UNIT-2

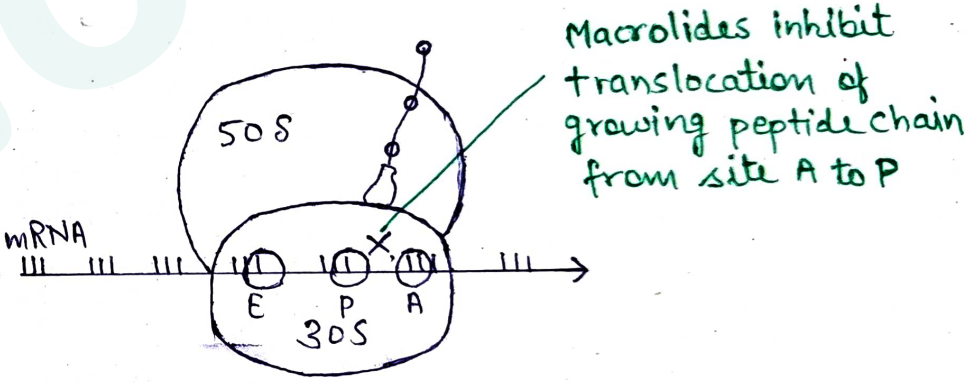
ANTIBIOTICS

Macrolides

- Macrolides are a group of antibiotics with a macrocyclic lactone ring (containing 14 or 16 atoms) to which one or more deoxy sugars are attached.
- Erythromycin is the first member discovered in 1950s. Roxithromycin, clarithromycin, Telithromycin and Azithromycin are the later additions.
- Telithromycin is the semi-synthetic derivative of erythromycin.
- Bacteriostatic in nature, inhibit protein synthesis in bacteria.
- active against gram +ve cocci and a typical pathogens and a few gram -ve bacteria.

Mechanism of Action

Macrolides act by inhibiting the bacterial protein biosynthesis and by preventing peptidyltransferase from attaching the growing peptide to t-RNA to the next amino acid. They also inhibit ribosomal translation and causes premature dissociation of the peptidyl-tRNA from ribosome.



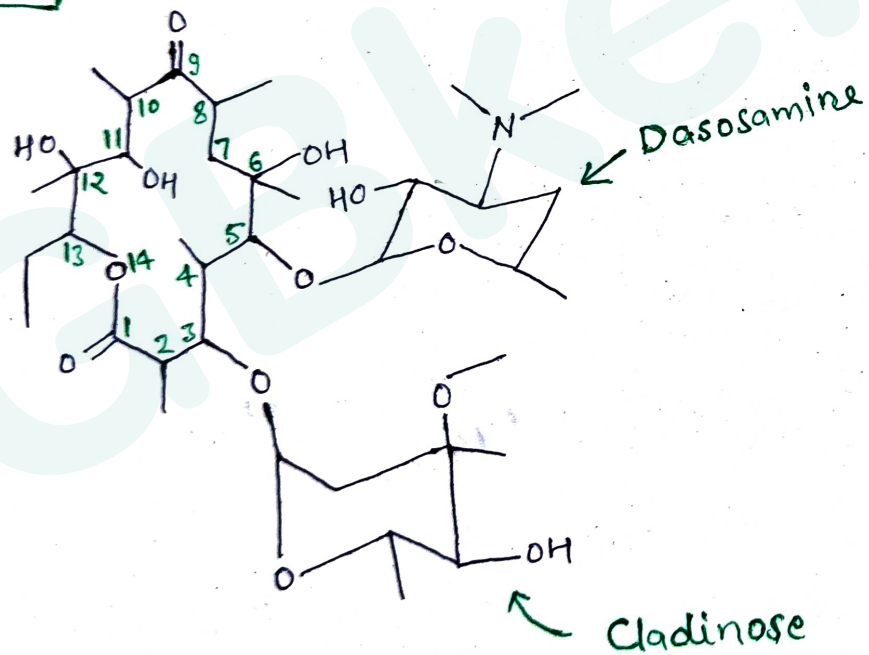
Classification

Macrolides are classified according to the number of atoms comprising the lactone ring.

