UNIT - 2

moety - molecules

Macrolide Antibiotics -

Macrolide antibiotics clinical important antibiotic used to treat infection caused by G(+) such as Staphylococcus aeruse, streptococcus pneumoniae & Streptococcus pyrogen

→ chemical macrolide are represended by 14, 15, 16 membered lactone ring which contain one or more sugar moiety (molecules) & additional subtituent Attached with various atom of lactone ring.

classification -

macrolide are classify on the basis of molecular struture.

① 14-membered
RED
F
C

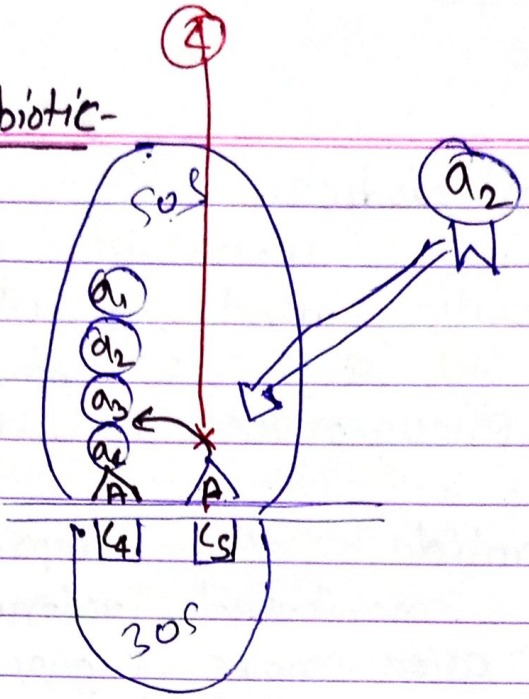
- clarithromycin
- Erythromycin
- Roxithromycin
- Flurithromycin
- Dirithromycin

② 15-membered - Azithromycin

③ 16-membered -
- miocamycin
- Josamycin
- spiramycin

Translocation

MOA of macrolid antibiotic-



④ Erythromycin and clindamycin also bind to 50S ribosome

⇒ Macrolid antibiotics bind with 50S and 30S Sub unit of ribosome and inhibit initiation, interfere with polysome formation & cause misreading of m-RNA codon & thus inhibit protein Synthesis in bacteria.

Use of Erythromycin -

① It is highly active again streptomycis pyrogen Streptomyeis pneumoniae and infection.

② use in the treatment of tonsilitis, Phoryngitis syphilis & Gonorria, pnemonia etc.

use of clarithromycin -

① Same as Erthromycin

② use in lower Respiratory tract infection, Synosytis, otitis.

use of azithromycin -

-> It is potent macrolide antibiotic have standard spectrum & improoved pharmacokinetic properties.

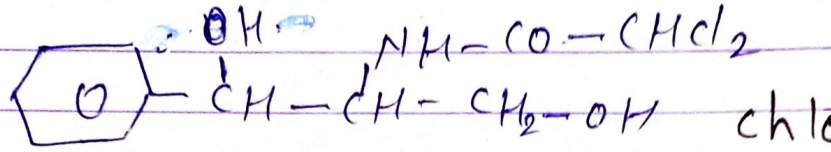
-> use in the treatment of Bronchitis tonsillitis laryngitis & other Respiratory tract infection (RTI)

Structure -

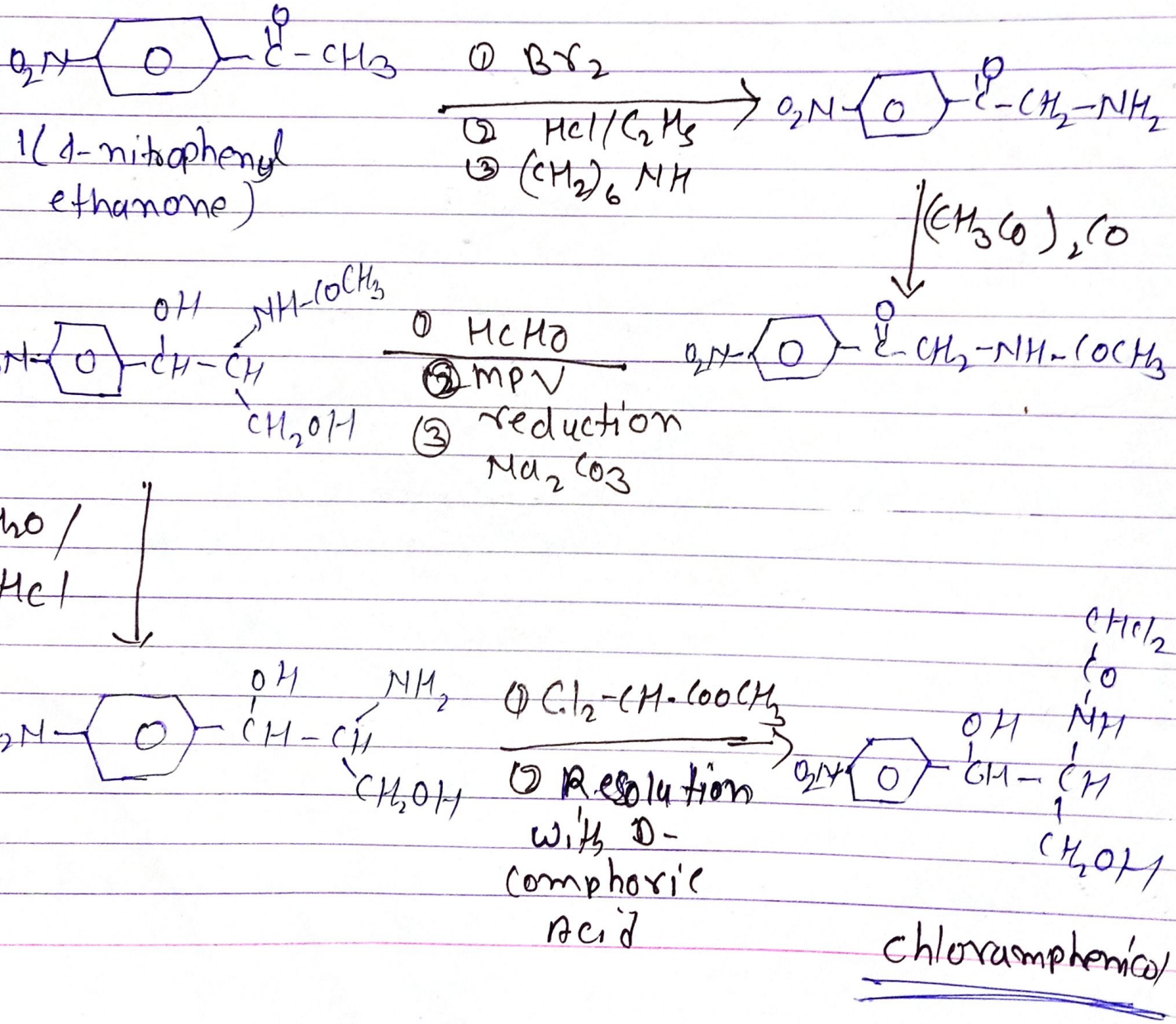
Chloramphenicol

chloramphenicol was initial obtained from Streptomycis venezuelea in 1947 but now it is Synthesis chemicaly

Synthesis of chloramphenicol



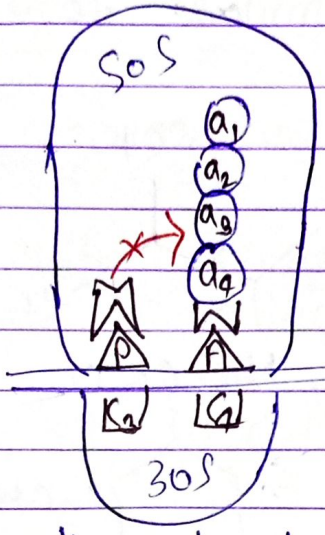
str. chloramphenicol



H -> Helicobacter

MOA of chloramphenicol

chloramphenicol bind with 50S subunit of Ribosome of A site & prevent peptide bond formation by inhibiting transfer of peptide chain P_2 A side



peptide bond formation

chloramphenicol bind to 50S subunit - interfere with peptide bond formation & transfer of peptide chain from P site.

