Name of Subject	:	Medicinal Chemistry
Subject Code	:	838805
Name of Chapter	:	Antiprotozoal Agents
Name of Topic	:	Introduction, Classification, M/A, Synthesis, SAR.
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Education	:	M.Pharm, Ph.D

	Division	Semester	Main Ans.Book	+ Suppli.	Total
-			1	+	

Q.No.	1	2	3	4	5	6	7	Total	Examiner's Signature With Date
Marks									

Antiprotozoal agents

(Begin Writing from here)

Parasites is an organism which lives in or on another organism (its host) and takes benefits by deriving nutrients at the other's expense.

→ Protozoa are defined as single celled organisms with animal like behaviours, such as motility and predation (Ris12)

Antimalarials

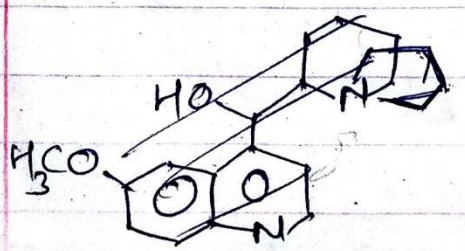
malaria is an infectious disease caused by plasmodium parasite.

It is transmitted by the infected female anopheles mosquito.

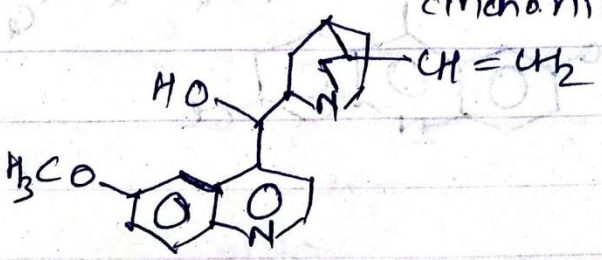
The agents which are used in the treatment of malaria are kn as Anti malarial agents