Macrolides

- **13-membered**
  - Semi-synthetic
    - Tulathromycin (203)
- **14-membered**
  - Natural
    - Erythromycin
    - Oleandomycin
  - Semi-synthetic
    - clarithromycin
    - Roxithromycin
- **15-membered**
  - Semi-synthetic
    - Azithromycin
    - Tulathromycin (903)
- **16-membered**
  - Natural
    - Tylosin
    - Spiramycin
  - Semi-synthetic
    - Tilmycocin
    - Miokamycin

SAR



- A lactone ring, ketonic group and an amino sugar are the basic characteristic groups that are desired for activity.
- Amino sugar must be glycosidically bonded.
- Dimethyl amino group provides basic properties to macrolides.
- Lactone ring contains 12, 14, 16 atoms in cyclic ring alongwith olephinic group.
- Reduction at C-9 results in more stable product but is less potent.
- Modification at C-8 leads to acidic stability.
- 11, 12 – carbonate were prepared which were more stable and had double activity but had hepatotoxic potential.
- Removal of hydroxyl group at C-6 leads to decrease in potency.
- Increasing the number of atoms in the core skeleton leads to greater acidic stability and improved bioavailability.

Important Products

1) Erythromycin

It is bacteriostatic, produced by a strain of Saccharopolyspora erythraea.

It blocks protein synthesis by inhibiting the transpeptidation of protein synthesis.

Uses

- Used in the infections of respiratory tract, diphtheria, whooping cough, etc.
- Also used in STDs like syphilis.
- prevent recurrent rheumatic fever.
- used to treat ear, intestine, urinary tract and skin infections.

Some common side effects of erythromycin are nausea, vomitting, diarrhoea, stomach pain, and loss of appetite.

2) Clarithromycin

- semi-synthetic macrolide anti-biotic which is derived from erythromycin.
- It may be bacteriostatic or bactericidal, depending on the organism or drug concentration.
- inhibits protein synthesis

Uses

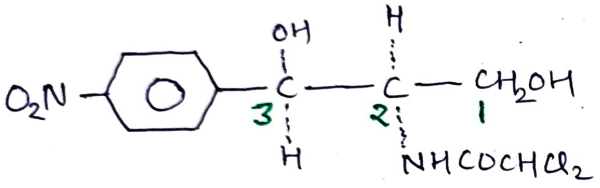
- Used in pharyngitis and tonsillitis caused by susceptible streptococcus pyogenes, RT infections.
- Adverse effects of clarithromycin include abnormal taste, elevated blood urea nitrogen, abdominal pain, heartburn, etc.

3) Azithromycin

- broad-spectrum antibiotic with a longer half-life and high degree of tissue penetration.
- Blocks transpeptidation step of protein synthesis.
- Used in treatment of sinus infection, COPD, tonsillitis, urethritis, etc.
- side effects are similar as of erythromycin and clarithromycin.

Miscellaneous

Chloremphenicol *



Chloremphenicol is bacteriostatic in nature, broad spectrum antibiotic.
It occurs as fine, white to greyish needle-like crystals or elongated plates. It is slightly soluble in water and freely soluble in acetone, alcohol, ethyl acetate and propylene glycol.

Chloremphenicol palmitate obtained from Streptomyces venezuelae is a fine, white, crystalline powder with a mild taste.

History

Chloremphenicol was isolated by Ehrlich in 1947, from Streptomyces venezuelae. Gargye and Dutta reported in 1959 that systemic administration of chloramphenicol causes ototoxicity.

SAR of Chloramphenicol

1) Effect on p-Nitrophenyl Group

a) Replacement of nitro group (NO_2) reduces antibacterial activity.
b) Shifting NO_2 from para position also reduces act.
c) Replacing the phenyl groups with alicyclic moieties form less potent compounds.
d) Replacing the p-nitrophenyl group with other aryl structures do not result in loss of activity.