Use - use in the treatment of infection caused by rickettsia

⇒ use in the treatment of menigitis caused by neisseria, in the treatment of pneumonia caused by streptococcus pneumoniae

⇒ It is used of H. pylori infection & duodenal ulcer

⇒ It is used an alternative to pen. & cephalosporin for the treatment of meningitis

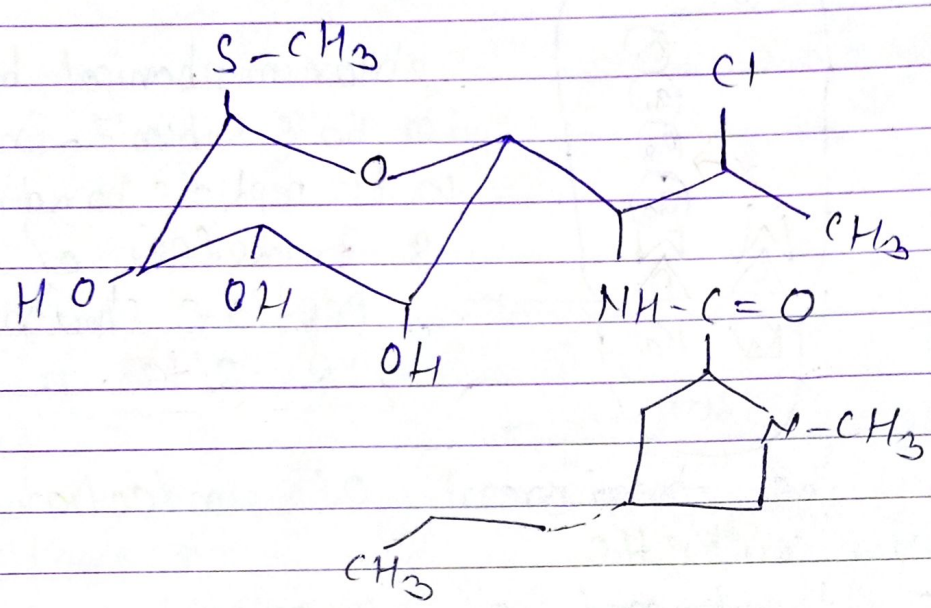
Adverse effect -

① Bone marrow depression
② fetal toxicity

Lincosamide Antibiotic

e.g - clindamycin ⇒

⇒ This is chlorinated lincosamide antibiotic, mechanism of action & antibacterial spectrum is similar to Erythromycin.



clindamycin

MOA of clindamycin - clindamycin bind with 50s ribosome at inhibit translocation of an alongated peptide chain back from A site to P site and inhibit peptide chain formation in bacteria.

use - ⇒ Antibacterial spectrum similar to Erthromycin.

Prodrug -

Prodrug

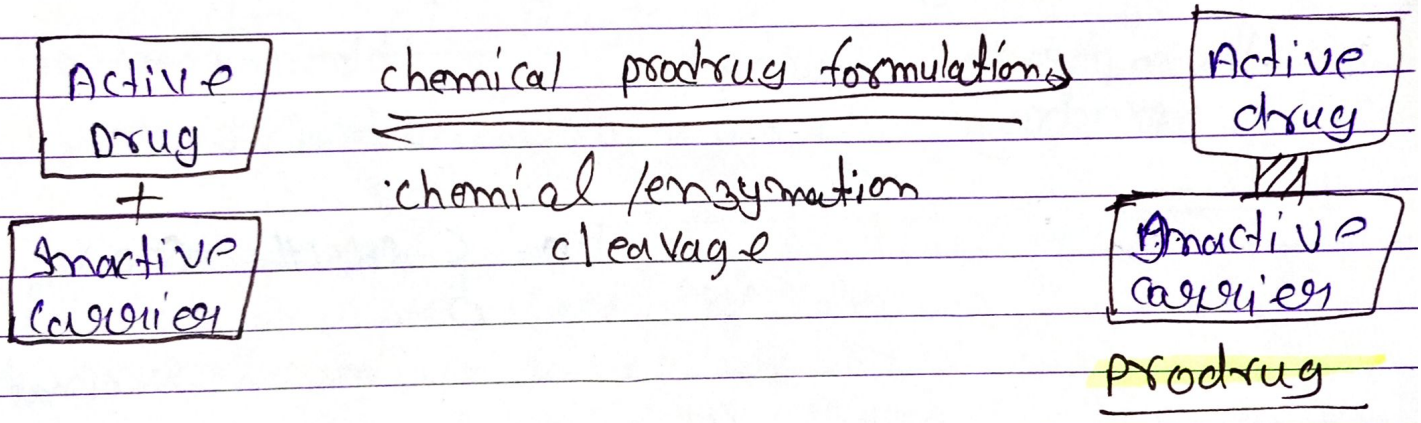
⇒ prodrug is chemicaly modified inert precursor of the drug which after bio-transformation. libraates pharmacologicaly active parent compound.

Ideal properties of prodrug -

① Drug and carrier linkage must be cleared in vivo.

② It should rapidly transform, chemicaly or enzymaticaly in to active drug where desired

③ metabolic fragment apart from active drug should be non-toxic



Classification of prodrug

Depending upon constitution lipophilicity and method of bioactivation prodrug are classification 2 categories -

① Carrier link prodrug -

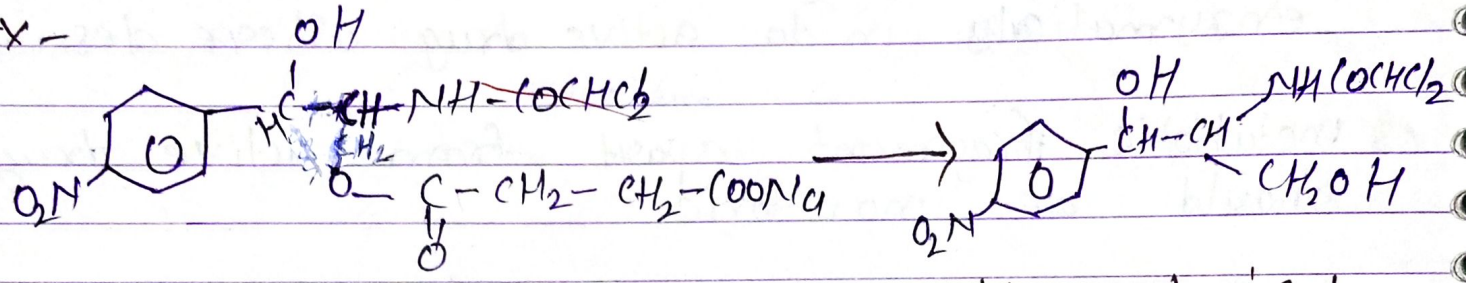
② Bio precures -

① Carrier linked prodrug -

They are generaly ester or amide.

⇒ In this active drug is covallently linked with inert carriers such prodrug modified the lipophilicity of active drug. due to attachment of lipophilic carriers. ⇒ the active drug is released by hydrolytic cleavage neither chemicaly or enzymaticaly

Ex -



chloramphenicol succinate prodrug

Chloramphenicol (Active drug)

+

Sodium succinate

② Bioprecursor -

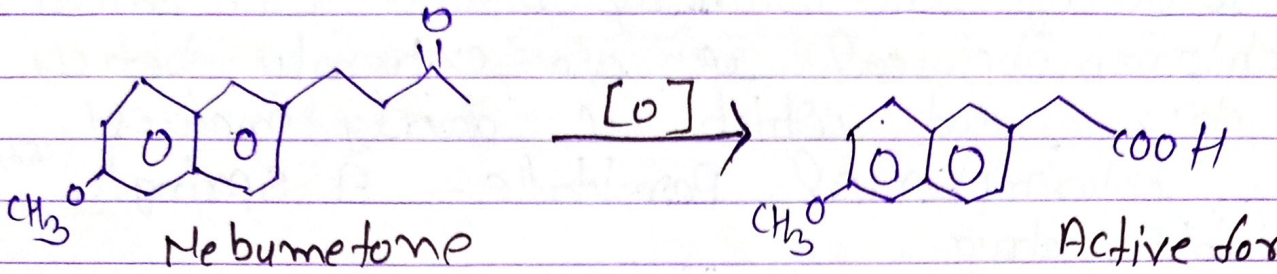
They are inert molecule obtained by chemical modification of Active drug but do not contain a carrier.

They are chemical or enzymadively transform in to drug molecule or Active drug.

They type of Activation involve phase I

Biotransformation such as oxidation Reduction Hydrolysis etc.

Eg- Nebumetone prodrug oxidize metabolatically prodrug & give active drug -



Nebumetone prodrug

Active form 6-methoxy 2-Naphthyl acetic acid (6-MNA)

Application of prodrug -

Prodrug are generaly used to over come pharmacokinetic, p'rological p'reutical problem.

