

## Macrolides

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→ It is isolated from actinomycetes

e.g. - erythromycin, clarithromycin, Azithromycin

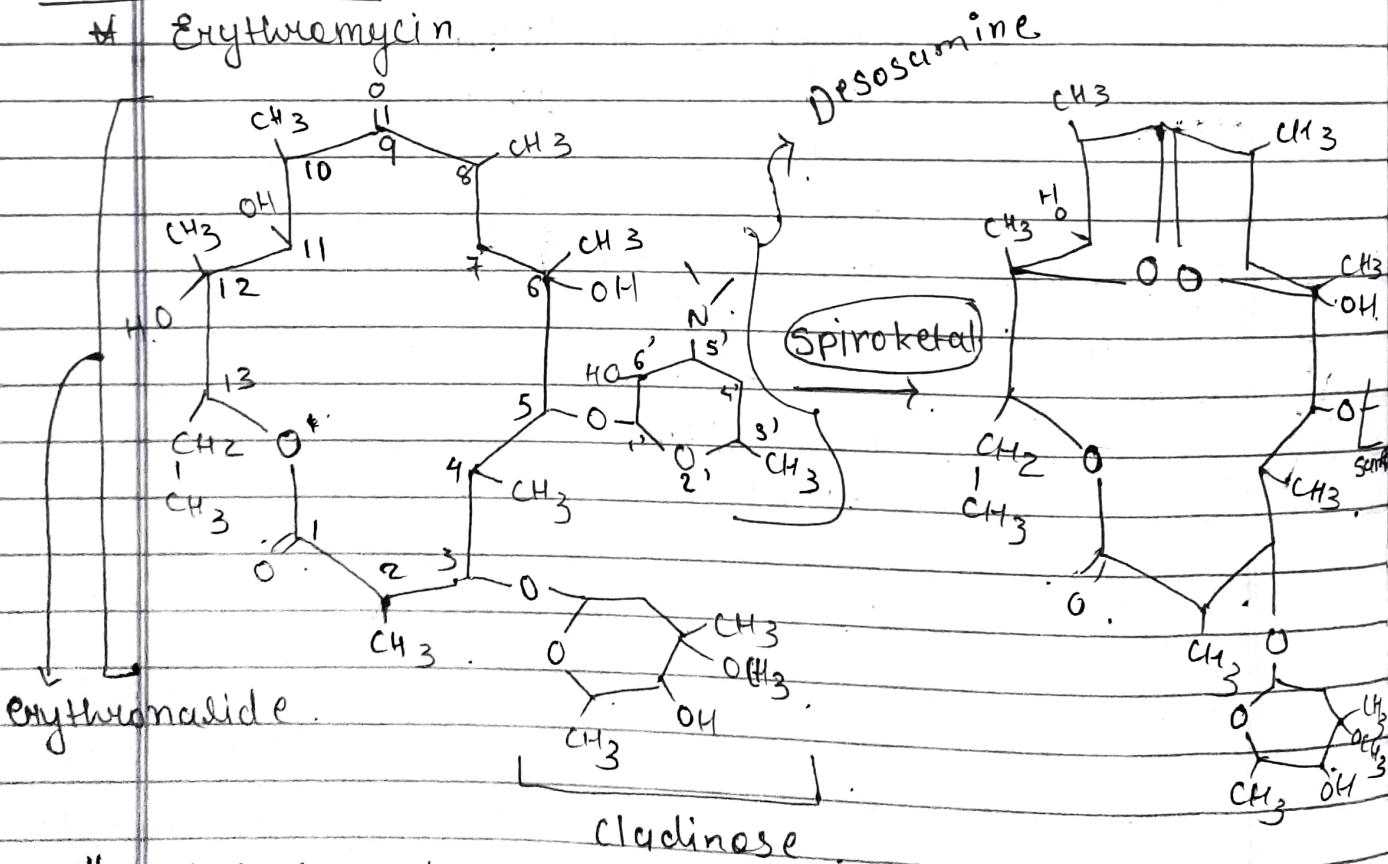
MOA → binds selectively to specific site on 50s subunit-ribosomal to prevent translocation step of bacterial protein sys.

Chemistry

- Lactone ring has 12, 14 or 16 atoms in it
- It's partially unsaturated with presence of double bond in conjugation with ketone fun'

## Structure

## ~~E~~ Erythromycin



\* Clinical grade - 90%. A - OH at C12.