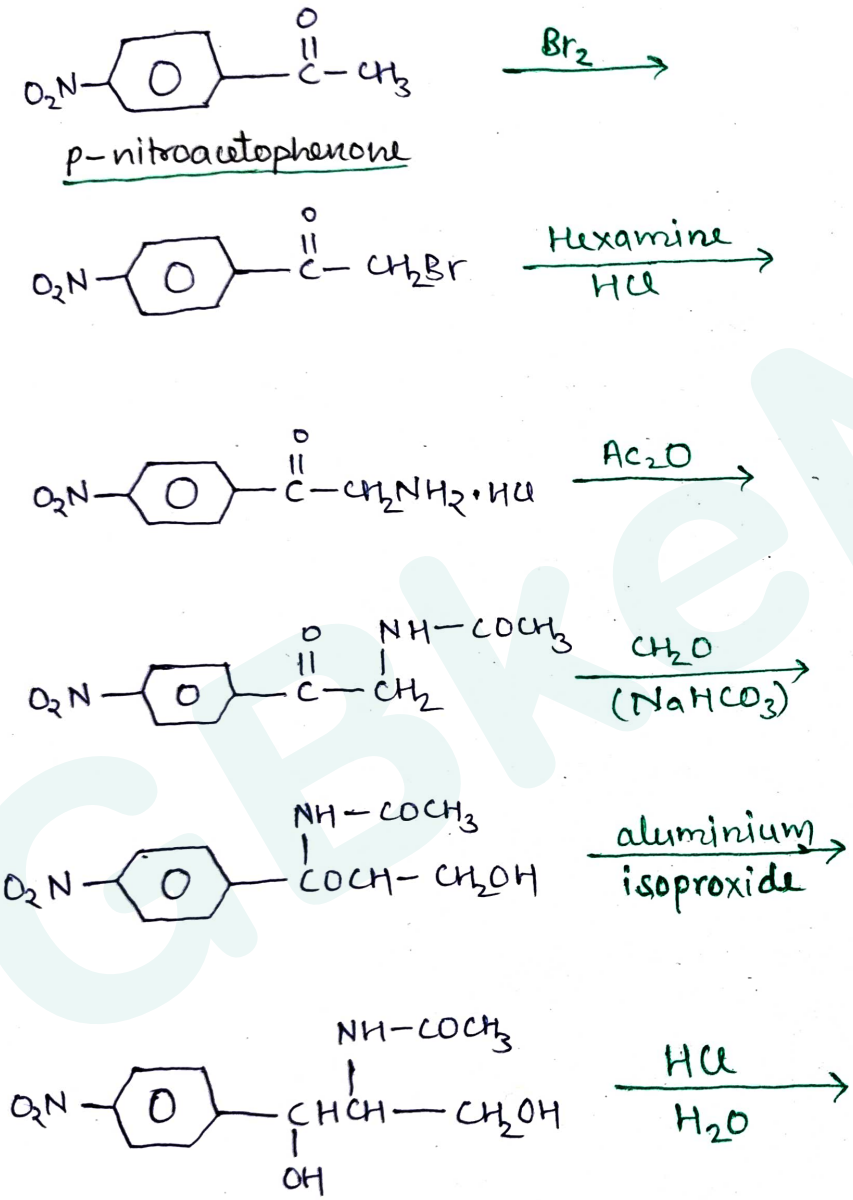
2) Effect on Dichloracetamido Side chain

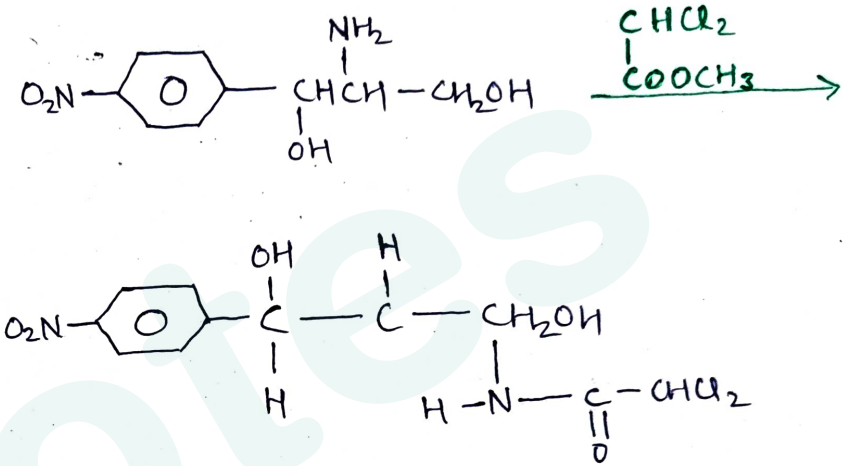
i) Other dihalo derivatives of the side chain are less potent, though major activity is retained.
ii) In case of trihalo derivatives, $NHCOCF_3$ derivatives would be 1.7 times as active as the chloramphenicol.