⇒ Various application of prodrug are as follows

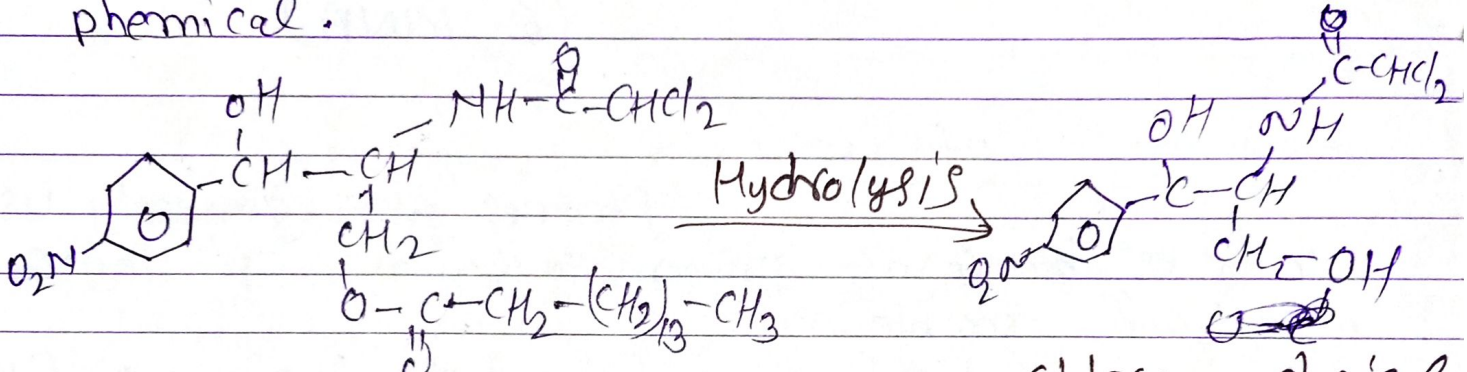
(i) To Improof test of the drug.
(ii) To Improof order of the drug.
(iii) To reduce the pain the site of injection
(iv) To improof bioavailabity of the drug
(v) To improof stability of the drug.
(vi) To improof solubility of the drug.
(vii) To decrease toxicity & adverse drug reactio
(viii) To protect presystmic metabolism.
(ix) To Increase site specificity
(x) To ↑es duration of p'rological action
(xi) To ↑es lipid solubility of the drug (xii) protection from rapid metabolism & excreation
(xiii) To Improve Pharmacokinetic properties (absorption metabolism, distribution etc.)

Improvement of the test (to mask better test)

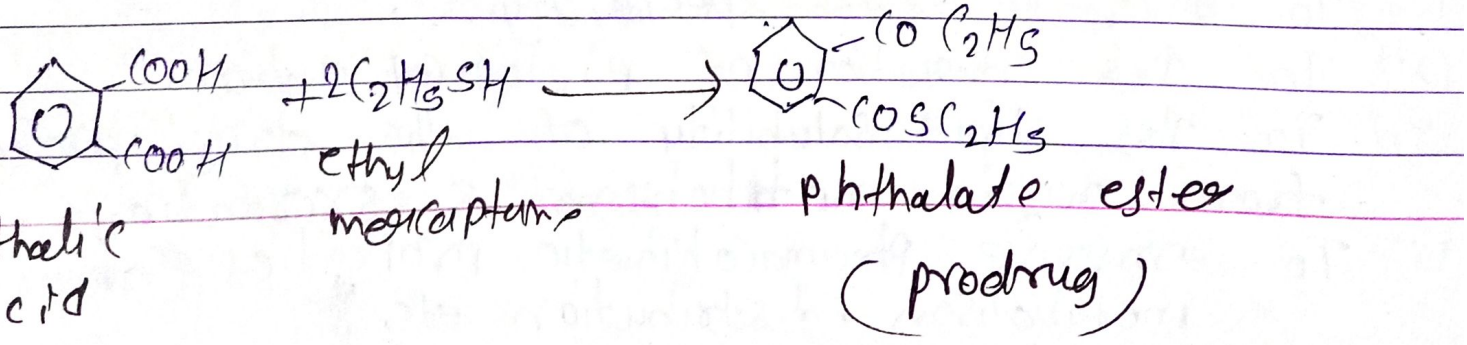
→ The undesirable test arises test due to adequate solubility & interaction of test with test receptor which can be solved by lowering the solubility of drug in saliva

e.g – chloramphenicol is an extremly better drug. and which is dirctly metaest in chloramphenical Pamitate – A springly soluble drug.

chloramphenicol palmitate undergo in vivo hydrolysis to give active chloramphenicol.

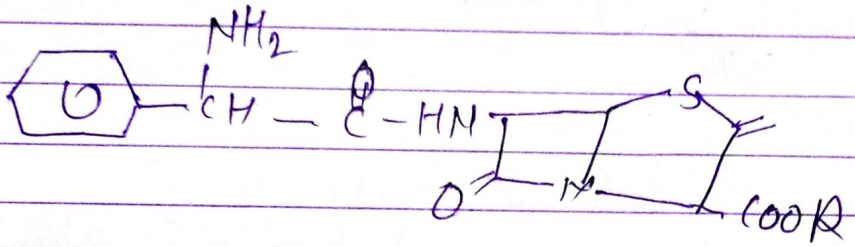


odour – Ethyl mercaptane a foul smell liquid use in the tretment of leprocy this is converted in to phthalate esters, a diethyl dithio phthalate which is odourless drug.



Improvement of bioavaibility –

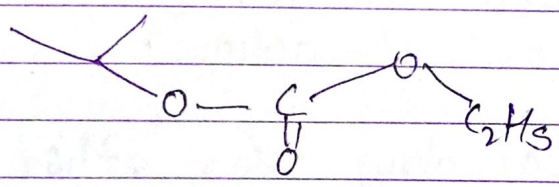
Ampicillin have low lipophilicity & it only 30 – 40 % absorbed when taken by oral route by altering polarity of this antibiotic by esterification of the carboxlic group result a compound that are completely absorb & with greater bioavability them apicillin.



Genearal structure

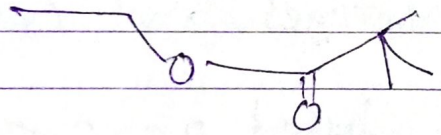
R = H – Ampicillin

R =



Bucampicilline

R =



Pivampicilline

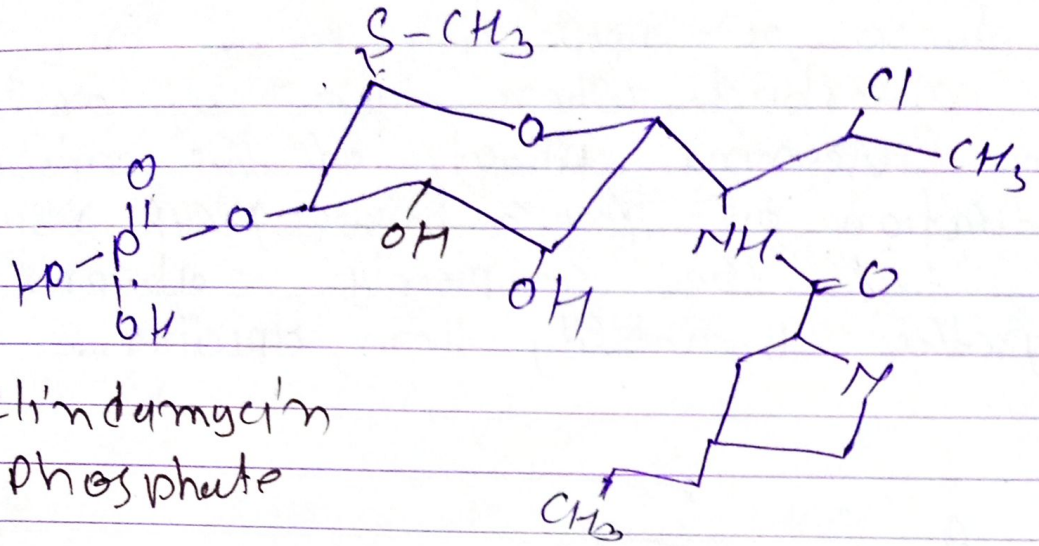
To reduce pain & redness –

⇒ Pain & redness caust by weekly acidic nature poor water solubility of the drug. when they are injected intramuscularly.

Ex– Intramuscular injection of clindamycin was found to be painful due to poor agous solubility which can be over come by making phosphate ester prodrug. and meintein the formation at pH – 12

elicic - [illegible]

e.g - clindamycin ~~prodrug~~ phosphate.



clindamycin phosphate

To inhance chemical stability :-

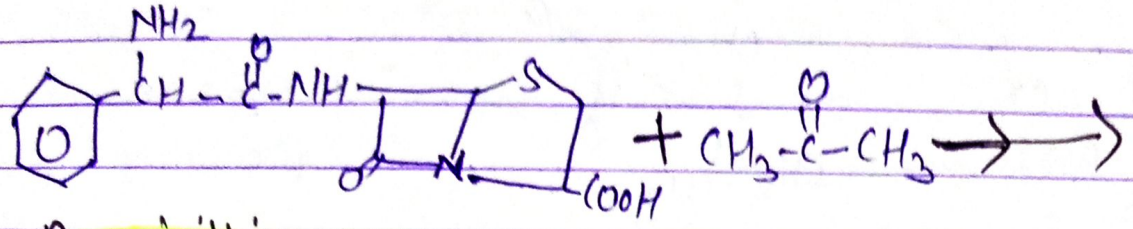
⇒ chemical stability is necessory parameter for every therapeutic agent to elicic pharmacological activity. for longer duration of action.

