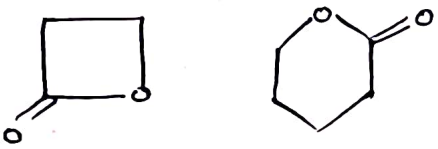
MACROLIDES

→ The macrolide antibiotics are group of compounds isolated from the Actinomycetes species.

→ In Macrolide, Lactone Ring is present.



Lactone Ring → O is heteroatom in Structure and ketone group is present in it.

→ In Macrolide, there are many no. of carbon [C] are in ring, and multiple Oxygen and Ketonic group attached in Ring.

→ Penicillin is good Antibiotic but hypersensitive for people

↓

To decrease the hypersensitivity & unstability, the macrolide Antibiotic is discovered, obtained from Actinomycetes bacteria.

Features of Macrolide Lactone Ring

→ Many numbered large Lactone Ring Present [Max. 12, 14, 16]

→ Many Ketone & OH group attatched

→ Glycosidic linkage with deoxy sugar [1 molecule attatched to other]

Lactone Ring

→ 12, 14 or 16 atom, unsaturated and Conjugated with Ketone

MECHANISM OF ACTION

They inhibit bacteria by interfaring in Ribosomal protein biosynthesis.

Macrolides binds on 50S Ribosome

↓

Prevent Translocation of Protein Synthesis

↓

Inhibit Bacteria

THERAPEUTIC USES

→ Used in Penicillin Resistant humans

→ Patient Allergic to Penicillin

→ Effective against gram positive and Gram Negative Bacteria

→ Not affected by Penicillinase

CLASSIFICATION

→ Erythromycin

→ Azithromycin

→ Clarithromycin

→ Clendamycin

→ Picromycin

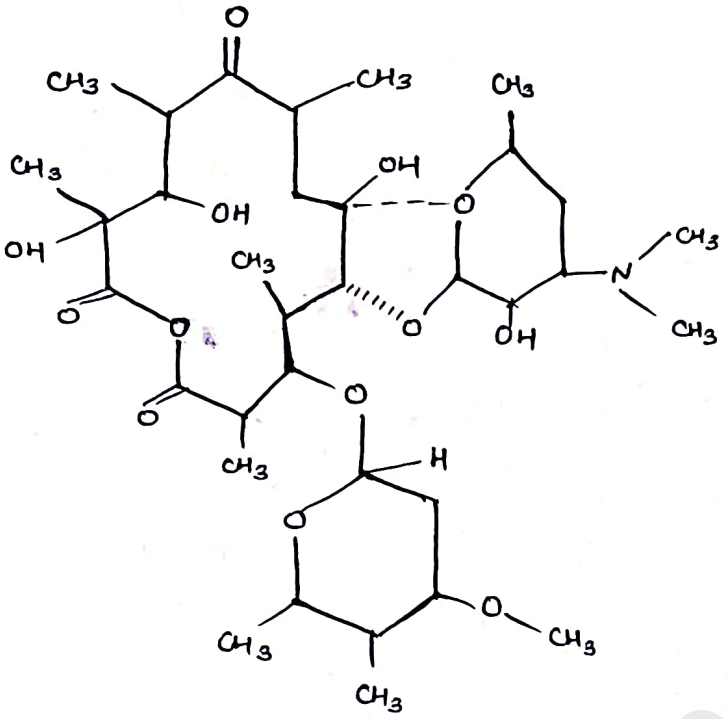
→ Spiromycin

→ Leuromycin

→ Josomycin

→ Rosomycin

1. Erythromycin