3) SAR of 1,3-Propanediol

Modification of alcoholic group at C-1 reduces activity, hence it is essential.

Synthesis





Chloramphenicol

Uses.

i) Enteric fever
ii) Meningitis
iii) Topical uses (eye, ear, etc.)
iv) Rickettsial infections, pneumonia.

Common side effects →

i) It depresses RBCs, WBCs formation.
ii) Gray baby syndrome
iii) GI irritation, stomatitis, glossitis, headache, mental confusion.

Clindamycin

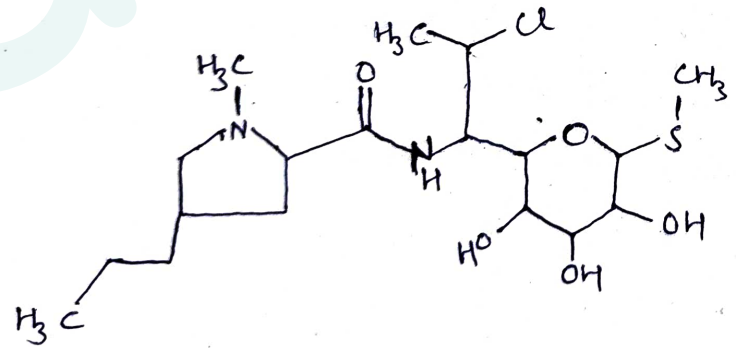
Clindamycin is a semi-synthetic antibiotic that has replaced lincomycin due to its improved side effect profile.

It inhibits protein synthesis in bacteria. It may be bacteriostatic or bactericidal depending on the organism or drug concentration.

Uses

i) Useful in pelvic infections, osteomyelitis.
ii) Treatment of MSSA and respiratory infections.
iii) topical use in treating acne.
iv) vaginal use to treat vaginosis.

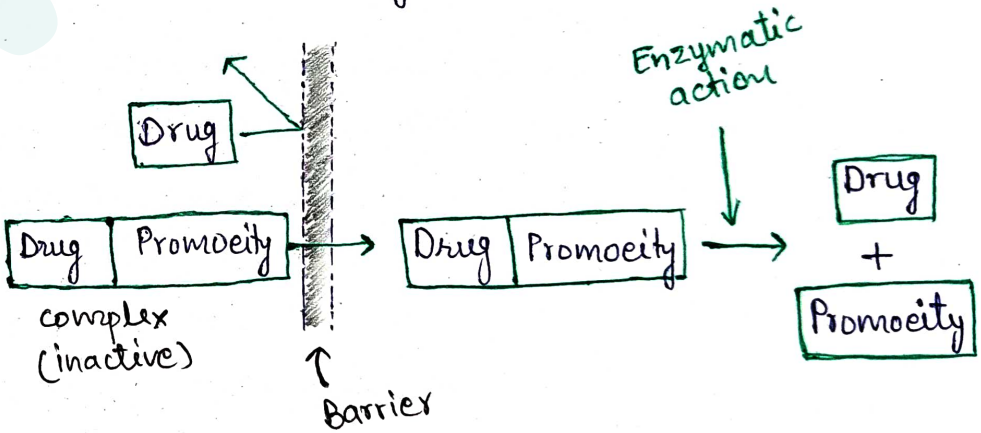
Common side effects → vomitting, diarrhoea, skin problems, low blood pressure, pain in swallowing, body aches, etc.



Prodrugs

Prodrugs are pharmacologically inactive compounds that can be used to modify the physical and chemical properties of a drug to increase its use and/or to decrease its toxicity.

Prodrug is made up of an active drug and promoiety. The latter is not required for pharmacological action but offers a desirable property to the drug.



Basic concept of Prodrug

Drug-promoeity complex is pharmacologically inactive prodrug.

The barrier in the diagram is the representation of the limitation of a parent drug that prevents optimal pharmacokinetic performance, and thus should be overcome so that a marketable drug can be developed. Drug and promoeity are covalently bonded which is reversible.

Both of them are separated by the enzymatic action inside the body once the barrier is crossed.