10.10 B - H at  $C_{12}$  (instead of  $CH_3$ )

little 'C - H instead of  $\text{OCH}_3$ .  
at Cladinese

- Large lactone str. - erythromide
- Amino sugar attach through glycoside linkage at C<sub>5</sub> → desosamine
- Cladinenose also linked glycosidically at C<sub>3</sub>

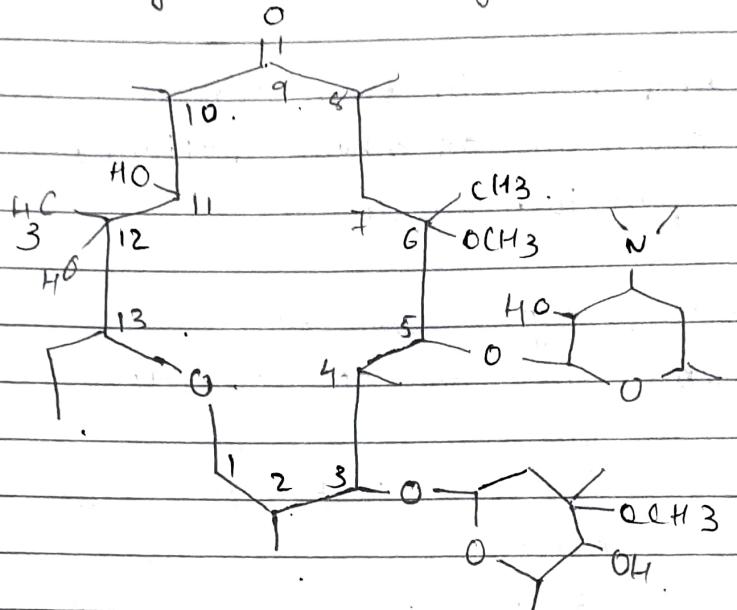
- Properties
- low water soluble.
  - bitter taste

• At acidic pH it is unstable so that after administration patient feels intestinal cramp b/c it cause intramolecular cyclisation to form spiroketal

- To improve its water solubility modification at C<sub>5</sub> (C'5'-N<sup>+</sup>)
- eg. Erythromycin lactobionate,  
Erythromycin glucoheptonate,  
Stearate

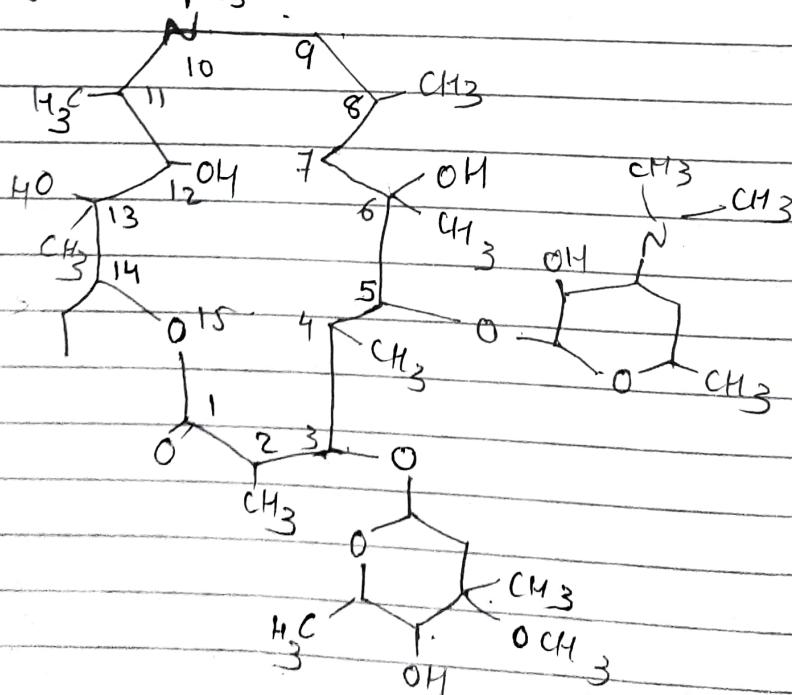
- To improve stability at acidic pH modification at C<sub>5</sub> (C'5'-OH)
- eg. ethyl carbonate,  
ethyl estolate,  
ethyl succinate

\* Clarithromycin (6-methyl. ether of erythromycin)



\* Azithromycin (Synthetic derivative of erythromycin).  
→ 15 member ring - Azalides

Removal of 9-keto coupled with incorporation of weakly basic  $\text{CH}_3$  3' amine into macrolide  $\rightarrow$  7se stability



## Spectrum of activity

- They're employed to treat infection due to penicillin resistant organism or where patient feels allergic towards penicillin analogues.
- Effective against gram +ve both cocci & bacilli but exhibit low spectrum of activity.

