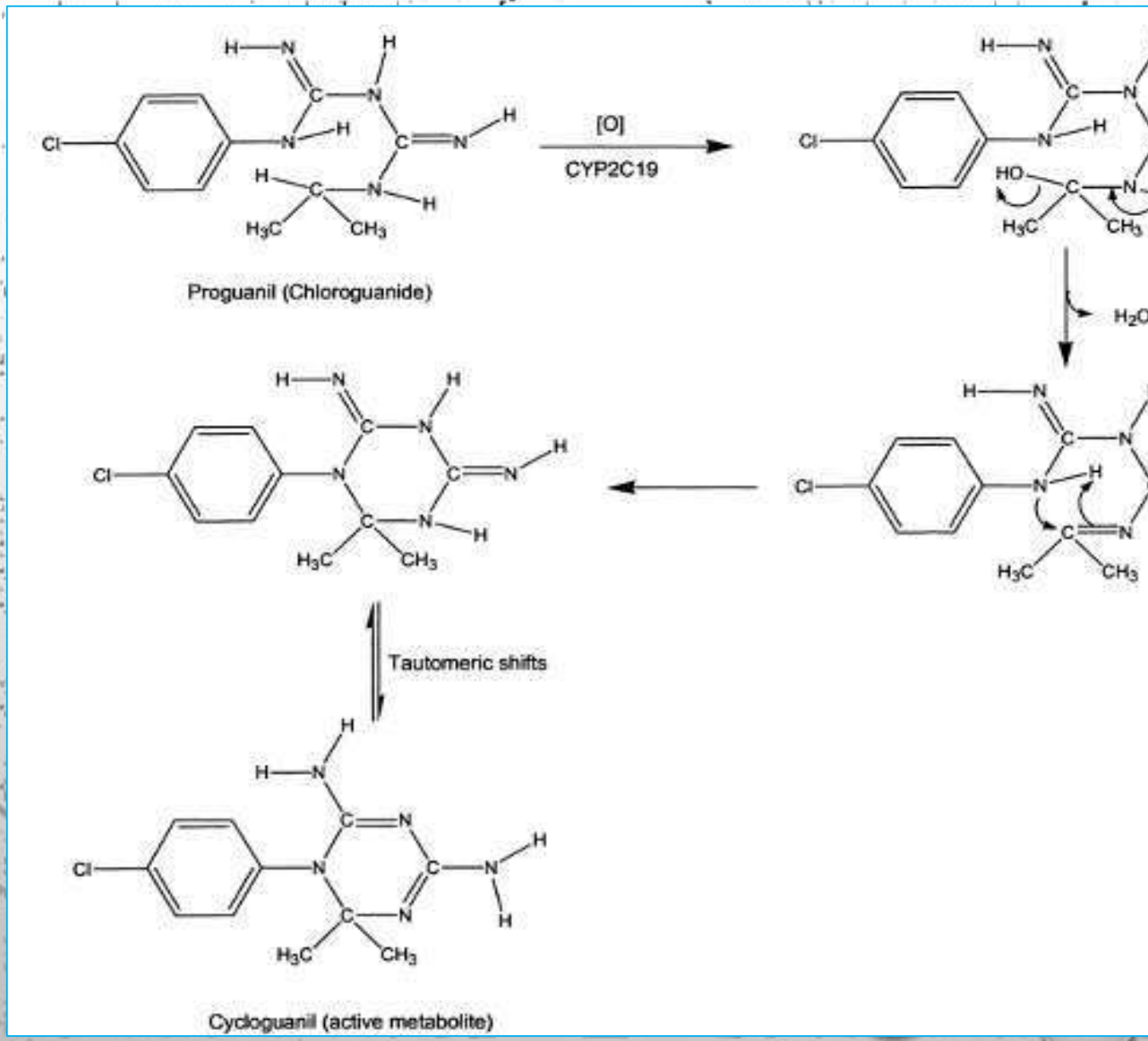
Quinoline Ring

1. Presence of m ethoxy group in quinine is not essential.
2. R eplacem ent of m ethoxy group by a halogen, especially chlorine, enhances activity.
3. A further increase in activity resulted from the introduction of a phenyl group at position 2'.
4. It was discovered that high activity without phototoxicity could be attained by blocking position 2' with a trifluorom ethyl group, a finding that eventually led to developm ent of m efloquine.