→ A self life of drug for atlist 2 years is desirable. except ~~me~~ vaccines and cytotoxic drugs.

→ prodrug aproch is based on modification of functional group responsible for in stability or by changing the physical properties of these drug resulting in reduction in contact b/w the drug & media in which a it is stable.

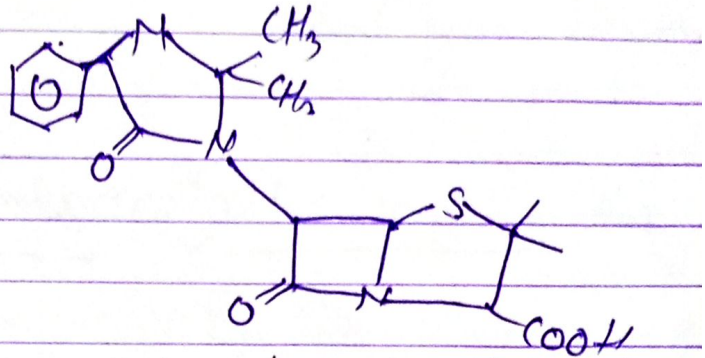
Ex - Ampicillin is unstable antibiotic in presence of amidase enzyme. so Ampicillin is converted in to prodrug ~~in~~ hetacillin, in hetacillin amide bond is stable in

the presence of amidase enzyme.



Ampicillin

Unstable



ititacillin (prodrug) stable

Site specific delivery (opthalmic prodrug):-

→ The cornial barrier limits permeation of topicaly administred opthalmic drug in to intra-occular tissue.

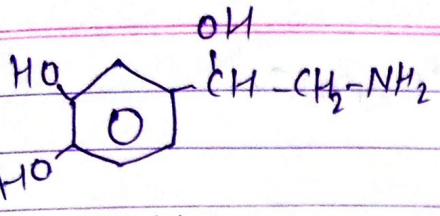
→ As a vision only a small % of applied dose is absorb

→ most of the drug about 50-99 % enter in to systemic circulation

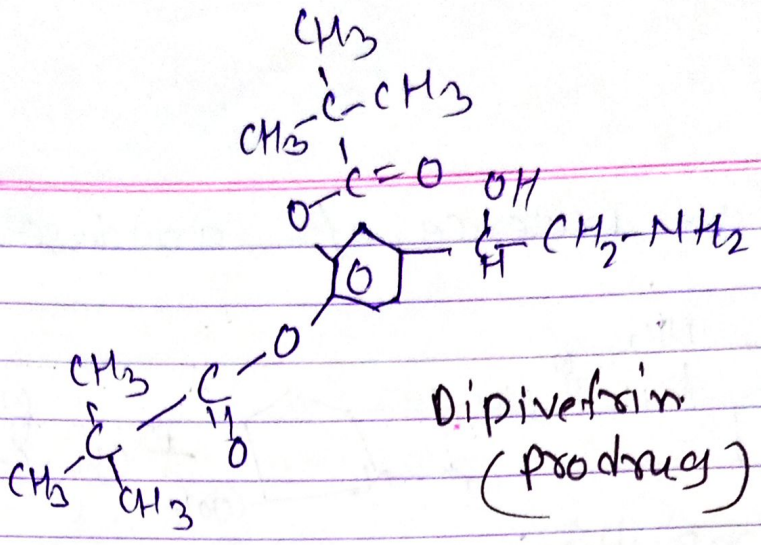
→ By prodrug aproch occular absorbtion of sub drug can be improoved

Ex- - Dipibecrine is prodrug of adrelin which penitrate human cornea 17 times more rapidly then adrelin.

bid- orted



Adrenalin or epinephrine



Dipivefrin (prodrug)

Antimalarials

Etiology of malaria –

→ Malaria is a serious tropical disease spread by mosquito

→ Malaria is caused by protozoa from the genus plasmodium & it is transmited to human through a bit of female Anaphilis mosquito

→ Infection may also occur through the contact of infected blood but it is very rare.

→ There are four major plasmodium species which cause malaria in human.

(i) plasmodium falciparum
(ii) plasmodium malariae
(iii) plasmodium vivax
(iv) plasmodium ovale

invade - बल करना

anarexia - भूख न लगना

Life cycle of malaria :-

① malaria is transmitted by female Anopheles mosquito.

② Infection is start from biting of infected mosquito to human.

③ parasite (sporozoits) inter in to blood of human and reaches to liver by circulation with in 1 hour.

④ In liver sporozoits are divided rapidly for 5 to 7 days

⑤ In the form of mirozoit they leave the liver and enter in to blood and there they invade RBC & erythrocyte & divide rapidly & 1-3 day.

⑥ Infected RBC rapture & release some chemical After 48 hour.
- which cause Symptom like fever chill, nausea, Vometing, anarexia (, fatige

⑦ Some merozoit enter in to brain & heart where they divide & grow.

⑧ Some merozoit develop in to female and male gamato cyte.

⑨ Gamato cyte from the human ie transfered to mosquito by biting & develop in to oocyte which form sperozoites.

⑩ malaria affect 500 million globlly & cause 2 million anually.

prophylaxis - chemoprophylaxis

Antimalarial drugs -

Antimalarial drugs are use for prophylaxis & treatment of malaria

classification of antimalarials drug :—

1. 4-amino Quinolones – chloroquine, Amadroquine, Piperaquine
2. 8-amino Quinolones – premaquine, Pamaquine
3. cinchona alkaloids – Quinine, quinidine, cinchonine
4. Biguinides – proguanil, cycloguanil
5. Diamino pyrimidine – pyrimethamine
6. sesquiterpene lactone – Arteether, Artemether, Artisunate.
7. Amino Alcohal – Halophantrine
8. Sulphonamide – Sulphadoxime, Dapsone, Sulphamethopyrazine.
9. Antibiotics – Doxycyclin, clindamycin
10. Naphthoquinone – Atovaquone

Mechanism of Action :-

1) Intercalation with DNA :-

The Tertiary amino group bind ionically to negatively charged phosphate back bone. The interaction alcoholic hydroxyl group of quinolone methanols from H bonds with any one DNA & 7 chloro atom in chloroquinine & analogs is electro-statically attracted to the guanine-2 amino group. There binding inhibit the separation of complementary strands of the Parent double helical DNA.

⇒ The Res the pH of acidic vesicles in sensitive malarial parasites.
⇒ The reactive the interfere with lysosomal degradation of haemoglobin.
⇒ The plasmodia selectively conc these drug However the functions of Ca^{2+} dependent protein are also inhibited.

2) Inhibition Folic Acid synthesis →
The compound similar to folic acid
The host receive folic acid from food.

(i) Inhibition of Dihydropteroate Synthase -
(ii) Inhibition of Dihydrofolate Reductase -
↳ Sulphonamides & Sulphones act as antimetabolite & inhibit dihydropteroate synthesis.