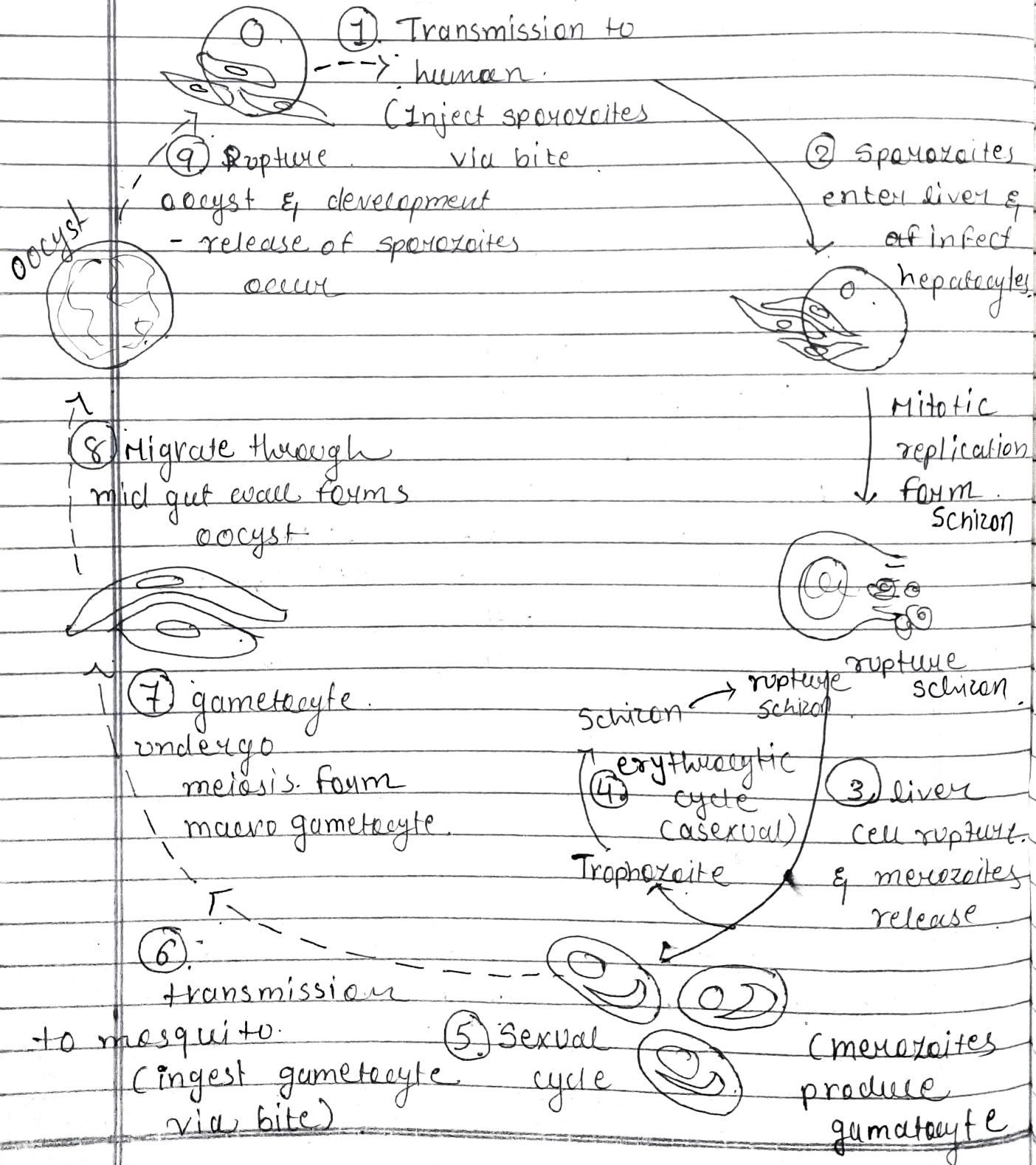
## Side effect

- Dizziness & Headache
- Ototoxicity
- It can prolong QT interval. The risk of Torsade's pointes & other like arrhythmias.

# Malaria

disease

→ 2 host - Malaria is infected by female Anopheles  
inoculate sporozoites into human



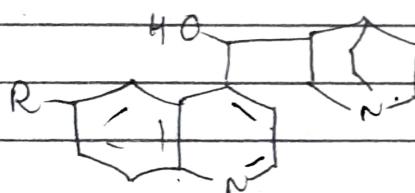
# Anti Malaria Drug



- (1) Quinolones
- (2) 9-amino acridines
- (3) 2,4-diaminopyrimidine
- (4) Sulfone
- (5) Biguanide
- (6) Miscellaneous