classification

1) cinchona alkaloids :- Ex. Quinine, Quinidine, cinchonine, cinchonidin



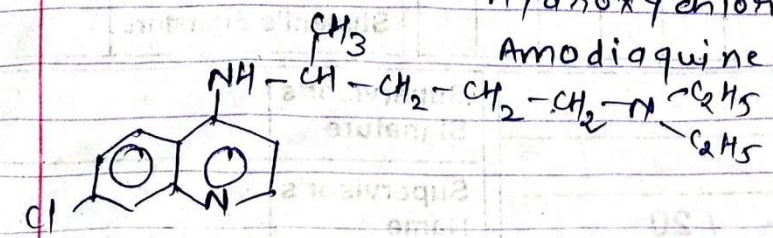
quinine



Quinine

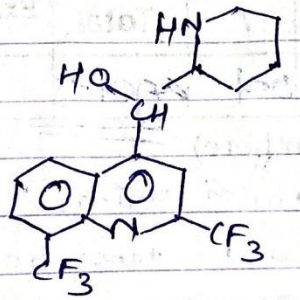
2) 4-substituted quinolines :-

a) 4-Amino quinolines :- chloroquine
Hydroxychloroquine
Amodiaquine, sontoquine



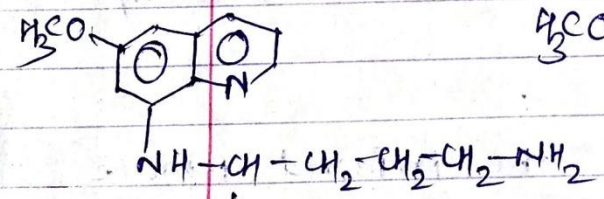
chloroquine

b) Quinoline-4-methanols :- mefloquine

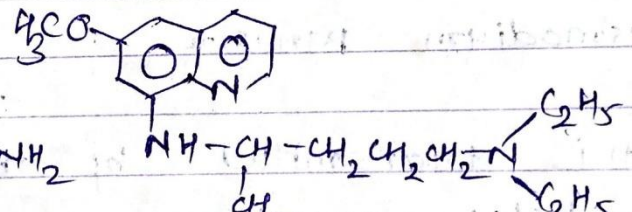


mefloquine

3). 8-Aminoquinolines :- Primaquine,
Pamaquine, Pentaquine,
Isopentaquine

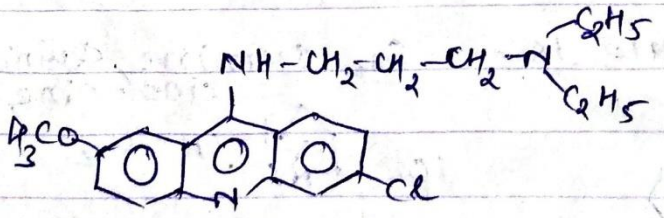


primaquine



Pamaquine

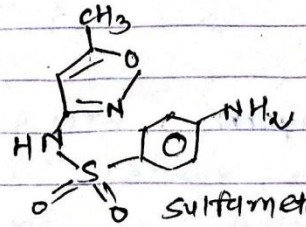
4) 9-Amino acridines :- Quinacrine,
Mepacrine



5). Antifolates :-

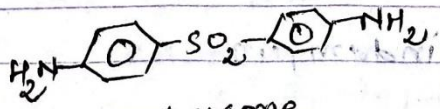
a) Dihydropteroate synthatase inhibitors :-

i) sulfonamides :- sulfamethoxazole, sulfasalazine, sulfadoxine



sulfamethoxazole

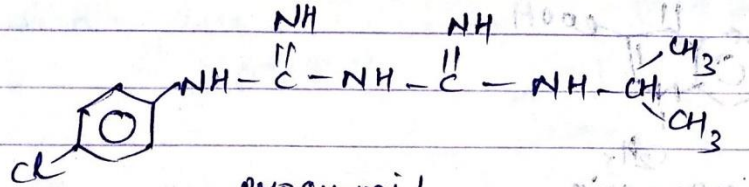
ii) sulfones :- Dapsone.



Dapsone

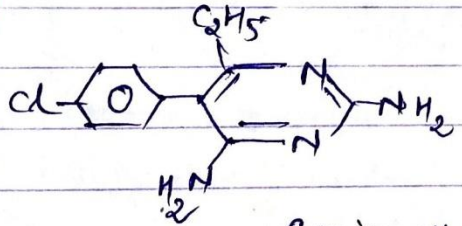
b) Dihydrofolate reductase inhibitors :-