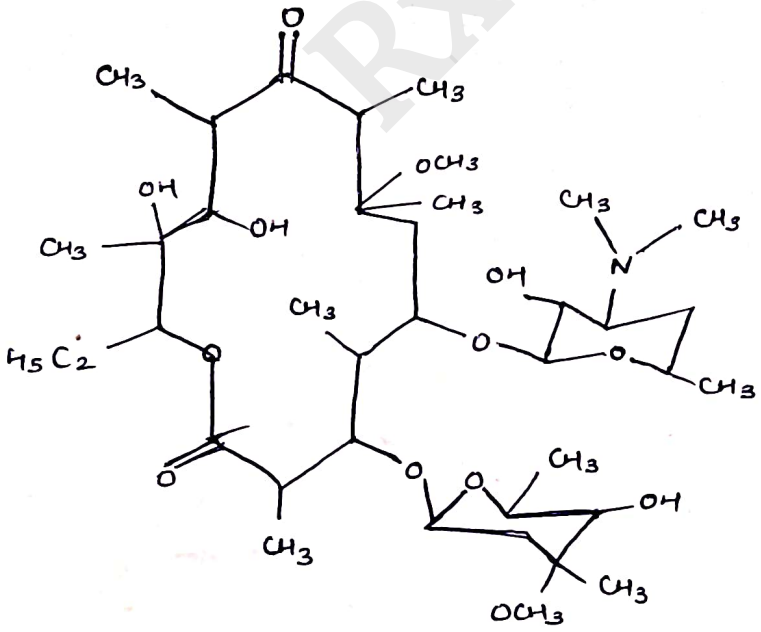


→ Used in Diptheria, Pertesis

→ Respiratory Tract Infections

→ Alterative to Penicillin Resistant Patient

2. Clarithromycin



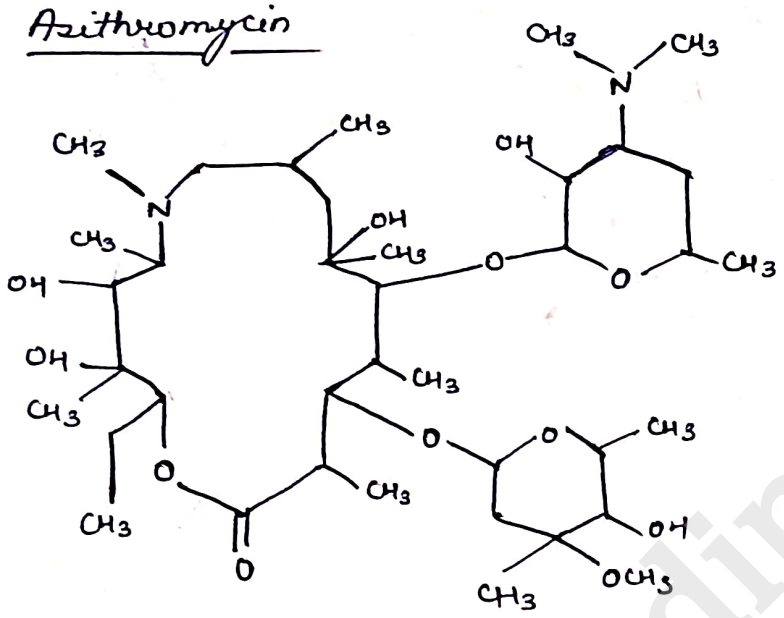
→ Used for H. Pylori Infection

→ Respiratory Tract Infections, Pharyngites

→ Used to treat Skin Infections

→ Used in Pneumonia

3. Azithromycin



→ Used in Respiratory Tract Infections

→ Mild moderate Pneumonia

→ Gonorrhea

→ Cholera

→ Typhoid (caused by Salmonella Typhi)

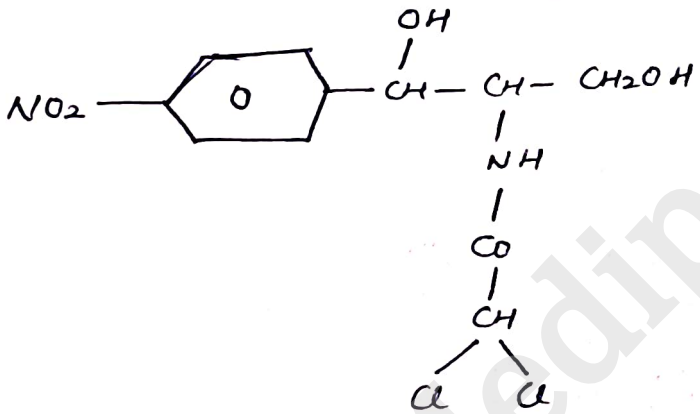
CHLORAMPHENICOL ANTIBIOTIC

→ Those compounds which synthesised from Steptomycates Venejevacle [Semi Synthetic]

→ Broad Spectrum, more in Gram negative Pneumonia, meningitis, Typhoid, influenza

→ They are Neutral

→ 1947 very popular in USA



MECHANISM OF ACTION

Bind with 50S unit of Ribosome

↓

Block 50S unit of Ribosome

↓

Stop Translocation Process

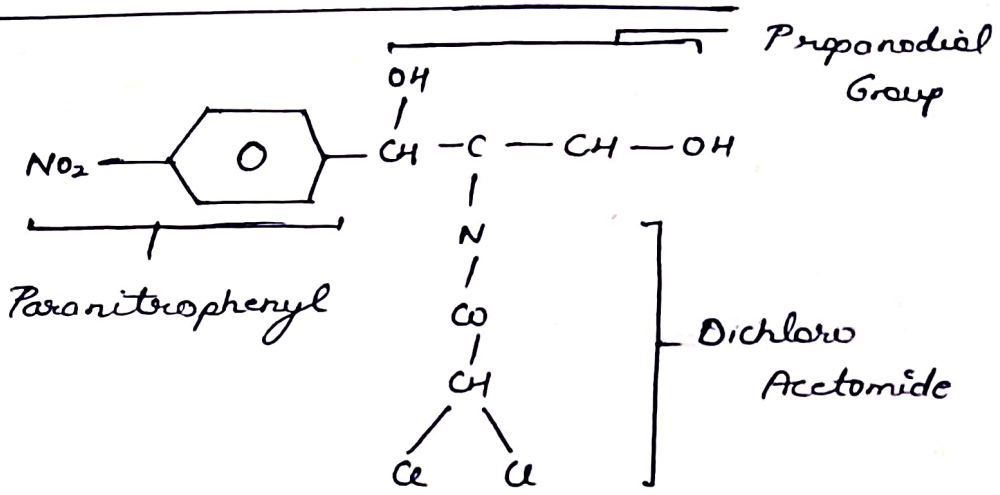
↓

No Protein Synthesis

↓

No Growth of Bacteria

STRUCTURE ACTIVITY RELATIONSHIP



⇒ Paranitro - Phenyl Group

→ Nitrogen group is essential for Activity.

→ Benzene Ring is also essential for Activity.

→ If Benzene is Replaced by Heteroatom group, activity decreases.

⇒ Dichloro - Acetamide

→ Ketone group, Dichloro groups and Nitrogen atom are essential for Activity.

→ R group [alkyl group] attached to Nitrogen and Nitrogen become Secondary to tertiary, activity decreases due to bulkiness of group.