Prodrugs

Carrier linked

Prodrugs are esters or amide.

Further types:

- Cascade-latentiated
- Macromolecular
- Site specific
- Mutual prodrugs

Bioprecursor

Unlike, carrier-linked prodrugs, no carrier is is involved in bioprecursor prodrugs.

Any salt is added to the drug during manufacturing.

Applications

The aim of prodrug development is to solve specific pharmaceutical or pharmacological and pharmacokinetic problems.

1) The Pharmaceutical applications

a) Improvement of taste, odour
b) Change of physical form for preparation of solid dosage forms.
c) Reduction of GI irritation
d) Reduction of pain on injection
e) enhancement of drug solubility and dissolution rate.

2) Pharmacokinetic Applications

a) enhancement of drug bioavailability
b) Improved stability and solubility
c) Prevention of pre-systemic metabolism
d) Prolongation of duration of action
e) Reduction of toxicity
f) Site-specific drug delivery.

Antimalarials

Antimalarial agents are the drugs which are used in the treatment of malaria.

Malaria is a mosquito-borne infectious disease caused by parasitic protozoans of Plasmodium type.

Malaria is transmitted by an infected female Anopheles mosquito, which introduces the parasites from its saliva into the person's blood.

Five species of Plasmodium can infect humans:

i) P. falciparum (causes most deaths)
ii) P. vivax
iii) P. ovale
iv) P. malariae
v) P. knowlesi (rarely causes disease in humans)

Etiology of Malaria

The causative agent of malaria is a protozoan parasite of the genus Plasmodium.

P. falciparum and P. vivax cause 80% of the malaria cases and accounts for 90% of deaths.

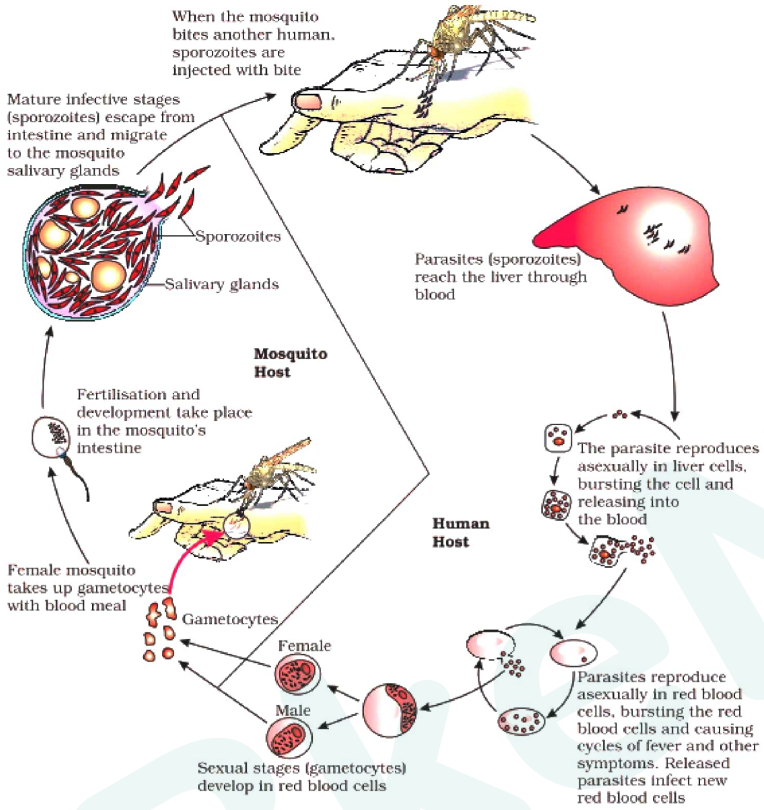
Mode of transmisioon

- An uninfected mosquito becomes infected by feeding on a malaria-infected person. Now, if this mosquito bites healthy individuals, the parasite is transmitted to them.
- Parasites then reach the human liver, where some types of them remain dormant for even a year. The parasites on maturing leave the liver and infect the RBCs. At this point, the symptoms of the malaria are observed.

Life cycle of Malaria Parasite

It is completed in three stages:

1) Infecting an individual with sporozoites
2) Asexual reproduction
3) Sexual reproduction.