4. BIGUANIDES

- ✓ It is an early example of a prodrug.
- ✓ It is a slow-acting erythrocytic schizontocide which also inhibits the preerythrocytic stage of *P. falciparum*. Gametocytes exposed to proguanil are not killed but fail to develop properly in the mosquito.
- ✓ It is cyclized in the body to a triazine derivative (cycloguanil) which inhibits plasmodial DHFRase in preference to the mammalian enzyme.
- ✓ Resistance to proguanil develops rapidly due to mutational changes in the plasmodial DHFRase enzyme.

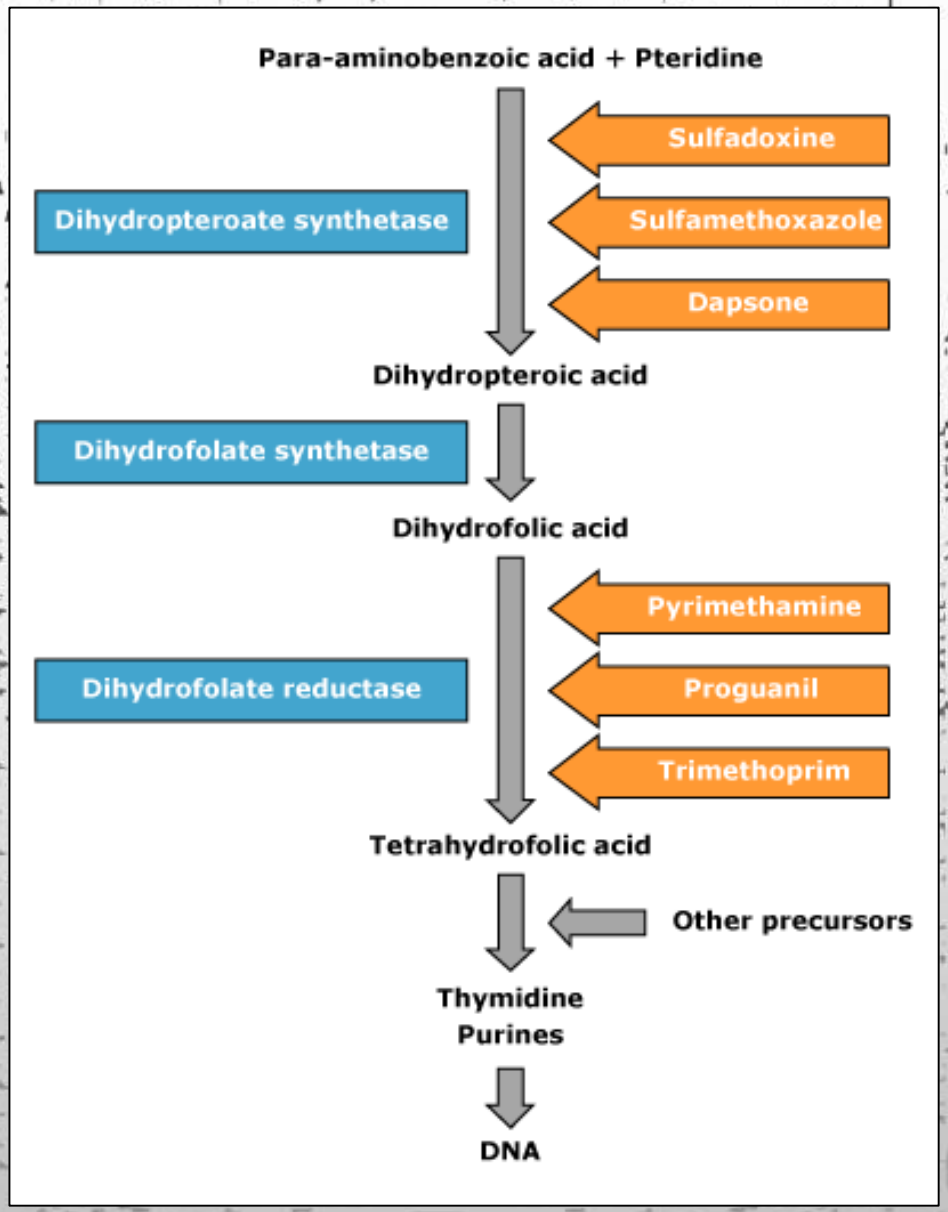
Conversion of proguanil to cycloguanil by CYP2C19