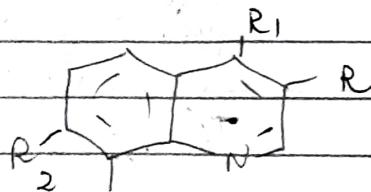
## 1) Quinolones

### i) cinchona alkaloids



Name	R
Quinine	-OCH <sub>3</sub> (-) (levo)
Quinklins	-OCH <sub>3</sub> (+) (dextro)
Cinchonine	-H      (+) (dextro)
Cinchonidine	-H      (-) (levo)

### ii) 4-amino Quinolines



Name	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
Chloroquine	-NH-CH <sub>2</sub> -C(CH <sub>3</sub> ) <sub>2</sub> -N <sub>3</sub>	-Cl	-H
Amodiaquine	-NH-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -N <sub>3</sub>	-Cl	-H

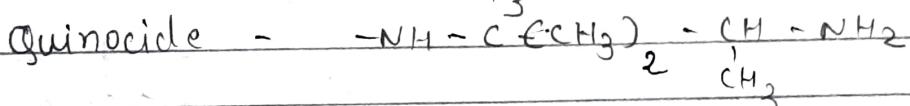
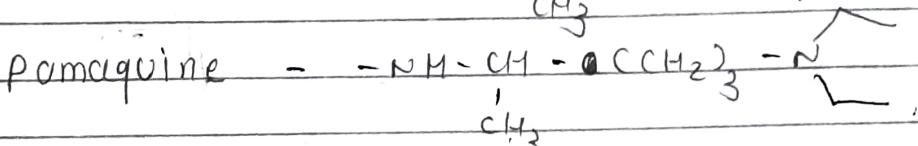
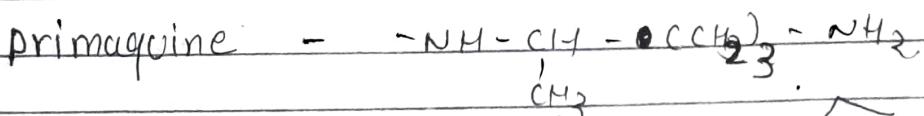
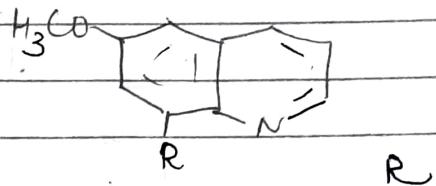
- Side eff
- nausea, vomiting, headache, dizziness
  - cardiotoxicity, Retinopathy (retinal damage)
  - Liver & kidney toxicity (long term use)
  - Myopathy, Ototoxicity

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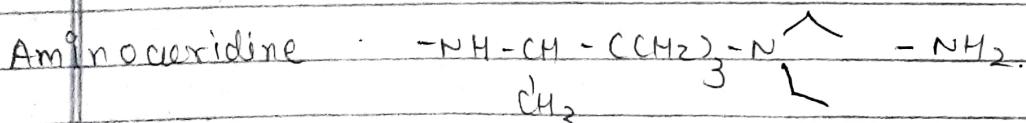
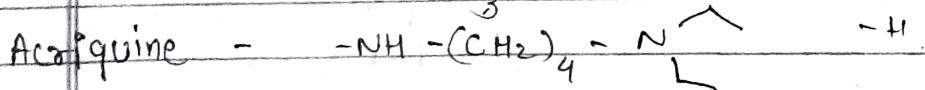
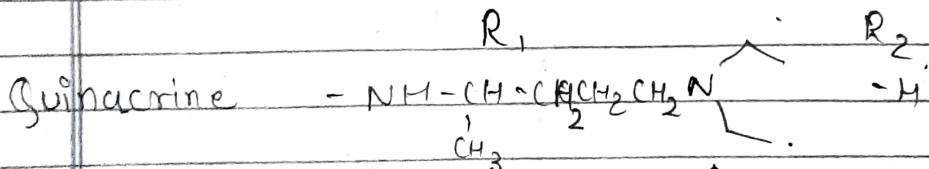
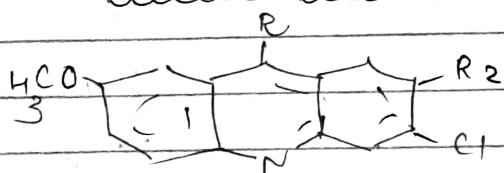
- MoA
- concentrate in blood → bind to double stranded DNA & inhibit DNA polymerase
- ↓  
stop cell growth.

3) 8-amino Quinalines



- MoA
- Show eff. on pre-erythrocytic & gametocytic phase
  - It inhibit protein synthetase & decrease cell growth.