⇒ Propanodial Ring

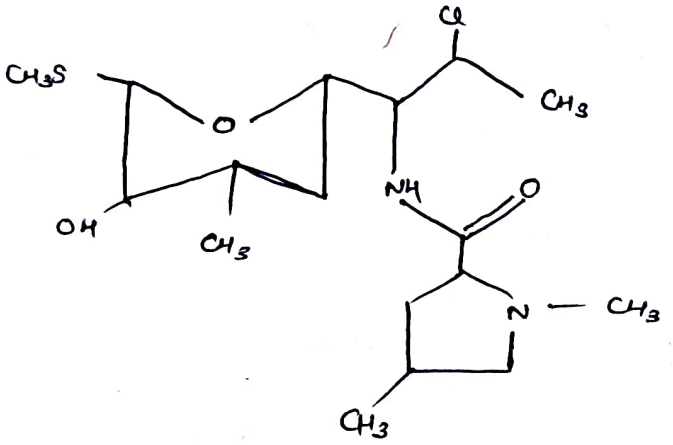
→ 2 OH groups are essential for Activity, it also increase H_2O Solubility.

→ Any branching will decrease the Activity.

CLINDAMYCIN

→ Clindamycin is a semi- synthetic Lincosamide Antibiotic.

→ Lincomycins / Lincosamides are sulfur containing antibiotics prepared from Streptomyces lincolnensis.



PROPERTIES

→ White crystaline, amorphous powder

→ Odourless

→ Soluble in Alchohal and Dimethyl Sulphur oxide

→ Stored in well closed Container

MECHANISM OF ACTION

→ It shows bactericidal effect.

Stop Protein synthesis

↓

by inhibting polypeptide chain synthesis

↓

No Translation process start

PRO DRUGS

BASIC CONCEPT

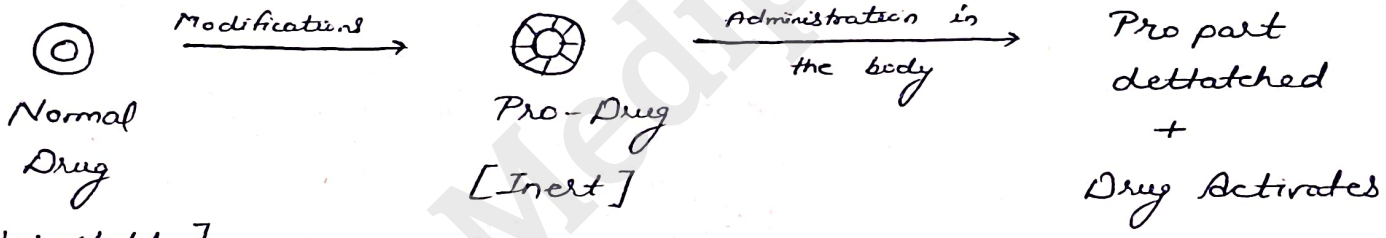
→ Modifications in drug to enhance its efficient properties that are non- suitable.

→ Pro - drug is Inactive form of drug in order to enhance & inhibit the adverse efficacy of drug by changing the physiochemical & Biological Properties.

In 1958 - Adrein Albert

↓

Gave pro drug word



Approaches [How to convert into Pro Drug]

1. Biological - Route of Administration [By change]
2. Physical - Design of dosage form [By change]
3. Chemical - Non toxicity

Objectives

→ Pharmaceutical Objectives

- To increase Solubility, Stability & organoleptic (Taste) properties.

- Decrease Irritation or Pain

→ **Pharmacokinetic Objectives**

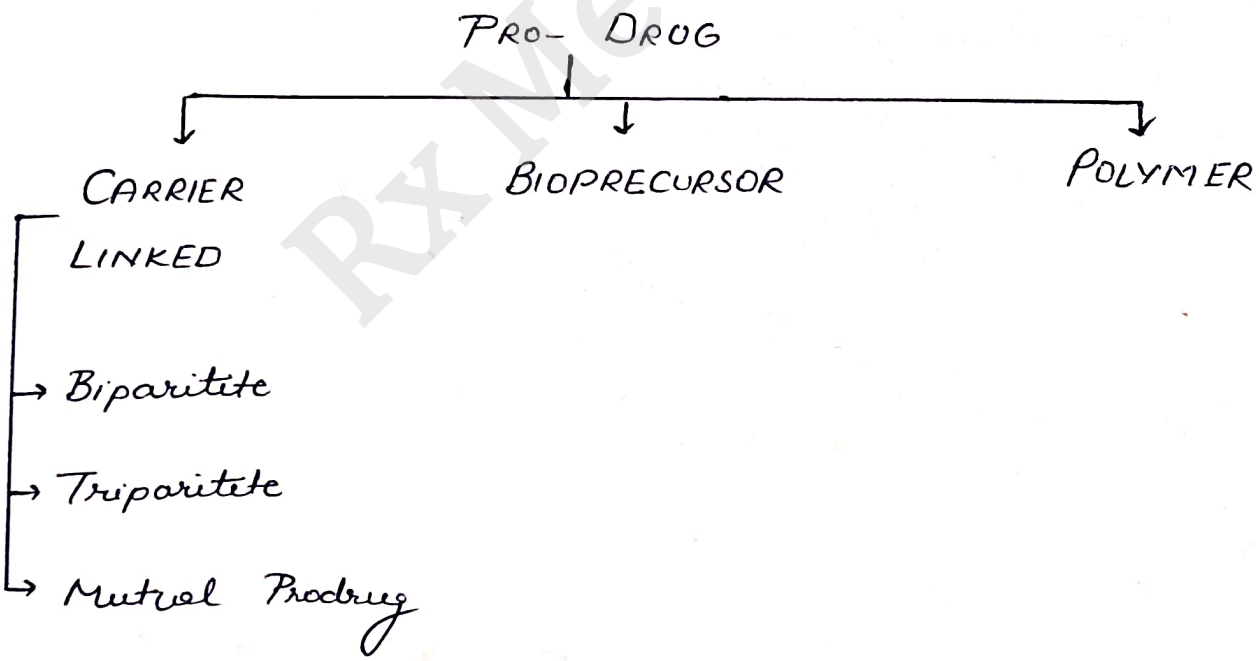
- To increase Absorption
- To decrease Pre Systemic Metabolism [first pass metabolism]
- Increase organ selective Delivery [Exact Receptor binding Action]