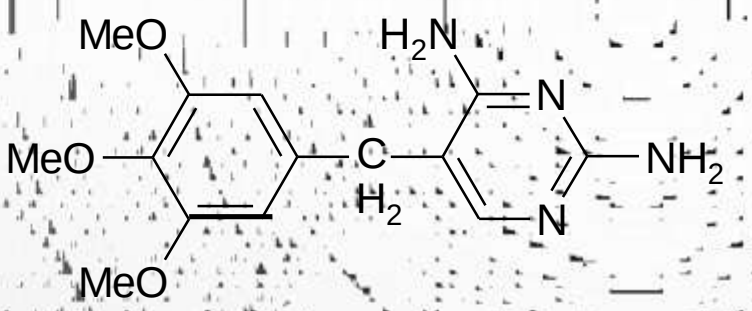
Adverse effects

- Mild abdominal upset, vomiting
- Occasional stomatitis
- Haematuria, rashes and transient loss of hair
- Note : safe during pregnancy

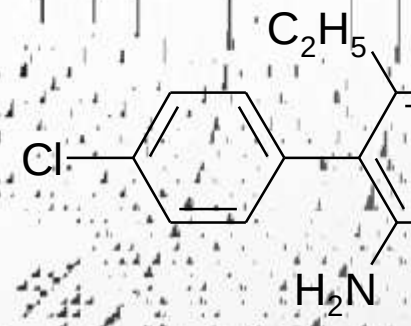
Mechanism of action of anti folates



5. DIAMINOPYRIMIDIN



Trimethoprim



Pyrimetham

- ✓ Slow acting erythrocytic schizontocide
- ✓ Direct inhibitor of plasmodial dihydrofolate reductase (DHFRas
- ✓ Conversion of dihydrofolic acid to tetrafolic acid is inhibited
- ✓ High doses inhibits *Toxoplasma gondi*
- ✓ Resistance develops by mutation in DHFRase enzyme
- ✓ Diaminopyrimidine more potent than proguanil & effective forms of all species.

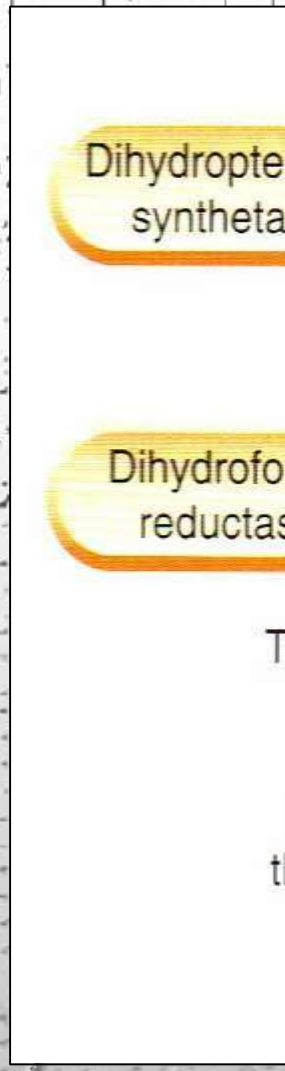
Pyrimethamine

Adverse effects

- Occasional nausea and rashes
- Folate deficiency rare
- Megaloblastic anaemia and granulocytopenia with higher do
- Can be treated with folinic acid
- Combined with a sulfonamide (S/P) or dapsone for treatmer malaria

SULFADOXINE – PYRIMETHAM

- Sequential blockade
- Sulfadoxine 500 mg + pyrimethamine 25 mg, 3 tablets once for acute attack
- Not recommended for prophylaxis
- Effective blood schizontocide against *plasmodium falciparum*
- Treatment and prophylaxis of *falciparum* malaria resistant to chloroquine