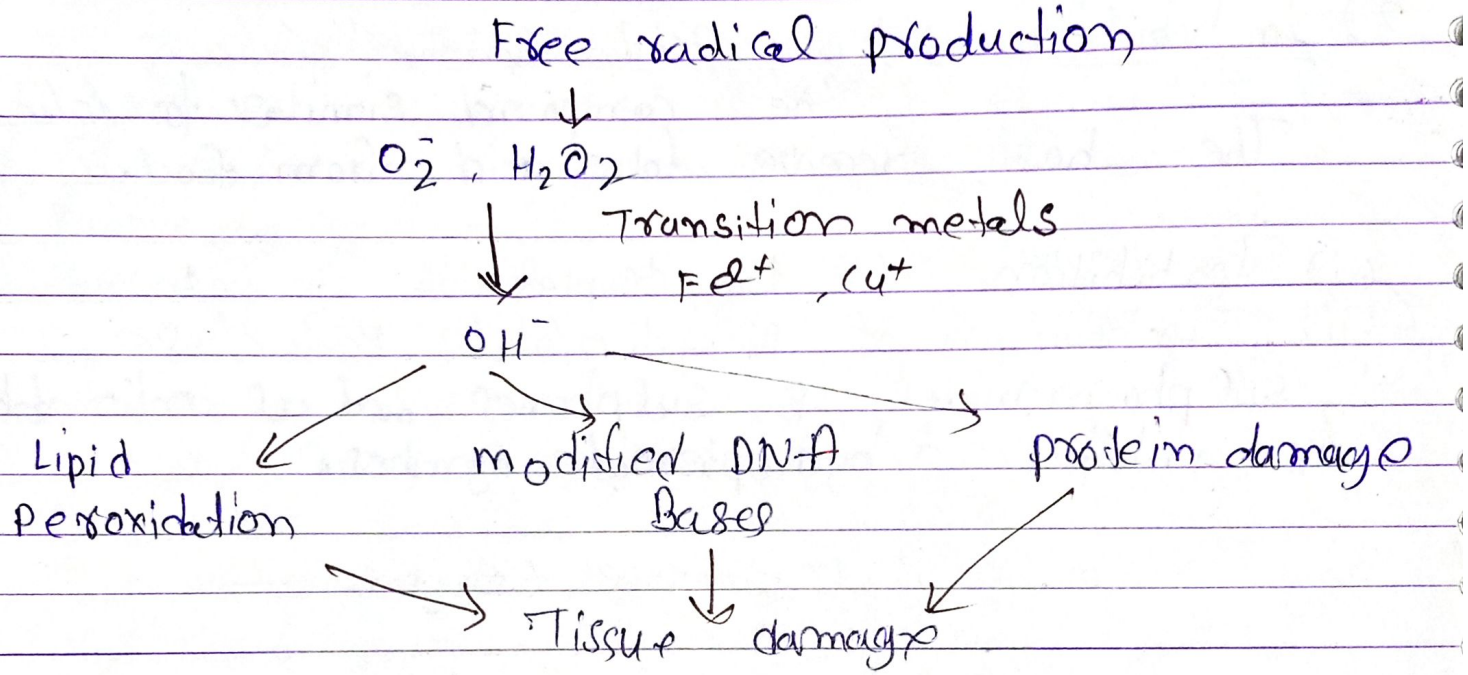
3) Inhibit of polymerase Enzyme —

Erythrocyte haemoglobin
↓ Ingestion
Haemoglobin in food vacuole
Digestion ↓
Ferriprotoporphyrin IX FP (Toxic) → FP - chloroquine complex (toxic)
to Parasite
polymerase ⫽
β - Hemalin haemozoin
(non toxic)

Chloroquine

Feedback inhibition of digestion

(9) oxidant drug - Antioxidant are compound that inhibit oxidation. oxidation is a chemical reaction that can produce free radicals thereby leading to chain reactions that may damage the cells of organisms. Antioxidants such as thiols or ascorbic acid (Vit. C) terminate these chain reactions.



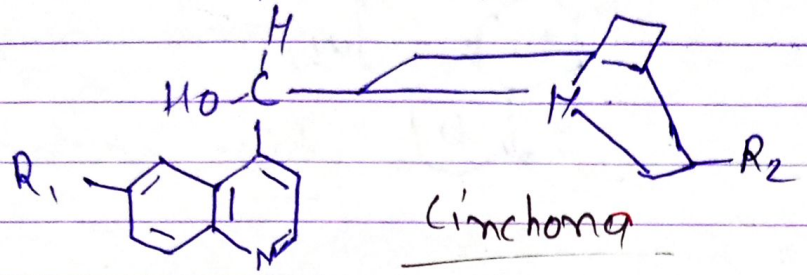
Quinolines :-

- Quinoline and it's fused heterocyclic derivat having various p'cological action. functional groups form an important class of compound for new drug develop.

Classification

① Cinchona Alkaloids - Cinchona more than 20 alkaloid. 4 major alkaloid are isola

(i) Quinine - $R_1 = OCH_3$, $R_2 = -CH=CH_2$ (-) isomer,
ii) Quinidine - $R_1 = OCH_3$, $R_2 = -CH=CH_2$ (+) isomer,
iii) cinchonine $R_1 = H$, $R_2 = -CH=CH_2$ (+) isomer,
(iv) cinchonidine $R_1 = H$ $R_2 = -CH=CH_2$ (-) isomer

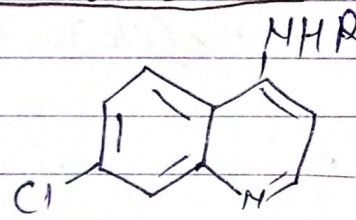


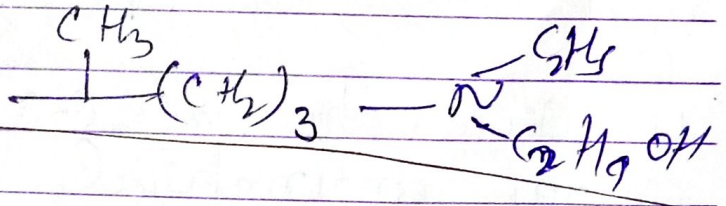
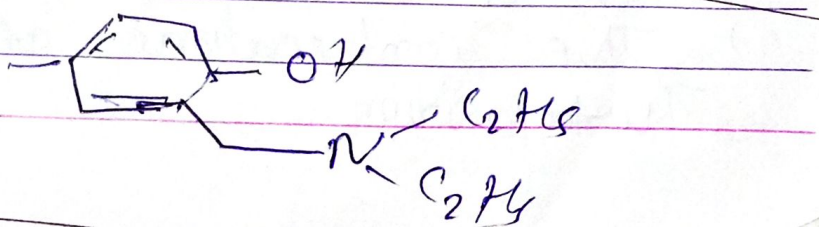
Cinchona

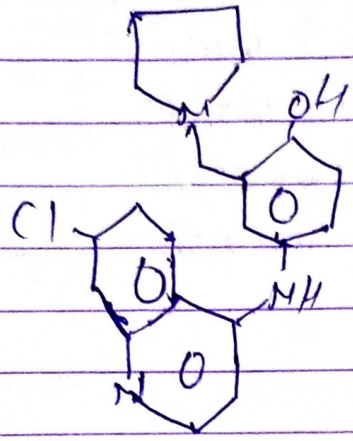
The sulfate salt of quinine is orally active & its dihydrochloride salt is used intravenously. Its levorotatory form shows antimalarial activity. It may cause local tissue damage.

Quinine is used chloroquine resistant P. falciparum infections.

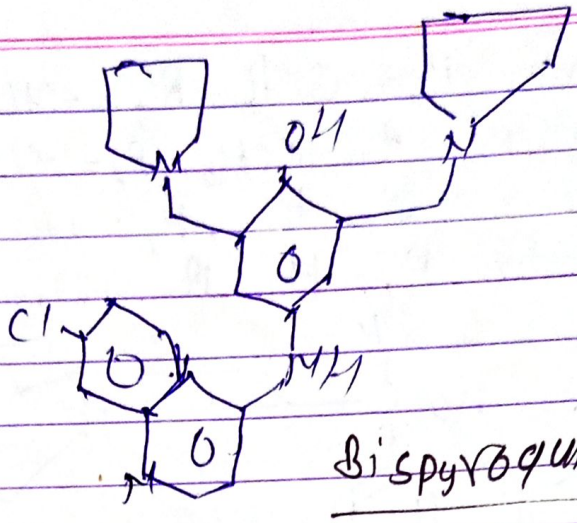
2) 4-amino Quindines:-



Drug	R
Chloroquine	$-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$
Hydroxy chloroquine	
Amodiaquine	

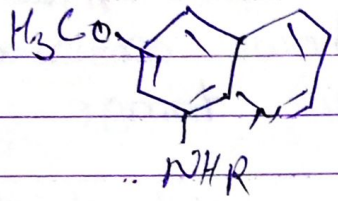


Amopyroquine



Bispyroquine

3) 8 amino Quinoline



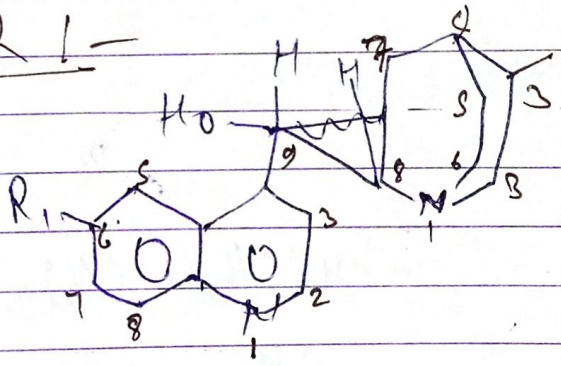
Drug

R

Primaquine — $-CH(CH_3)-(CH_2)_3-$

Panaquine — $-CH(CH_3)-(CH_2)_3-$

SAR :-



1) Asymmetry at C-3 & C-4 is not essential for antimalarial activity
2) The configurations at C-8 & C-9 affect the Tuxic position

3) Methoxy group is not show antimalarial activity then the Replacing methoxy group with a halogen enhance activity.
placing a phenyl group at C-2 further les activity