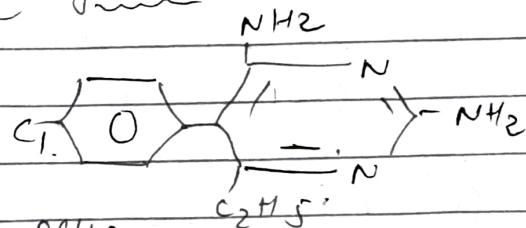
(2) 9-amino acridines



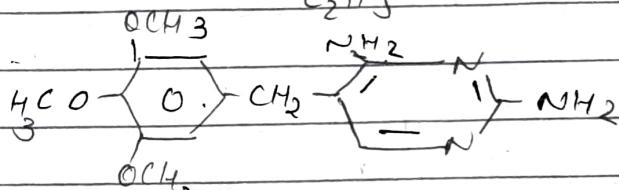
- MoA
- Inhibit various enzyme of ETC. → patient observed yellow coloration of skin

(3) 2,4 diamino pyrimidine

Pyrimethamine -



Trimethoprim -

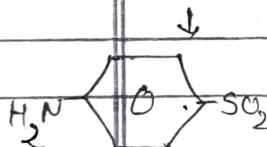


Mef - Inhibit trihydrofolate reductase & inhibit parasitic DNA synthesis

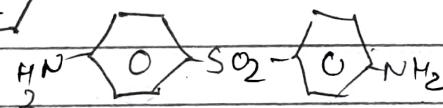
(4) Sulfone



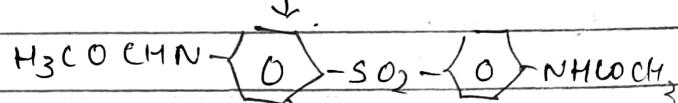
Sulphadiazine



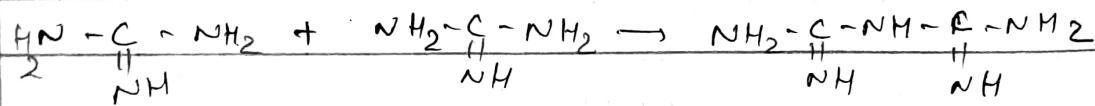
Dapsone



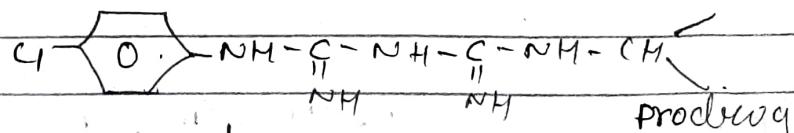
Diacetyldapsone



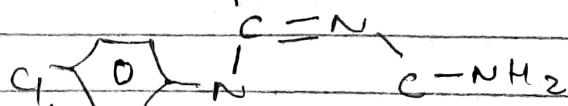
(5) Biguanide



• Chloroguanil -



↓ invivo cyclisation

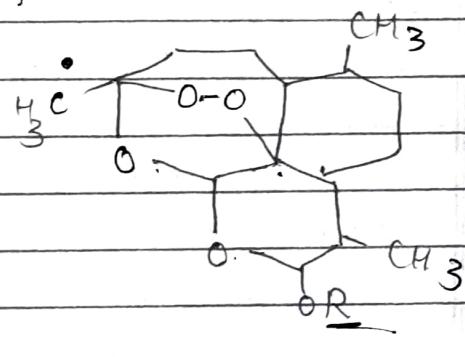
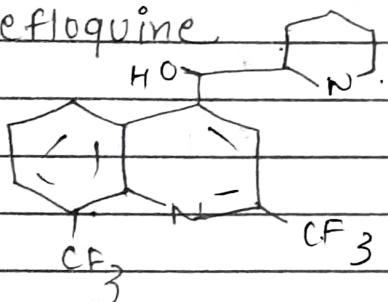


1,2-diamine triazin-ring)

which inhibit dihydro-folate enzyme require for production of dihydrofolate as well as tetrahydrofolate acid. → require fum DNA & RNA syn.

## (6) Miscellaneous

• Mefloquine



R

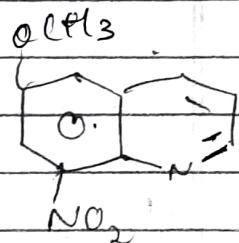
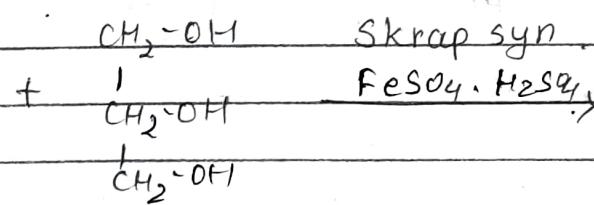
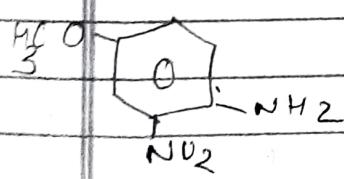
-CH<sub>3</sub> → Artemether.