i) Biguanides :- cycloguanide, cloguanil, proguanil



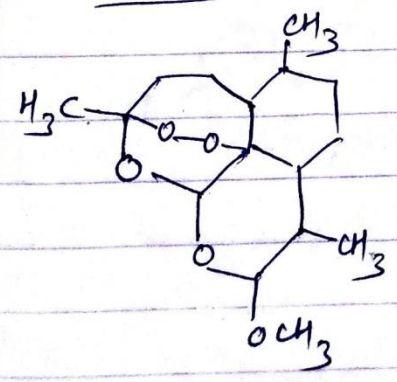
Proguanil

ii). Diaminopyrimidines :- pyrimethamine, Trimethoprim

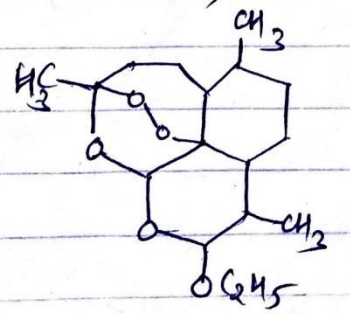


Pyrimethamine

c) Antimisins :- Antemether, Arthether, Artesunate



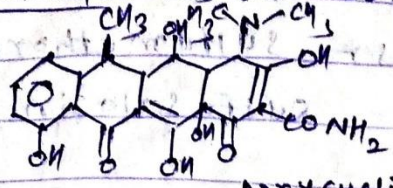
Antemether



Arthether

7). Antibiotics :-

a). Tetracyclines :- Doxycycline

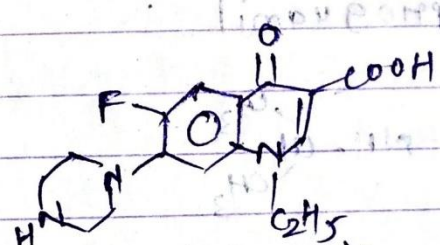


Doxycycline

b) macrolide :- Azithromycin

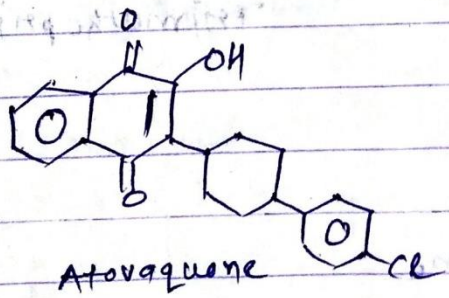
c). Lincosamide :- clindamycin

d) Fluoroquinolones :- Norfloxacin, ciprofloxacin



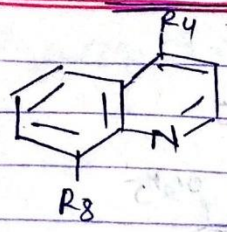
Norfloxacin

8). Miscellaneous :- Atovaquone
Halofantrin



Atovaquone

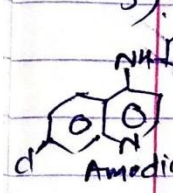
SAR of Quinolines

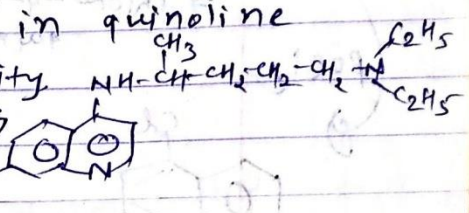


1) A Dialkyl amino alkyl side chain, having 4-5 carbon atoms between the nitrogen atoms is optimal for anti malarial activity.
Eg chloroquine, Hydroxy chloroquine, sontoquine,

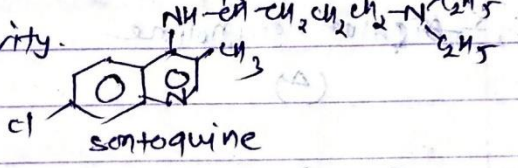
2) The "3° amino" gp. in the side chain is essential for activity.
Eg chloroquine, Amodiaquine, Hydroxychloroquine, sontoquine

3) chlorine at 7th position in quinoline nucleus is optimal for activity.
Eg chloroquine Amodiaquine, Hydroxy chloroquine, sontoquine

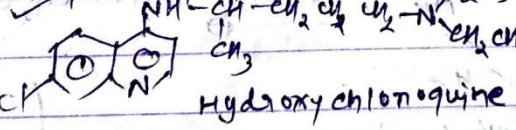

Amodiaquine



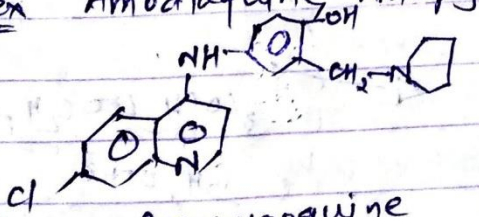
4) Alkylation at C-3 & C-8 diminish the anti malarial activity.
Eg sontoquine


sontoquine

5) The substitution of one ethyl gp. with —OH gp. reduce toxicity and increase plasma conc^{n}.
Eg. Hydroxy quinoline