Drug	R_1
Quinine	OCH_3
Quinidine	OCH_3
Cinchonine	H
Cinchonidine	H

4) The antimalarial activity is les by substituting a halogen at C-8
5) By modifying the secondary alcohol at C-9 through oxidation, esterification reduces the antimalarial activity
6) The quinuclidine portion is not essential for activity but attaching an alkyl tertiary amine at C-9 is essential

Mechanism

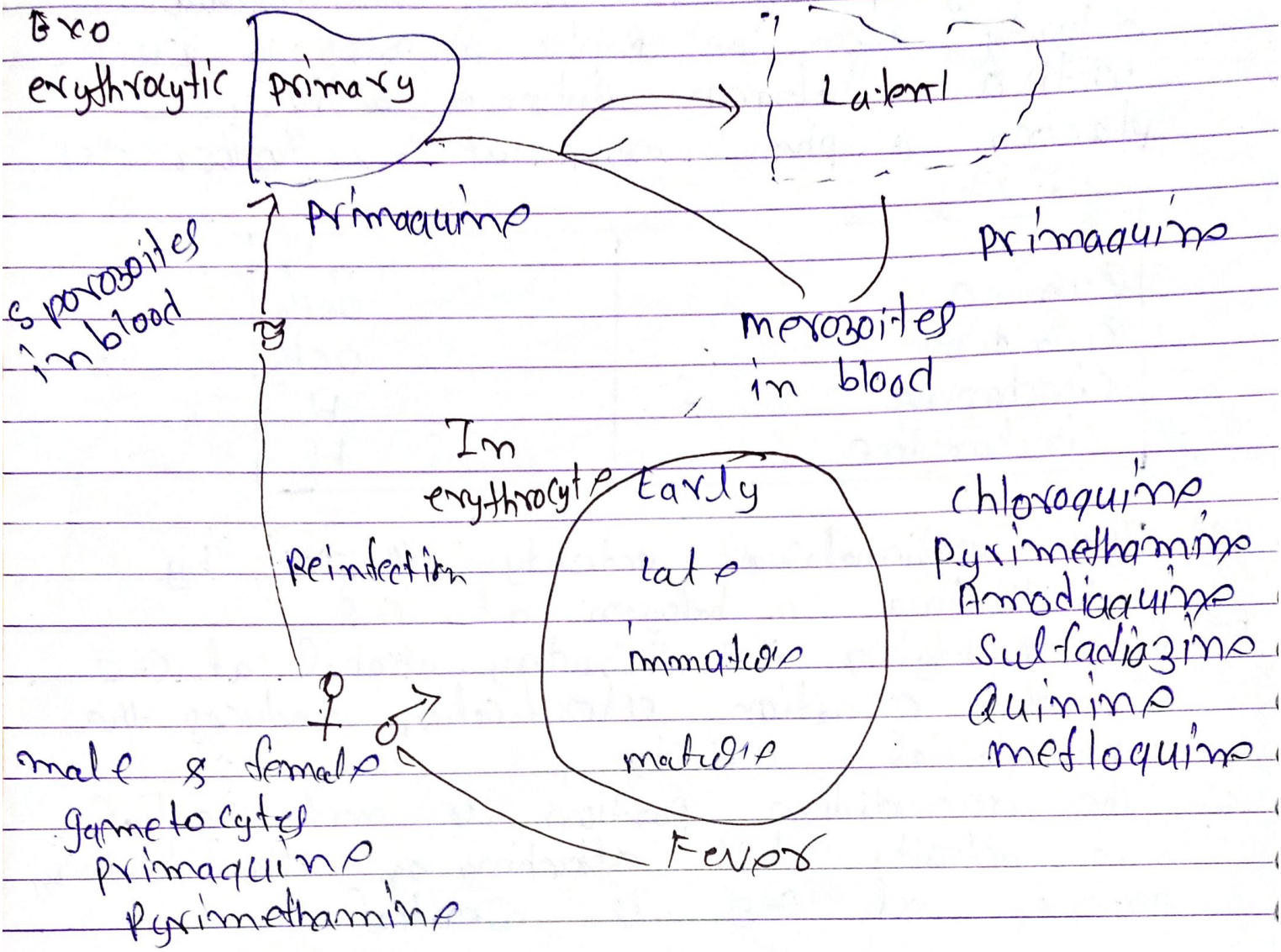
Antimalarial

Hemoglobin → Globin Utilized by malarial parasite

Heme (highly toxic for malaria parasite)

Chloroquine
Quinine
Mefloquine (-) ↓ + Heme polymerase

Hemozoin (Not toxic to plasmodium)



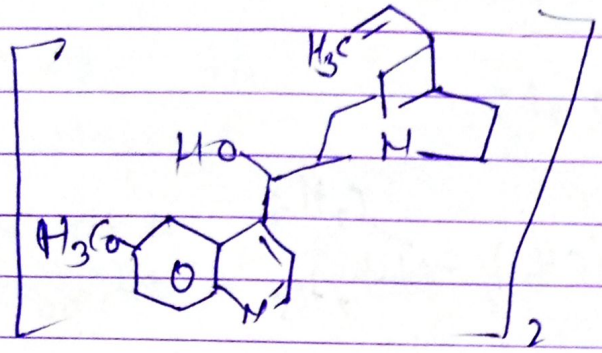
Important products :-

1. Quinine sulphate
2. Chloroquine
3. Amodiaquine
4. primaquine phosphate
5. Pamaquine
6. Quinacrine hydrochloride
7. Mefloquine.

① Quinine sulphate - Alkaloid derived from cinchona bark.

mechanism -

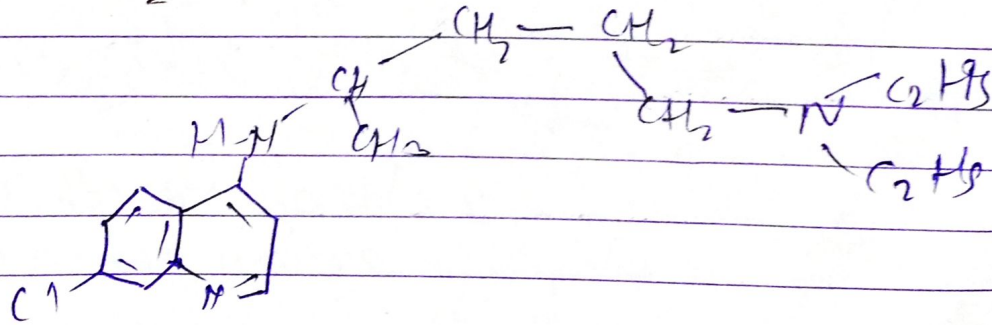
They interfere with the parasite's ability to breakdown & digest haemoglobin



Use :- ① Treating malaria
② It is mild antipyretic & analgesic & has been in common cold preparation.
③ Bitter & flavouring agent
④ It is used in treatment of babesiosis.
⑤ used in muscle disorder.

Adverse effect - ① nausea, ② restlessness, ③ Difficulties in hearing ④ ringing in ear ⑤ Nervousness ⑥ Rash ⑦ hives ⑧ Itching ⑨ Flushing ⑩ Hoarseness ⑪ swelling in face

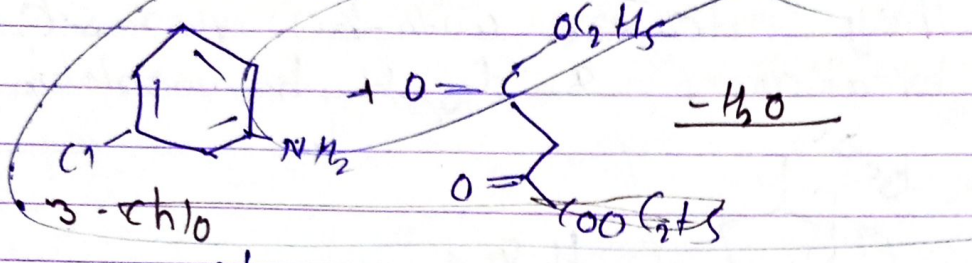
② chloroquine -

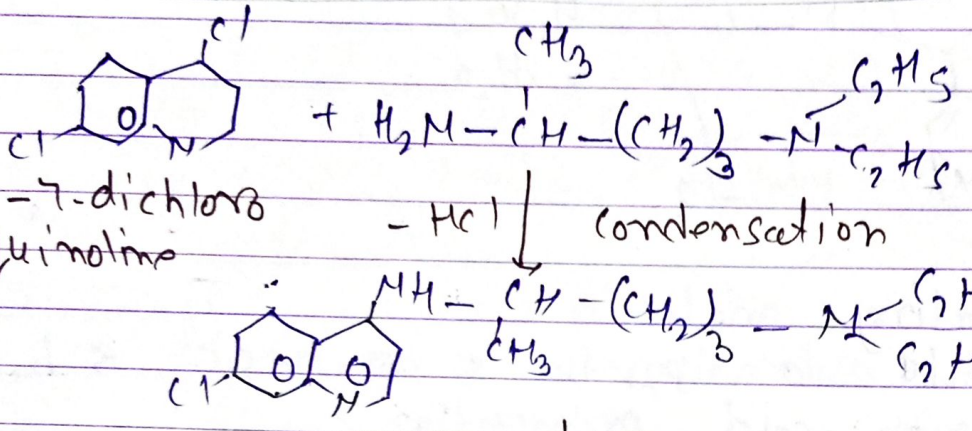


Chloroquine

Synthesis –

1) Step A - This step involves synthesis of quinoline moiety.