-C<sub>2</sub>H<sub>5</sub> → artether.

-CO-CH<sub>2</sub>CH<sub>2</sub>COONa → Artesunate

## \* Synthesis

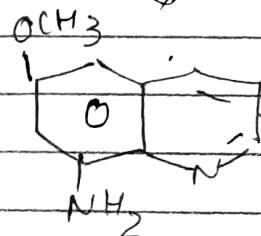
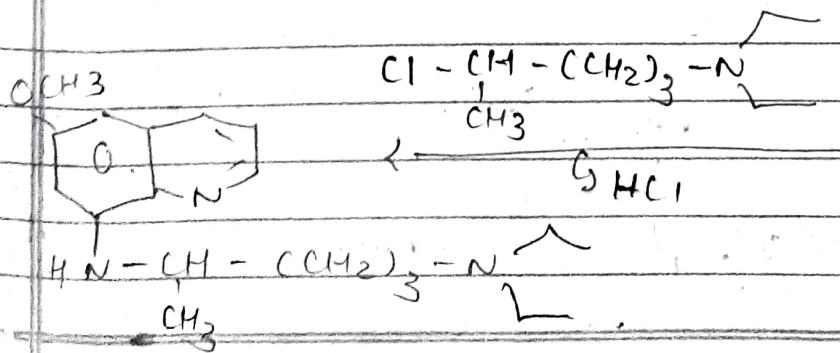
### (1) Parاقinine