→ Anopheles mosquito bites a person and injects Plasmodium parasites, in the form of sporozoites into the bloodstream.

→ Sporozoites pass quickly to the human liver, and multiply asexually in the liver cells over the next 7–10 days causing no symptoms.

→ From liver, merozoites (parasite in form of vesicles) are released, journey through the heart, arrive in the lungs. The vesicles eventually disintegrate, freeing the merozoites to enter the blood phase of their development.

→ Merozoites invade RBCs and burst them. This causes fever.

→ Merozoites starts to develop into sexual forms called gametocytes that circulate in bloodstream.

→ Now, these gametocytes enter mosquito through mosquito bite and develops into mature sex cells called gametes.

→ The fertilised female gametes develop into actively moving ookinetes that burrow through the mosquito's midgut wall and form oocysts on the exterior surface.

→ Inside the oocysts, thousands of sporozoites develop. The oocyst eventually bursts, releasing sporozoites into the body cavity that travel to the mosquito's salivary glands.

→ The cycle of human infection begins again when the mosquito bites another person.

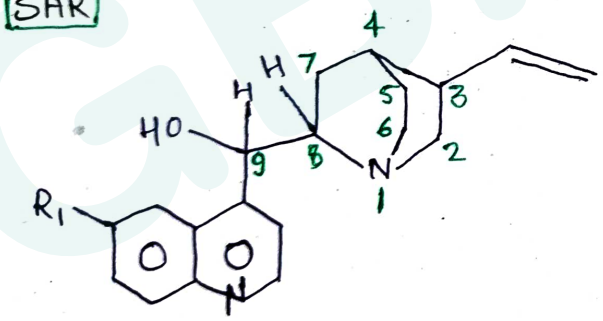
Example of some antimalarial agents are:

i) Quinoline derivatives: Cinchona alkaloids
ii) 9-amino acridines: Quinacrine, Acriquine
iii) Biguanides: Proguanil, Chlorproguanil
iv) Pyrimidine Analogue: Pyrimethamine
v) Sulphone: Dapsone
vi) Artemisinin, Primaquine, Chloroquine

Quinolines

Quinoline is a heterocyclic aromatic organic compound with the chemical formula C_9H_7N. It is a colourless, hygroscopic liquid with a strong odour.

SAR



1) Asymmetry at C-3 and C-4 is not essential for antimalarial activity.
2) Replacing the methoxy group in quinine, with a halogen enhances the activity.
3) Substitution at C-8 by a halogen increases anti-malarial activity.
4) Oxidation or esterification reduces the anti-malarial activity.

Quinine Sulphate

Quinine is an alkaloid derived from Cinchona bark. It is an anti-malarial agent.

MOA → They interfere with the parasites ability to breakdown and digest haemoglobin. As a result, the parasite starves.

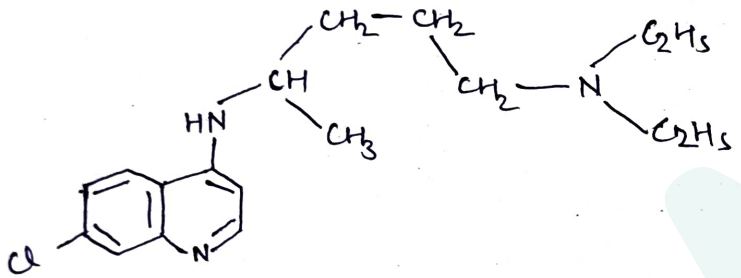
Uses

i) Used for treating malaria.
ii) mild antipyretic and analgesic.
iii) Used in some muscular disorders, especially nocturnal leg cramps

Side effects may be nausea, restlessness, difficulty in hearing, ringing in the ears.