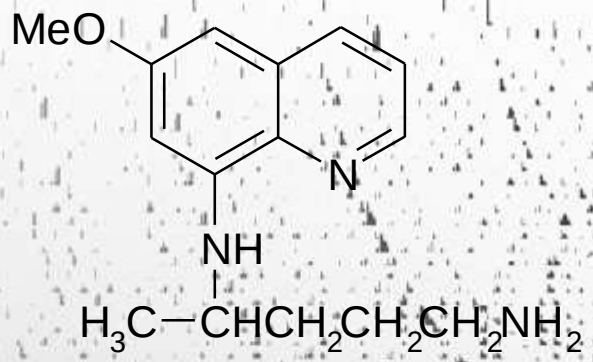
Adverse effects

- Mild GIT upset
- Megaloblastic anemia, bone marrow depletion
- Rashes, urticaria, serum sickness, drug fever
- Exfoliative dermatitis, stevens johnson syndrome
- Nephrotoxicity

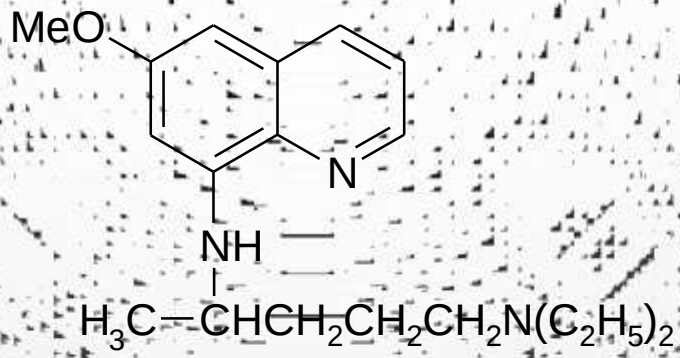
Uses:

- Single dose treatment of uncomplicated chloroquine resistant falci
- Patients intolerant to chloroquine
- First choice treatment for toxoplasmosis

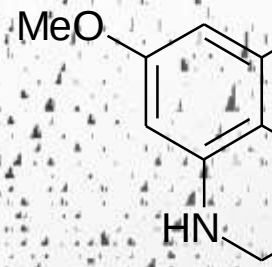
6. 8–AMINOQUINOLINE



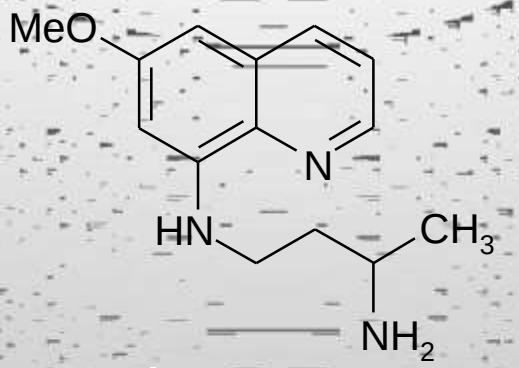
Primaquine



Pamaquine



Pent



Quinocide

Primaquine:

- It is the only 8-aminoquinoline in clinical use.
- It is largely used to prevent relapse of p. Ovale and P. Vivax m dormant hypnozoites, and it also has activity against the pr and gametocytes of P. Falciparum.
- It is not used for prophylaxis. Its spectrum of activity is one of currently used antimalarial drugs being indicated only for exo malaria

Mechanism of action primaquine:

- Not clear, its converted & produces active oxygen interfere with mitochondrial function

Uses of primaquine

1. Radical cure

A) P.Vivax & ovale :

- Given in acute attack or throughout incubation period
- Prevents relapse

Prophylactically: before & after leaving the endemic area to eradic

- Effective vector control is possible or used in areas of low transm

B) falciparum malaria:

- 45mg with chloroquine used like gametocidal & cut down t effective control is needed.

Adverse drug reaction

Therapeutic doses:

- Haemolysis & methaemoglobinaemia commonly seen in g6pd de
- Causes nausea, headache, epigastric pain &abdominal cramps or
- Rarely : leucopenia, leucocytosis & agranulocytosis
- Precaution – primaquine
- Should not be given during pregnancy because fetus is glu dehydrogenase (g-6-pd) deficient