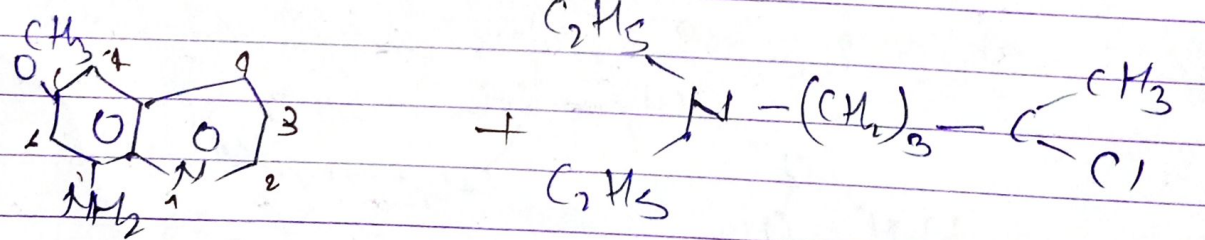


chloroquine

Use - primarily we to treat malaria we do treat infection caused by Amoeba.

Tamaquine

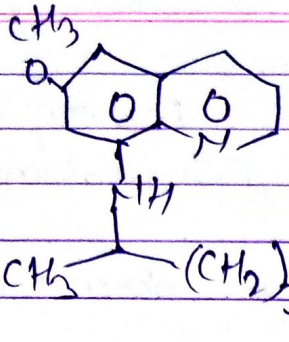
Synthesis –



8-amino-6 methoxy Quinoline

2 chloro diethyl amino pentane

condensation, Δ, $-HCl$



primaquine

use – use to treat malaria caused by various species of plasmodium

Mechanism of Action –

A recent mechanism of action of chloroquine is shown:

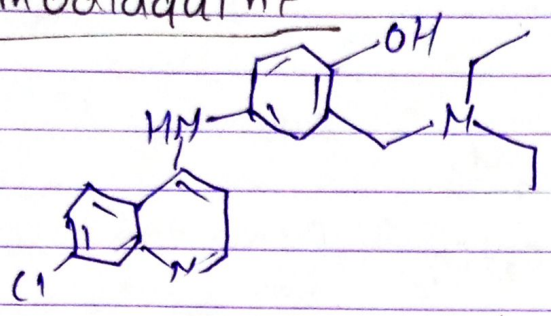
Erythrocyte haemoglobin
↓ Ingestion
Haemoglobin in food vacuole
Digestion ↓
Ferriprotoporphyrin IX (FP) ⇒ polymerase ⇐ chloroquine
FP-chloroquine complex (Toxic)
feedback inhibition of digestion

B. Hemetin hemozoin (Non-toxic)

use – ① It is used for acute malarial attacks caused by P. malariae, P ovale & susceptible strains of P. falciparum
② It is also used for suppressive treatment of malaria