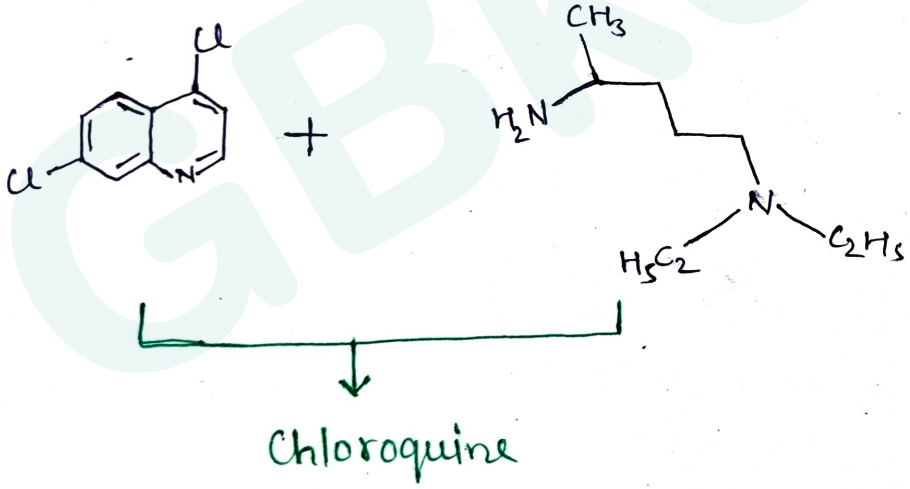
Chloroquine *

Chloroquine is the precedent anti-malarial drug. It is used for treating all types of malaria excluding P. falciparum.



Chloroquine

Synthesis



Chloroquine

MoA → Mechanism involves interaction between ferriprotoporphyrin IX (FP) and chloroquine. FP induces haemolysis of RBCs and lysis of malarial parasite. Heme is released as FP after the digestion of haemoglobin. A complex forms between chloroquine and FP that is toxic to the cell.

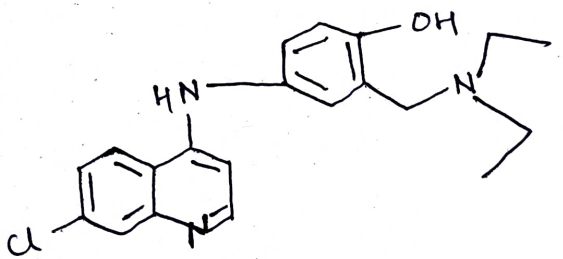
Uses

suppressive treatment of malaria.

side effects → GI problems, stomach ache, itch, headache, nightmares.

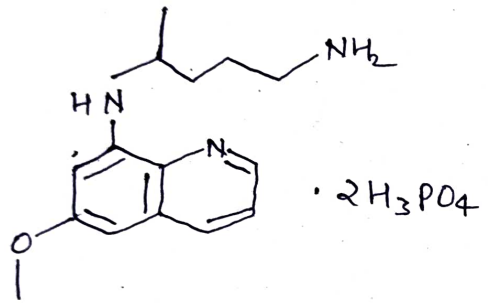
Amodiaquine

Amodiaquine is a 4-aminoquinoquinoline derivative containing anti-inflammatory properties.



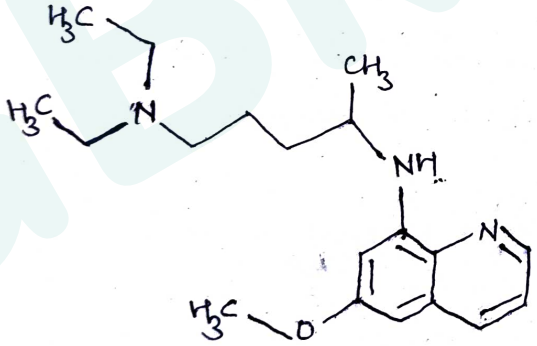
Primaquine Phosphate

It prevent relapse of vivax and ovale malaria.

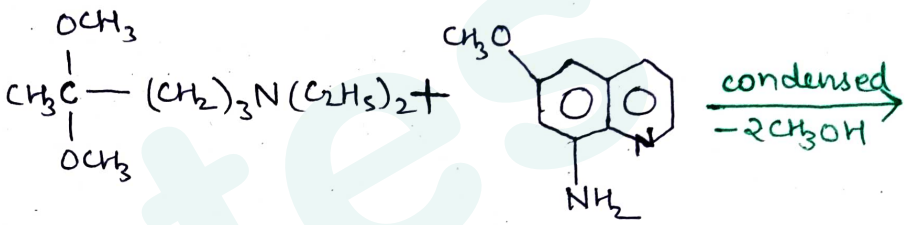


Pamaquine *

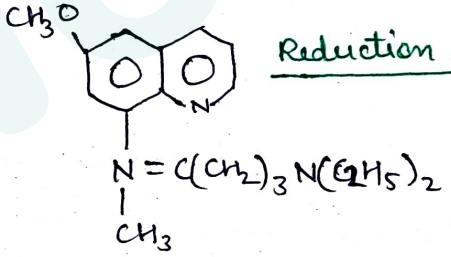
Pamaquine is an 8-aminoquinoline drug that is closely related to primaquine.