→ **Phamacodynamic Objectives**

- To decrease Toxicity
- To increase Therapeutic Effect

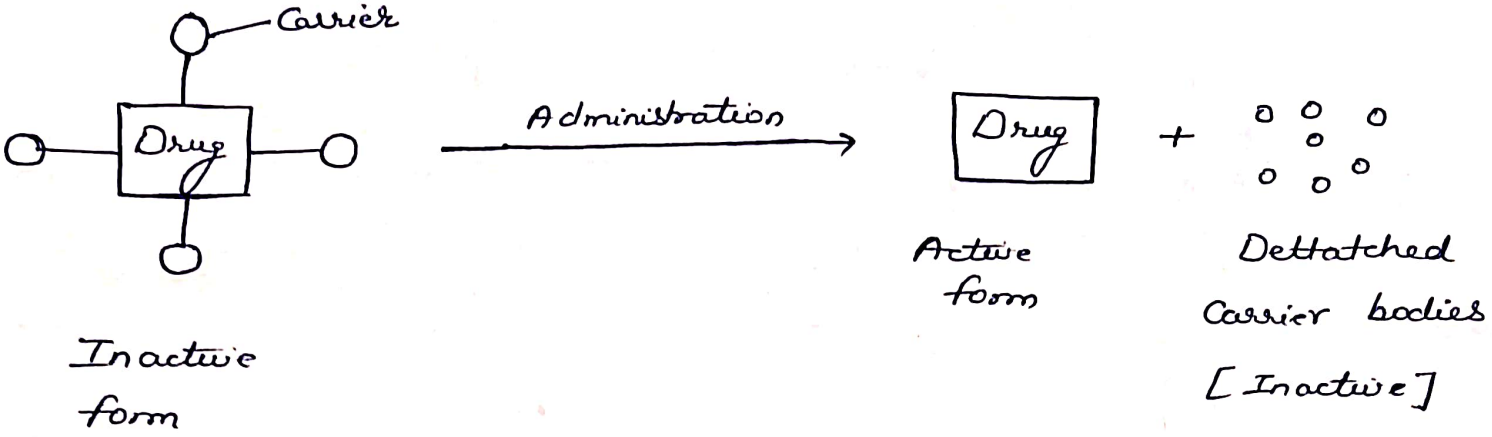
CLASSIFICATION

→ **On the basis of Modifications**



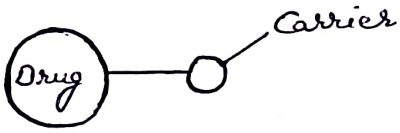
1. **Carrier linked Pro - Drug**

→ Attatchment of carrier



→ **Biparitite**

In this, Only 1 carrier is attatched with drug.



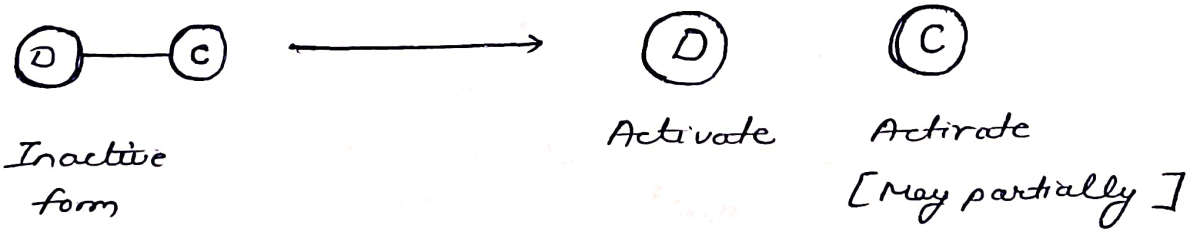
ex.→ Talmerin glycin

→ **Triparitate**

In this, Only 2 carrier is attatched with drug.

→ **Mutual Prodrug**

In this, carrier have some effect on body with drug.



→ Basis of Novel Classification

1. Type I

Drug converts into Active form after entry into ICF [Intra cellular fluid]

2. Type II

Drug Activates outside the cell [ECF - Cellular fluid] or before entering into ICF [Intra cellular fluid].

APPLICATIONS OF PRODRUGS

1. PHARMACOKINETIC APPLICATIONS

[A] Prodrugs for Improvement of Bioavailability

Chemical Modifications to improve physiochemical properties such as Solubility, Lipophilicity etc.

→ Pro Drugs to increase Lipophilicity

Pro drugs used to increase Lipophilicity so that drugs are available for oral administration or topical drug delivery.

Main Reason for design prodrug to:

- Increase oral bioavailability
- Intestinal Absorption

→ Pro drugs to increase Polarity

Designed to increase aqeous Solubility by esterification

with Amino Acids.