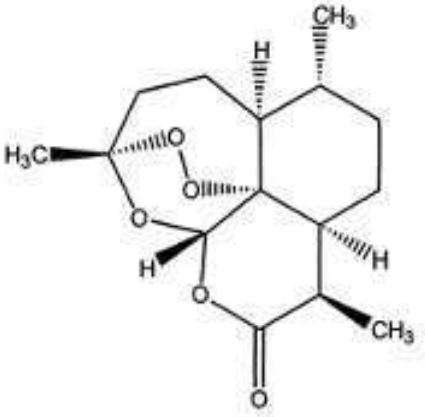
9. SESQUITERPINE LACTON

- The artemisinin series are the newest of the antimalarial drugs and are structurally unique when compared with the compounds previously and currently used.
- The parent compound, artemisinin, is a natural product extracted from the dry leaves of *artemisia annua* (sweet wormwood).
- All of the compounds given in figure are active against the plasmodium genera that cause malaria.

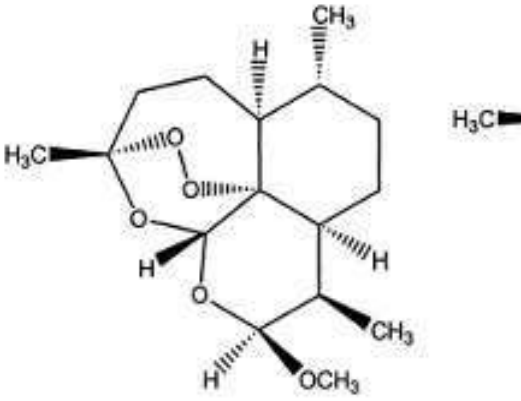
PLANT– ARTE

- The key structure characteristic appears to be a “trioxane” consisting of the endoperoxide and dioxepin oxygens.
- Note that the stereochemistry at position 12 is not critical.
- These are the artimisinin derivatives used in malaria:

1. Artesunate
2. Artemether
3. Arteether
4. Arterolane



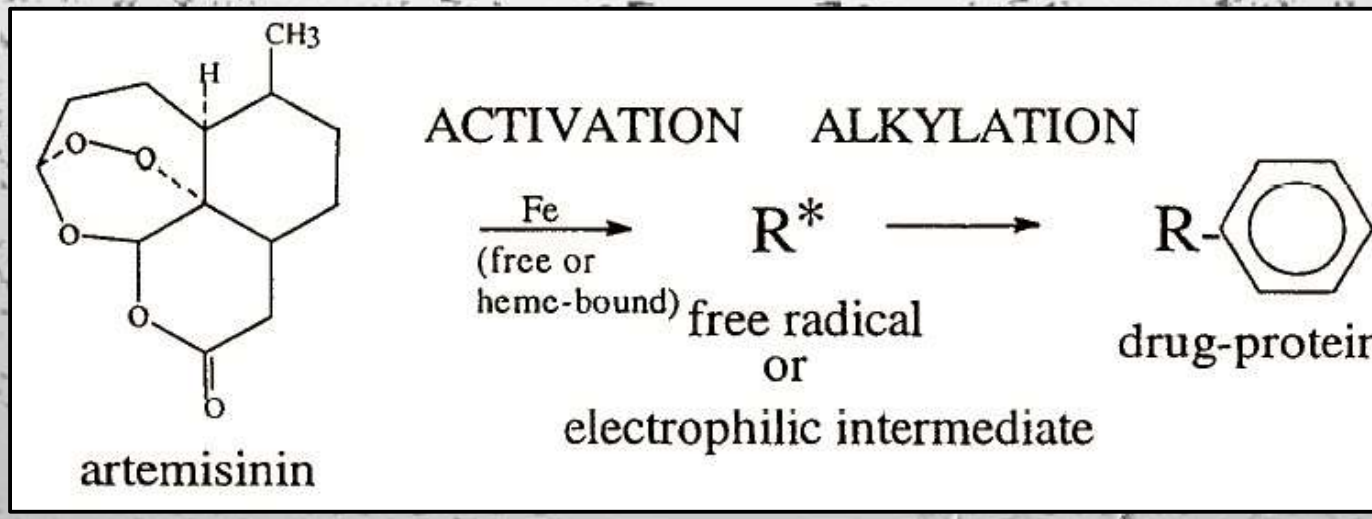
Artemisinin



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

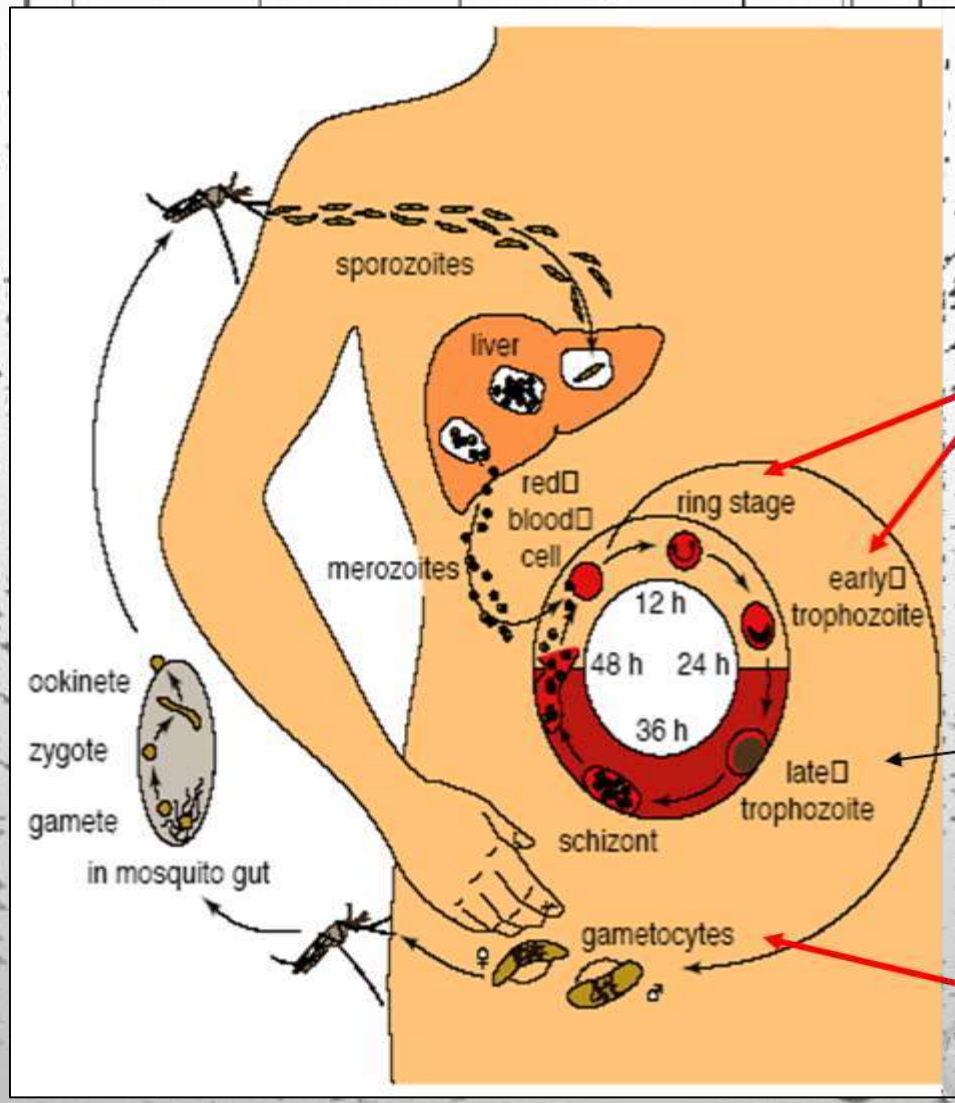
MECHANISM OF ACTION

- These compounds contains endoperoxide bridge.
- Endoperoxide bridge interacts with heme in parasite.
- Heme iron cleaves this endoperoxide bridge.
- There is generation of highly reactive free radicals which membrane by covalently binding to membrane proteins.



- They act rapidly, killing blood stages of all plasmodium speci
  parasite biomass.
- Artemisinins have the fastest parasite clearance times of any
- Artemisinins are active against gametocytes, the parasite forn
  mosquitoes, and their use has been associated with reduced
- Safe & 10–100 times potent compared to other antimalarials.