Synthesis

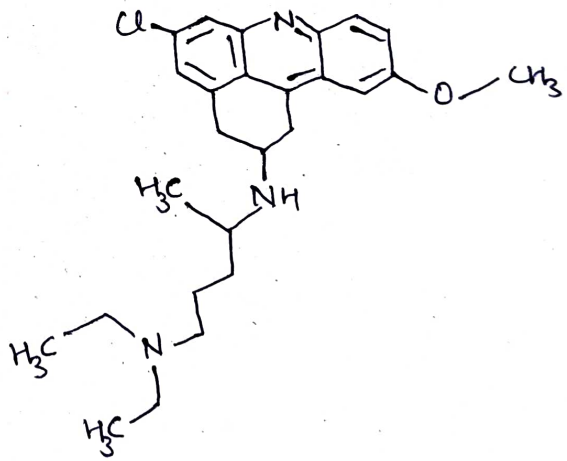


8-amino-6-methoxy quinoline

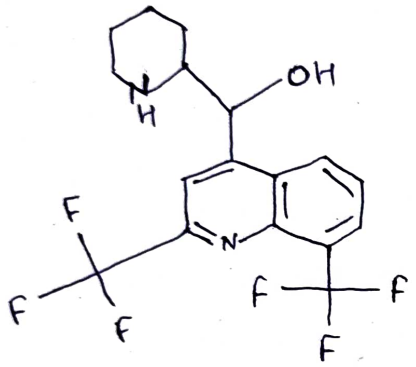


Pamaquine

Quinacrine HCl



Mefloquine



Biguanides and dihydrotriazines

Biguanides are prodrugs and are not active till they are metabolised in vivo to dihydro triazine derivatives.

Guanidine analogues remain inactive till they get cyclised metabolically to a dihydro-s-triazine analogue that is somewhat similar to either the pteridine moeity of folic acid or pyrimethamine.

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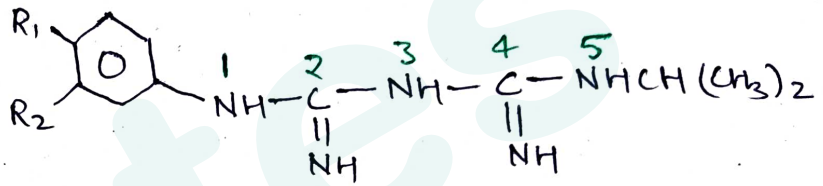

1) Presence of N^1-aryl is essential for anti-malarial activity but introducing a second group reduces the activity.
2) Dihalogen substitution at C-3 and C-4 of the benzene ring yield potent drugs.
3) Alkyl substituents on N^1, N^2, N^4 reduces the antimalarial activity.
4) Replacing the isopropyl group with a normal propyl group at N^5 gives essentially equal activity.
5) Introducing shorter or longer alkyl chains reduces the anti-malarial activity.

Cycloguanil Pamoate

Cycloguanil is the active metabolite of proguanil.

Proguanil

Proguanil is a biguanide compound which forms cycloguanil (an anti-malarial) by getting metabolised in the body.

Pyrimethamine

Pyrimethamine is a synthetic derivative of ethyl pyrimidine. It has potent antimalarial properties and also inhibits Dihydrofolate Reductase (DHFR).

Artisunate

Artisunate is a part of the artimisinin group of drugs used for treating malaria. It is a semi-synthetic derivative of artemisinin that is water-soluble and thus given by injection.

Artemether

Artemether is used to treat acute uncomplicated malaria. It is administered as a combination therapy with lumefantrine for improved efficacy and to exert its effects against the erythrocytic stages of Plasmodium species.

Atovaquone

Atovaquone is a hydroxynaphthoquinone or an analogue of ubiquinone, that is an anti-microbial and antipneumocystic.