[B] Prodrugs for Site selective drug delivery

→ Tumour targeted Drug Delivery

Cancer chemotherapeutics are toxic and Non Selective. Therefore to improve toxicity & efficacy chemotherapy prodrugs are designed to target tumour cells.

→ Membrane transporter prodrug Targeting

Membrane transporter Selectively transport peptides, amino Acids, phosphates, ascorbic acid, bile Acids etc.

[C] Prodrug for longer duration of Action

Drugs with short half life require frequent dosing to maintain blood concentration, which cause fluctuation in drug dose. To overcome these problems long duration pro drug designed.

[D] Prodrug for minimizing toxicity

Ideal drug have minimum or No toxicity, therefore pro-drug can used to minimise toxicity of many drugs.

[E] Prodrugs for Protection from Pre-systemic Metabolism

Pre-systemic metabolism cause low oral bioavailability of drug, Therefore pro-drug can be used to block these sites and increase oral bioavailability.

2. PHARMACEUTICAL APPLICATIONS

[A] Taste Masking

Some drugs are bitter in Taste. To Reduce the bitter

taste, drugs are chemically modified to improve the taste of drug.

[B] Odour Masking

Some drugs have bad smell, To Reduce the bad smell drugs are modified to improve odour.

[C] Change of Physical form of Drug

Some drugs are in liquid form are unstable, So drug are converted into solid form by modification to make it stable for patient use.

[D] Reduction of GI Irritation

Some drugs cause irritation and damage to gastric mucosa. To reduce these problems pro drug is designed.

[E] Minimizing Pain at Injection Site

Pain at injection site is caused by precipitation of drug which cause cell death and tissue injury. To overcome these problems pro drug is design.

ANTI - MALARIALS

→ Malaria is one of the most wide-spread disease caused by a Plasmodium parasite.

→ It is a symptomatic fever spread due to transfer of Plasmodium protozoa by female Anopheles Mosquito.

→ Malerial Person
↓
Insect bite & Suck Plasmodium inside its body with blood
↓
Bite to another healthy person
↓
Spread Malaria.

SPECIES OF PLASMODIA

1. P. falciparum
→ cause approx. 50% of all malaria
→ Incubation period 1 to 3 weeks

2. P. virax
→ cause approx. 40% of all malaria
→ Incubation period 1 to 4 weeks

3. P. Malariae
→ cause approx. 10% of all Malaria
→ Incubation period 2 to 4 weeks

4. P. ovale
→ less ommon species
→ Incubation period of 9 to 18 days

TYPES OF MALERIA

1. Uncomplicated Maleria

Common symptoms are;

- fever & Headaches
- Nausea & Vomiting
- General weakness and body aches

Other signs and symptoms :

- sweating
- chest & abdominal pain
- Cough

2. Complicated or Severe Maleria

Most common symptoms;

- Anemia
- kidney failure
- Seizures, unconsciousness or confusion
- Low Blood Sugar (In pregnant women after treatment with quinine)

In Most Cases, Maleria cause deaths including;

→ **Cerebral Maleria**

If Parasite - filled blood Cells block small blood vessels to brain, brain damage may occur.

→ **Breathing Problems**

Spreading fluid in lungs can make it difficult to breath.

→ **Organ failure**

Maleria can cause kidney or liver fail.

DIAGNOSIS OF MALARIA

- It depends upon transmission of parasite in the blood.
- It can dignose by usually Microscopy.

PREVENTION OF MALARIA

- Wear pants and long-sleeved Shirts
- Spray containing DEET (Diethyltoluamide) can be used on skin
- Sleep under a Net

TREAMENT OF MALARIA

→ Kill the sporozoites injected by Mosquito or prevent the sporozoites from entering the liver

→ Kill the schizonts residing in Hepatocytes or prevent them from becoming merozites

→ Kill the Merozites in the blood or prevent them from developing into gemetocytes.

→ Kill the gametocytes before they can enter the Mosquito

→ Using Anti-Malerial Drugs

PARASITE TRANSMISSION CYCLE

→ Uninfected Mosquito : A mosquito becomes infected by biting on a person who has malaria.