ANTIMALARIAL ACTION



ARTEMISININ-BASED COMBINATION TH

- In general, artemisinins should not be used as a single emergence of drug resistance and to avoid the need for prolo
- Artemisinin-based combination therapy (acts) combine the h acting artemisinins with a longer-acting partner to protect resistance and to facilitate dosing convenience.
- Acts are typically administered for 3 days and are often ava tablets.
- Four acts are recommended by the who for the treatme malaria: artemether-lumefantrine, artesunate-amodiaq mefloquine and artesunate-sulfadoxine-pyrimethamine.

ARTEMISININS

- Intravenous artesunate is used for the treatment of severe ma
- It is superior to quinine for treatment of severe malaria with parasitemia and reducing mortality.
- Given the short half-life of artemisinins, intravenous therap by a longer acting agent once the patient is able to tolerate o
- If used alone (via the parenteral, rectal or oral route), a administered for 5–7 days.
- Treatment for less than 5 days results in recurrent parasit after therapy due to the very short duration of action, rather resistance.

- Artemisinins are generally well tolerated.
- Type 1 hypersensitivity to the artemisinin compounds has beer
- Adverse effects of orally-administered artemisinins dem neurological abnormalities (nystagmus and disturbances in ba resolved without lasting sequelae.

Advantages of act

- Rapid clinical and parasitological cure
- High cure rates(>95%) and low recrudescence rate
- Absence of parasite resistance
- Good tolerability profile
- Dosing schedule is simpler

1. ARTESUNATE – SULFADOXINE + PYR (AS–S/P)

- First line drug for uncomplicated *falciparum* malaria.
- Not effective against multidrug-resitant strains which are r s/p.
- Fewer side effects than s/m cl

2.Artesunate/mefloquine (AS/MQ)

- Highly effective and well tolerated in uncomplicated *falciparum* malaria

3. Artemether – lumefantrine (AS/LF)

- ✓ Clinical efficacy: 95–99%
- ✓ Must be administered with fatty food or milk to allow abson adequate blood level of AS/LF
- ✓ Quickly reduces parasite biomass, resolve symptoms, prevent recru gametocyte population

4. DIHYDROARTEMISININ (DHA)–PIPERAQUINE

- Used in dose ratio of 8:1 for multidrug resistant *plasmodium falci*
- Good safety profile and even tolerated by children (>98% response

5. ARTESUNATE–AMODIAQUINE(AS/AQ)

- First line therapy of uncomplicated *falciparum* malaria
- To be taken twice daily for three day treatment

Other recently developed ACT are:

6. ARTEROLANE–PIPERAQUINE

- Acts rapidly at all stages of asexual schizogony of malaria multidrug resistant *P. Falciparum*

7. ARTESUNATE–PYRONARIDINE

- **Under clinical trial**

10. NAPHTHYRIDINE

- Newer drug from Mepacrine developed in china.
- Mechanism similar to chloroquine.
- High effective erythrocytic schizonticide, effective against chloroquine sensitive & resistant vivax & falciparum malaria.
- Slow onset & long duration of action, concentrated in RBC.
- Water soluble, t1/2 : 7days
- Orally & parenterally used , well tolerated
- At high dose used analgesic/anti pyretic

11. NAPHTHOQUINONE

- ✓ Hydroxy naphthoquinone antiparasitic drug active against all Plasmodium species.
- ✓ Rapid acting erythrocytic schizontocide & inhibits pre-erythrocytic stage of falciparum.
- ✓ Also active against pneumocystis jiroveci & Toxoplasma gondii.
- ✓ Combined with proguanil Where its resistant, reduces relapse & which is synergistic.
- ✓ Collapses mitochondrial membrane interferes with cytochrome electron transport.

12. ANTIBIOTICS

Tetracycline & doxycycline

- Erythrocytic schizonts are inhibited by all malarial parasite.
- Tetracycline used in combination with quinine in treatm resistant as well vivax malaria.
- Avoid in children & pregnant women.
- Doxycycline used in places where high resistance present.
- 200mg doxycycline combined with artesun mefloquine/chloroquine/s-p resistant malaria.
- 100mg/day of doxycycline used 2nd line prophylactic f chloroquine resistant p. Falciparum.

CLINDAMYCIN:

- Slow erythrocytic schizontocide, bacteriostatic
- With quinine used in treatment of resistant P.Falciparum
- Its used where tetracyclines can not be used in pregn than 8 years old


Thank you