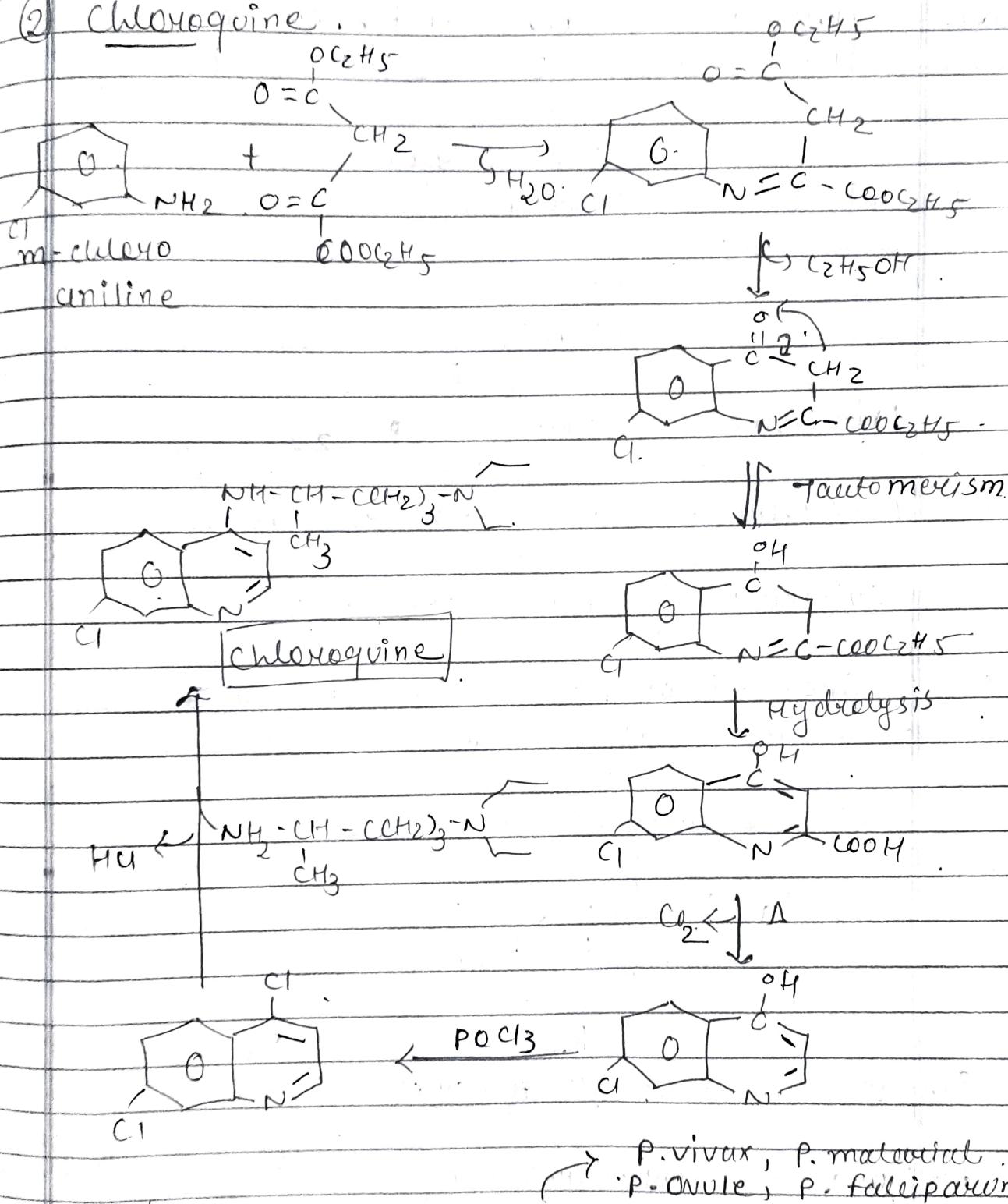
p-methoxy o-nitro aniline

glycerol.

↓ red n.



## ② Chloroquine



## Question

- (1) which plasmodium species affect & which are the carriers.
- (2) define & classify antimalarial agent
- (3) life cycle of malarias
- (4) 4-amino quinoline syn, side eff., MOA

## Prodrug

⇒ Biologically inert deriva. of drug mole that undergoes enzymatic & chemical conversion in vivo to release the pharmacologically active parent drug.

### ⇒ Objectives

- { • To improve solubility, chemical stability & organoleptic properties.
- To use irritation after local administration.
- To reduce problems related with pharmaceutical technology of active agent.

- p'co kinetic
- { • To improve absorption.
  - To use pre-systemic metabolism to improve time profile.
  - To use organ/tissue-selective delivery.

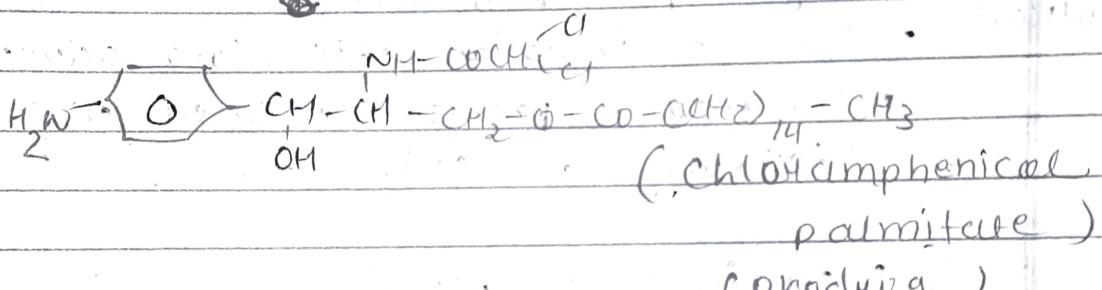
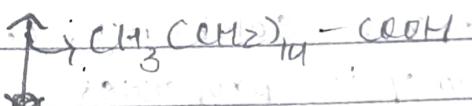
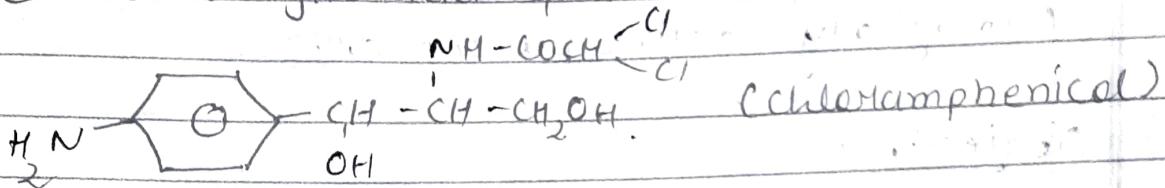
- p'codynamics
- { • To use toxicity & improve therapeutic index.
  - To design single chemical combining 2 drug.

### ⇒ Ideal requirement

- The prodrug is inactive or less active than the parent comp.
- linkage b/w drug & carrier.
- carrier mole released in vivo must be non-toxic.
- Metabolic fragment of carrier mole, apart from drug should be non-toxic.