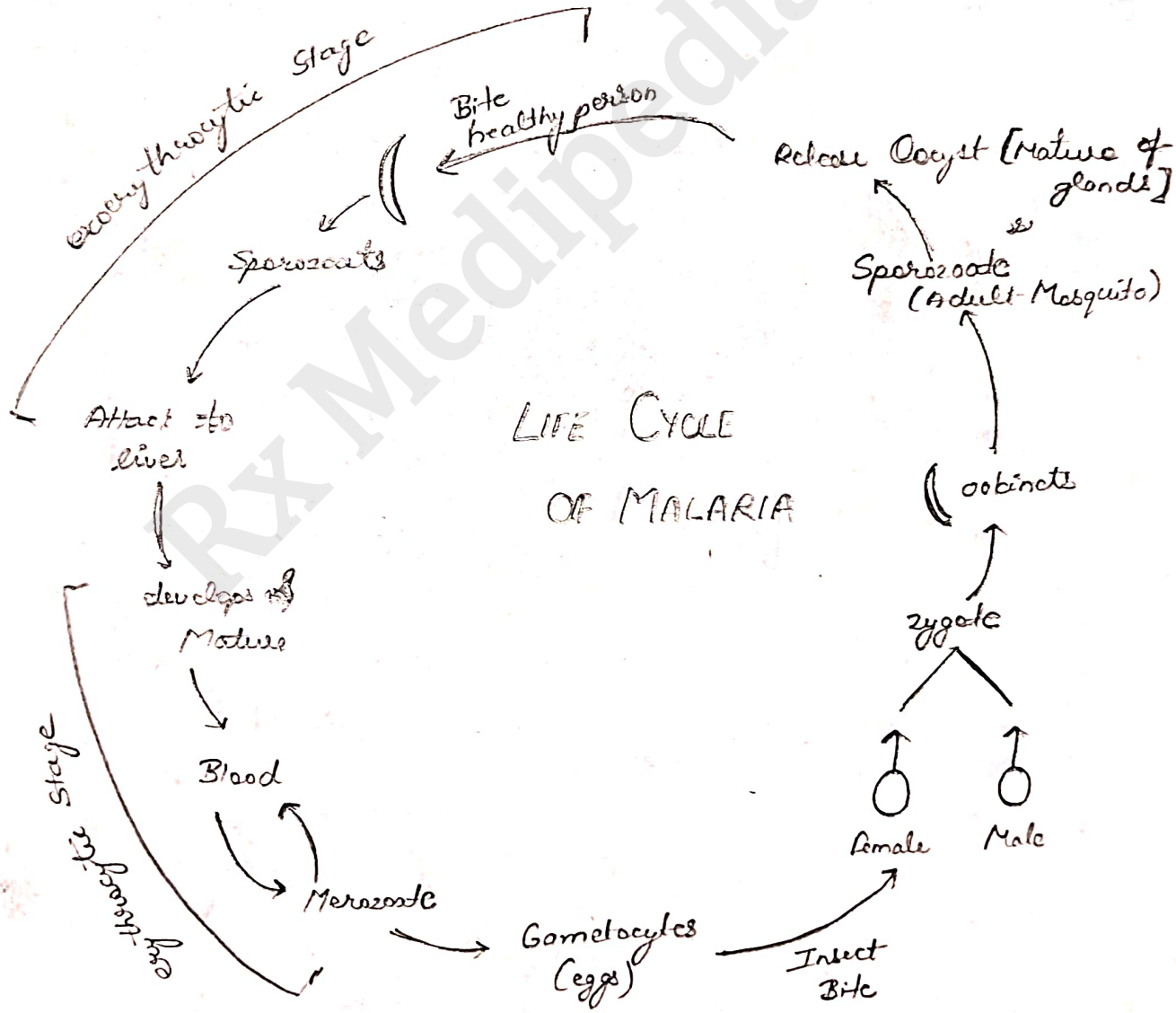
→ Transmission of Parasite : If this mosquito bites in the future to any person, it can transmit malaria parasites to that person.

→ In the liver : Once the parasite enter in the body of that person, they travel to liver.

→ Into the bloodstream: When the parasites mature, they leave the liver and infect Red blood Cells.

→ On to the Next person: If an uninfected mosquito bites to that infected person at this point in the cycle, it will become infected with malaria parasites and can spread them to the other people it bites.

LIFE CYCLE OF MALARIA

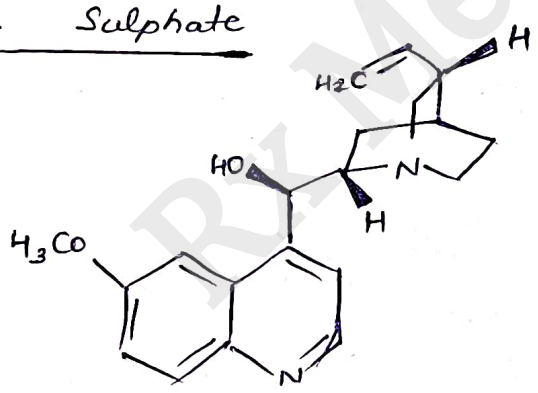


CLASSIFICATION

1. Cinchona alkaloids : Quinine sulphate
2. 4-aminoquinolone : Chloroquine , Hydroxychloroquine , Amodiaquine , Mefloquine
3. 8-aminoquinolone : Primaquine phosphate, Pamaquine, Pentaquine
4. 9-Aminoacridines : Mepacrine hydrochloride
5. Biguanides and dihydro triazines : Cycloguanil pamoate, Proguanil
6. Pyrimidine Analogues (Diaminopyrimidines) : Pyrimethamine , Trimethoprim
7. Miscellaneous : Artesunate , Artemether, Atovaquone