Adverse effects GIT, stomach ache, itch headache

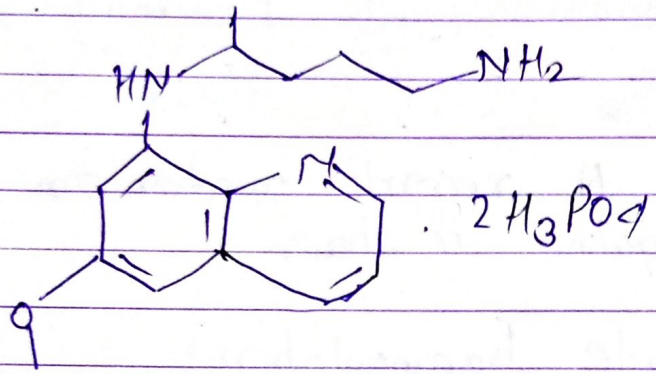
③ Amodiaquine



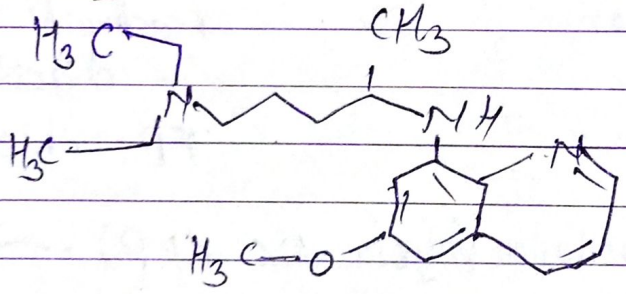
use = fever, chills & sweating

A.E - Same above

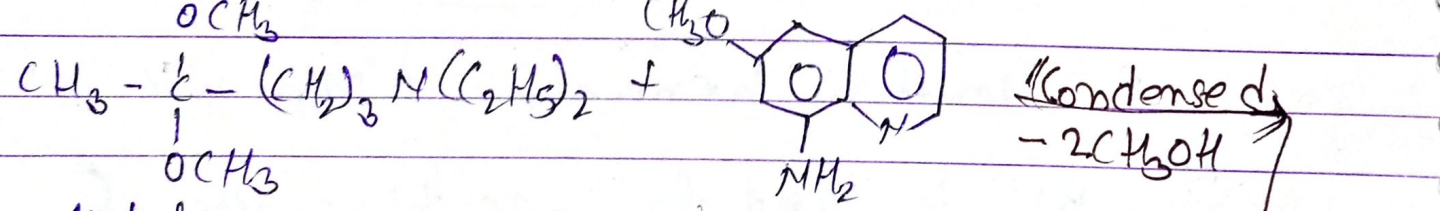
④ primaquine phosphate

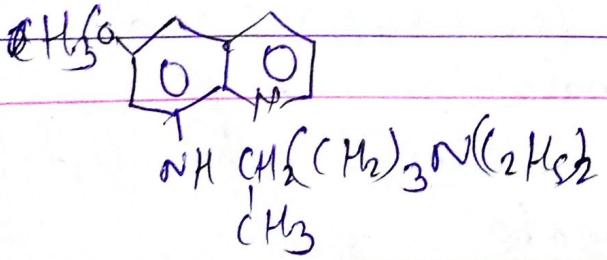


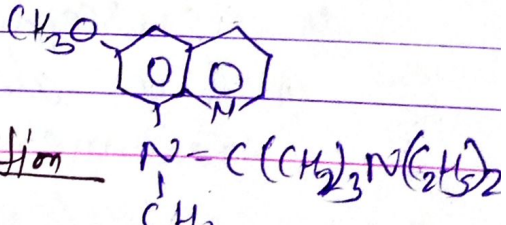
⑤ Pamaquine



Synthesis -

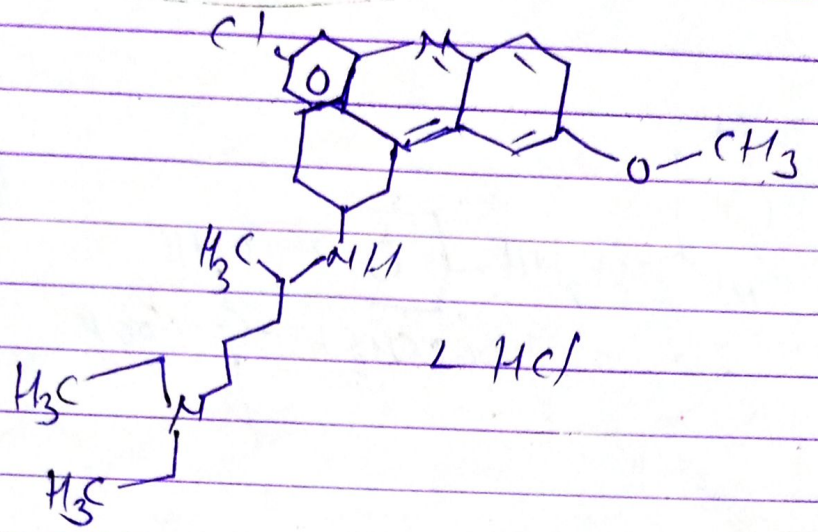




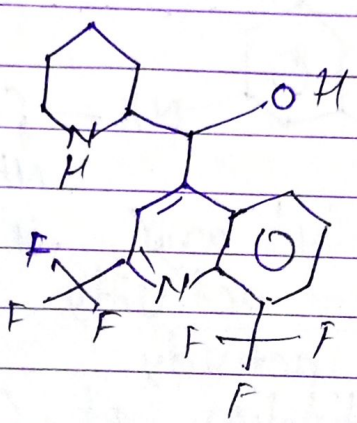


A.E. – Anaemia with G6PD deficiency

⑥ Quinacrine Hydrochloride -



⑦ Mefloquine



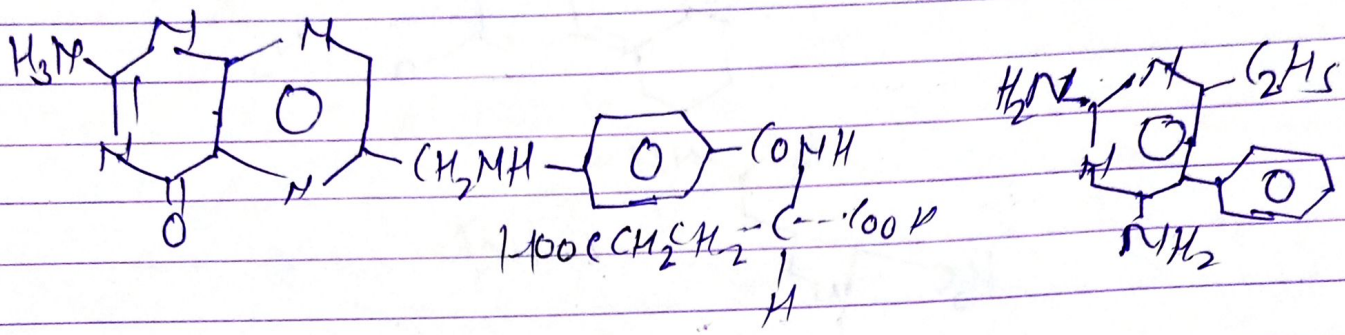
Biguanides And Dihydrotriazines :-

⇒ Several biguanide & dihydrotriazines have been synthesised & tested for their antimalarial activity.

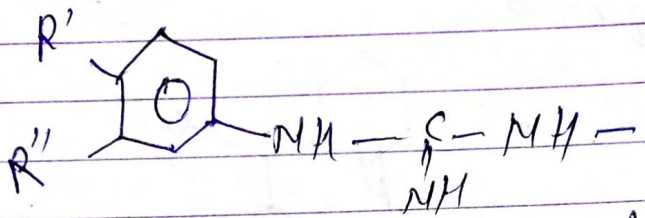
⇒ Biguanides are prodrugs & are not active till they are metabolised in vivo to dihydrotriazine derivatives

Guanidine analogues remain inactive till they get cyclised metabolically to a

dihydro s triazine analogue that is somewhat similar to either the pteridine moiety of folic acid or pyrimethamine as show below.



SAR —



(1) presence of N' aryl is essential for anti-malarial activity but second group reduces the activity
(2) Di halogen substitution at C-3 & C-4 of the benzene ring yields potent drugs.
(3) Alkyl substituents on N^1, N^2, or N^4 reduce 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 antimalarial activity.

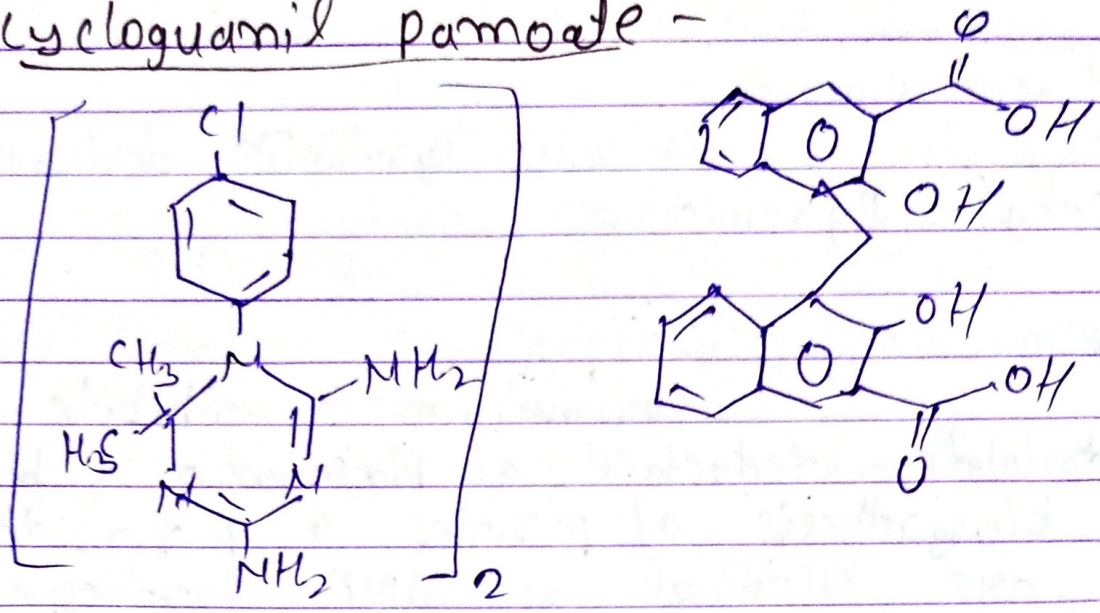
Drugs

- proguanil
- chloroproguanil
- Bromoguanil
- Nitroguanil

Important product –

1) Cycloguanil pamoate
2) Proguanil

① Cycloguanil pamoate –

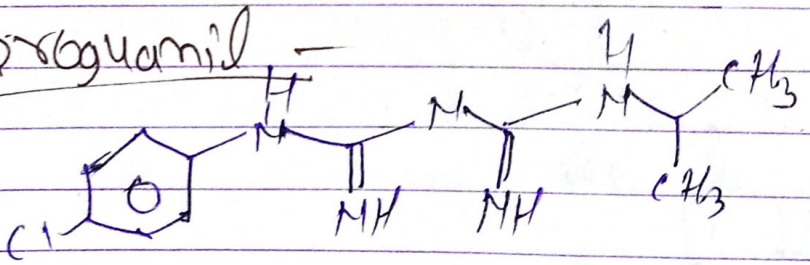


Mechanism

Cycloguanil exerts little therapeutic value in cases where resistance to proguanil or pyrimethamine is prevailing. Cycloguanil & amodiaquine should administered in every 4 months for prolonged immunisation in areas infected with hyperendemic malaria

Use – malaria treatment

② Proguanil –



Miscellaneous -

① Pyrimethamine ② Artesunate
③ Artemether ④ Atovaquone

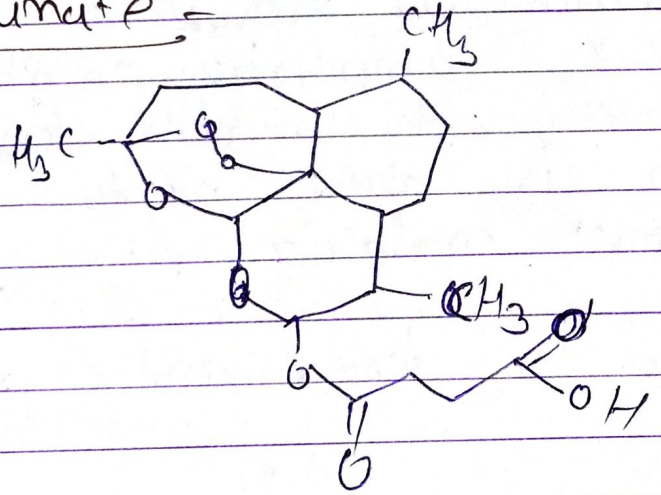
① Pyrimethamine -

It is synthetic derivative of ethyl pyrimidine.

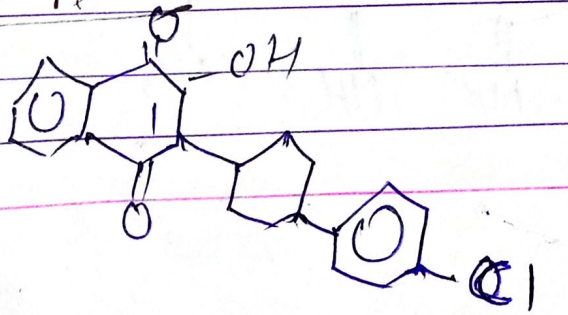
Mechanism of Action -

Pyrimethamine inhibits the dihydrofolate reductase of plasmodia & blocks the biosynthesis of purines & pyrimidines which are essential for DNA synthesis & cell multiplication. As a result nuclear division fails to occur at the time of schizont formation in erythrocytes & liver.

Artesunate -



Atovaquone



Chief editor –

Contact – 7905871310 (whatapp) number).

Rajneesh Tiwari