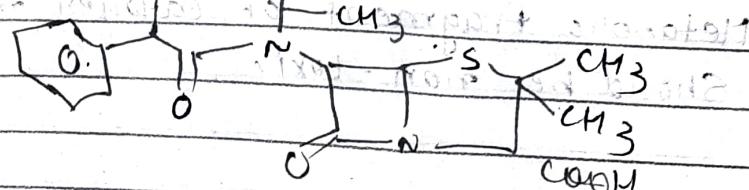
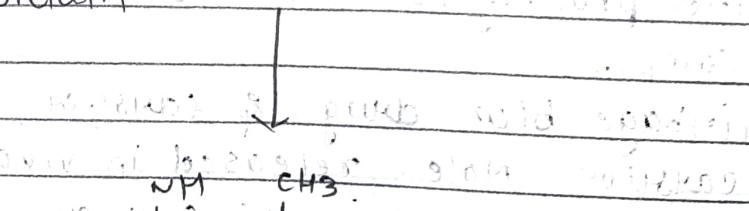
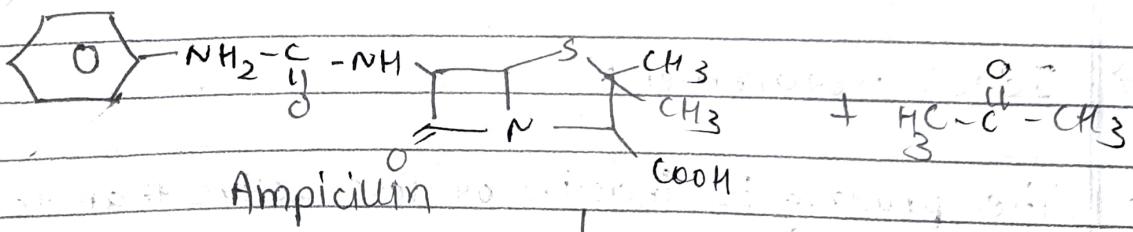
## \* Classification :

### ① Carboxylic acid & alcohol



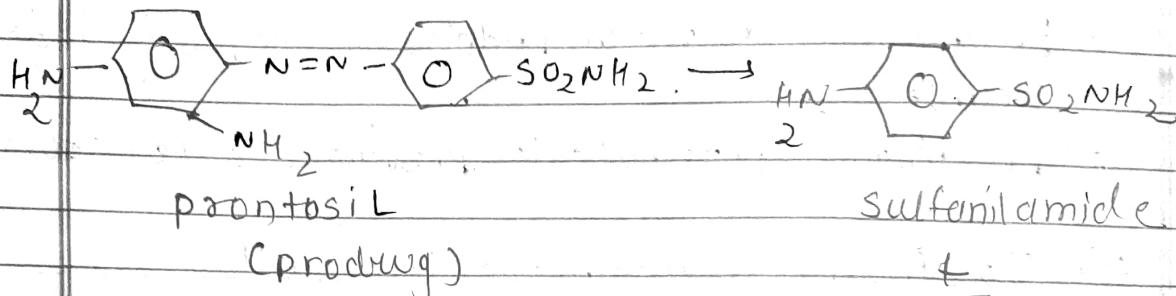
- Pivampicillin, talampicillin & cirampicillin  
are prodrugs of ampicillin.
- enapril is prodrug of enaprilant.

### ② Amines

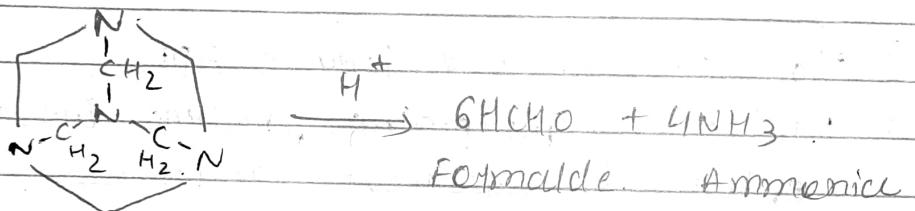


Heterocillin (producing)

### ③ Azo linkage



### ④ Carbonyl comp.



(prodrg) Methamine

### ★ Application

- 1) To improve patient acceptance
  - eg - clindamycin has very bitter taste.  
so clindamycin palmitate is ester prodrg that is tasteless than it convert into active clindamycin after administer
- 2) To reduce gastric irritation
  - Several drug cause irritation. Eg damage to gastric mucus.
    - eg - salicylic  $\alpha$   $\rightarrow$  aspirin.
    - nitrocyclol  $\rightarrow$  nicotinic  $\alpha$  hydrazide

3) prodrug for poor water solubility

- Prednisolon & methylprednisolon are poorly water soluble.
- prednisolon phosphate is prodrug - water soluble

4) To improve membrane transport

- Dopamine use for treatment of parkinson can be improve by administering prodrug L-Dopa.

5) To less drug's toxicity & ADE

- Dipivaloyl-epinephrine prodrug instead of epinephrine to treat glaucoma.

6) Prolonged activity

- Nordazepam an anxiolytic less activity too quickly due to metabolism.
- prodrug introduce (cliazepam) to improve retention.