1. Cinchona alkaloids

→ Quinine Sulphate



• H_2SO_4

• $2H_2O$

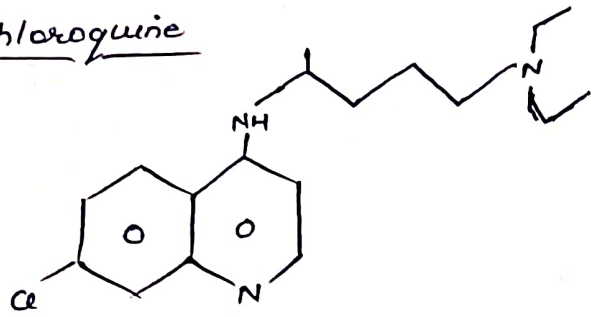
→ first known anti-material

→ Mild antipyretic

→ Analgesic

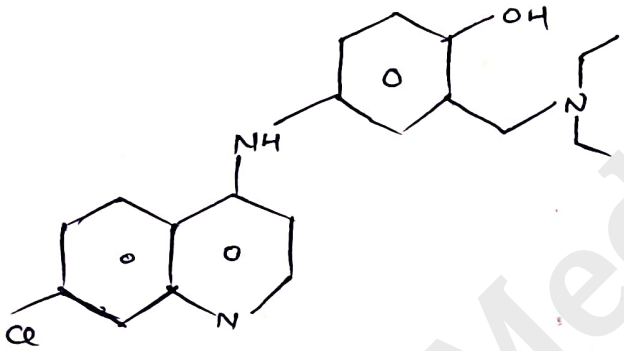
2. 4-Aminoquinolines

→ Chloroquine



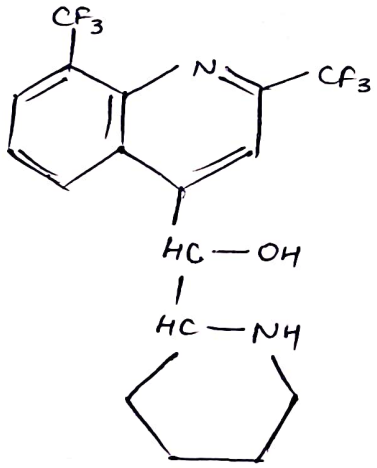
- Used for prevention & therapy of Malaria
- Anti-inflamatory agent for therapy of Rheumatoid Arthritis

→ Amodiaquine



- treatment of Malaria
- Anti-inflamatory agent

→ Mefloquine

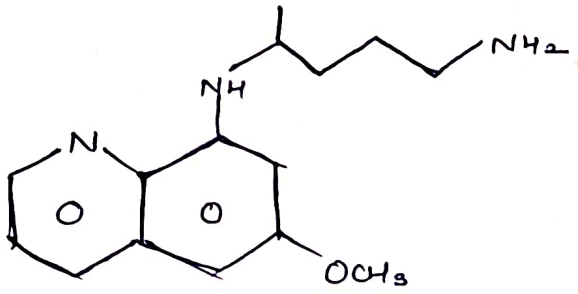


- Used for prevention & treatment of P. falciparum Malaria.

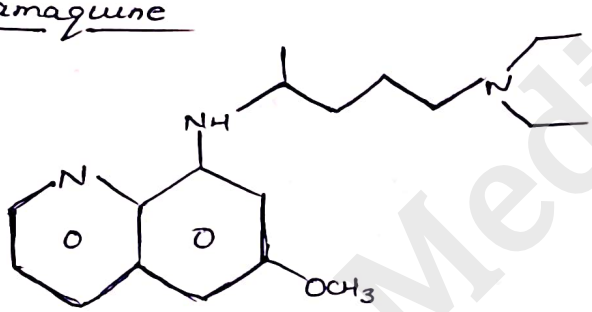
3. 8 - Aminoquinolones

They have diff. mechanism of Action. The disrupt the Parasite's Mitochondria which results in inhibtion of maturation.

→ Primaquine Phosphate

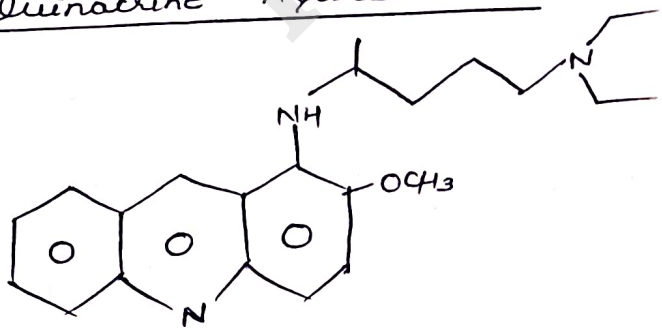


→ Pamaquine



4. 9 - Aminoacridines

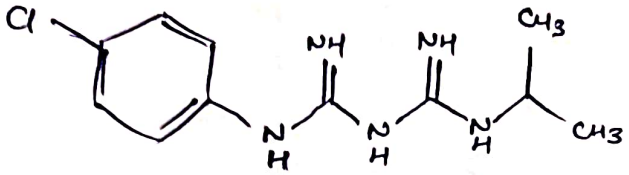
→ Quinacrine Hydrochloride



- Anti-malerial agent
- also have antineoplastic and antiparasitic Activities.

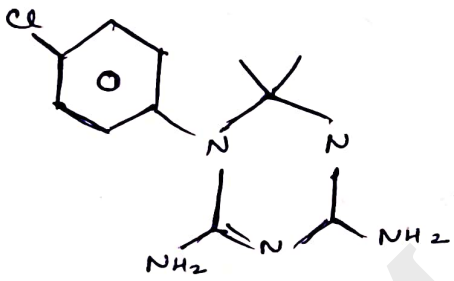
5. Biguanides and Dihydro Triazines

→ Proguanil



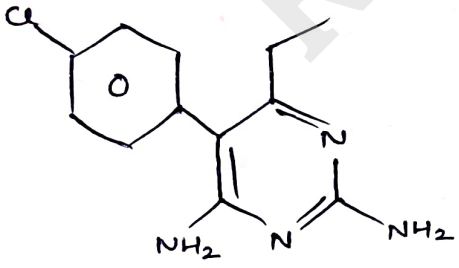
- Used as an antimalarial
- Also used antiprotozoal drug

→ Cycloguanil Pamoate



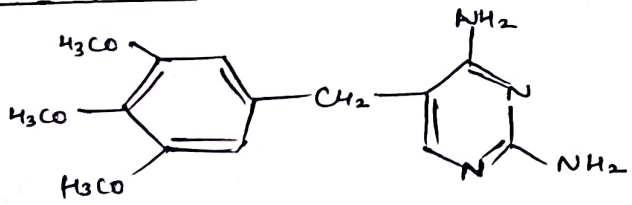
6. Diaminopyrimidines

→ Pyrimethamine



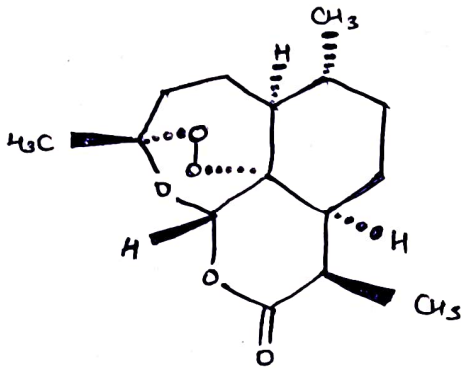
- Used as immunosuppresive Agent.

→ Trimethoprim

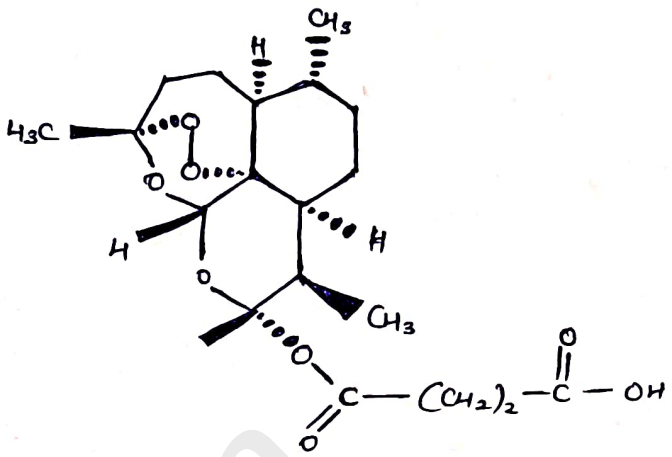


7. Miscellaneous Drugs

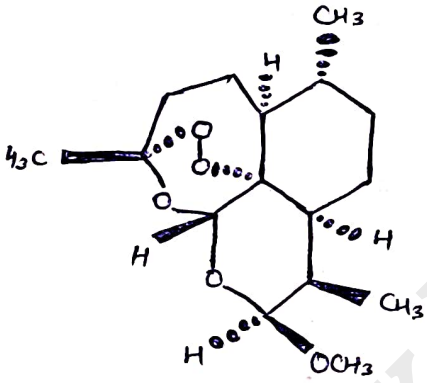
→ Artemisinin



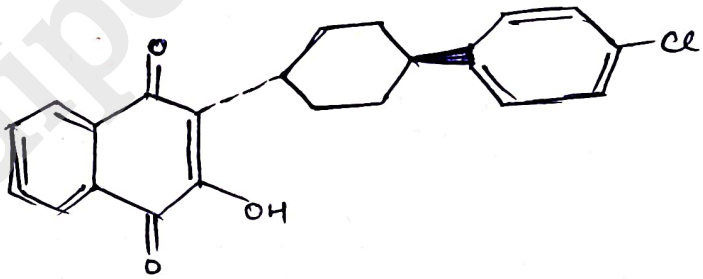
→ Artesunate



→ Artemether

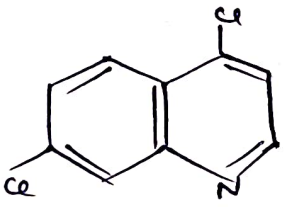


→ Atovaquone



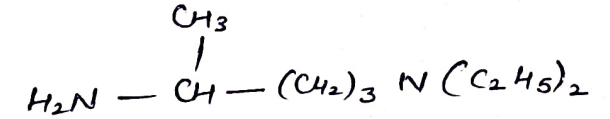
SYNTHESIS

1. Chloroquine

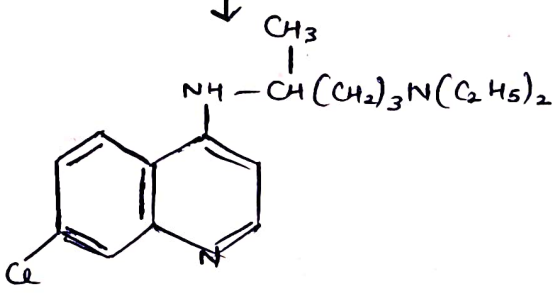


4,7 Dichloro-quinoline

+

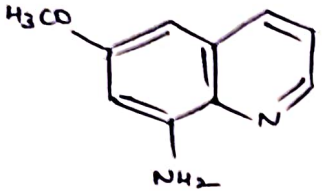


4-Amino-1-diethyl amino pentane



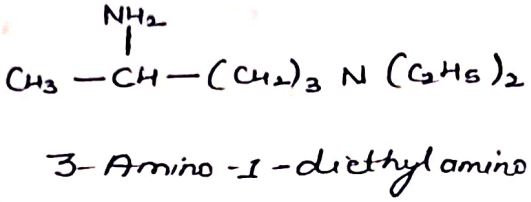
Chloroquine

2. Pamaquine



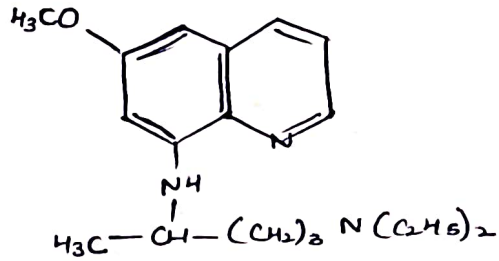
8-Amino-6-methoxy quinoline

+



3-Amino-1-diethyl amino butane

$-NH_3$ Condensed



Pamaquine