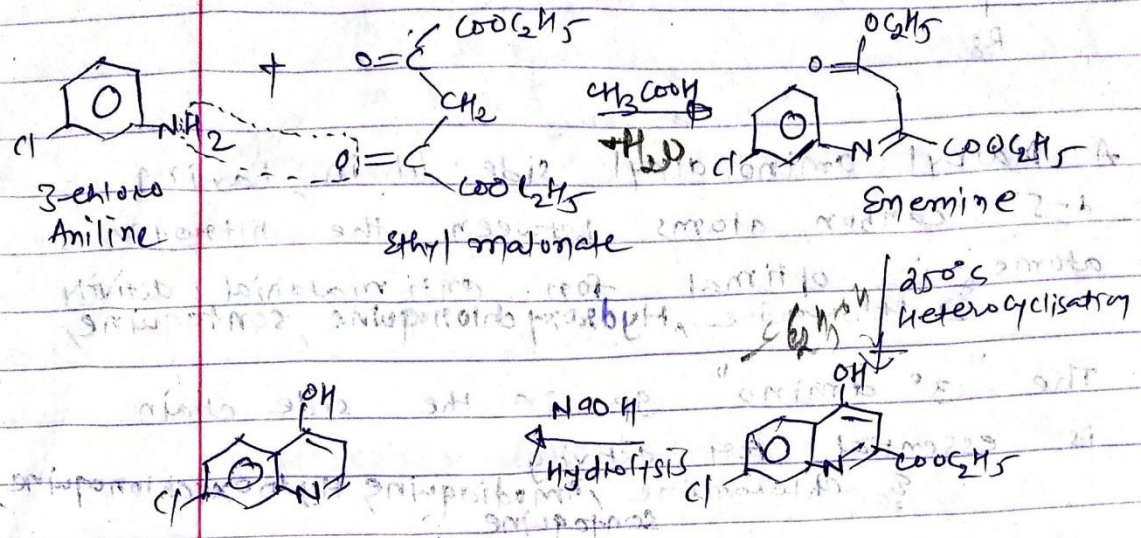

Hydroxychloroquine

6) Incorporation of aromatic ring in the side chain gives compound with reduce toxicity and use activity.
Eg Amodiaquine, Amopynoquine

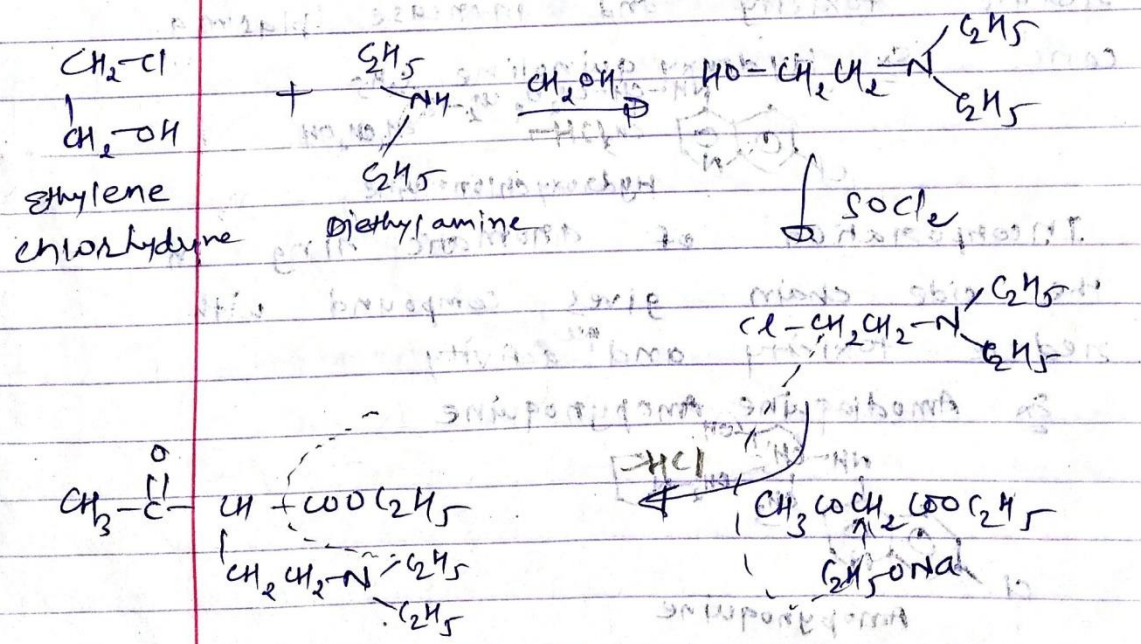

Amopynoquine

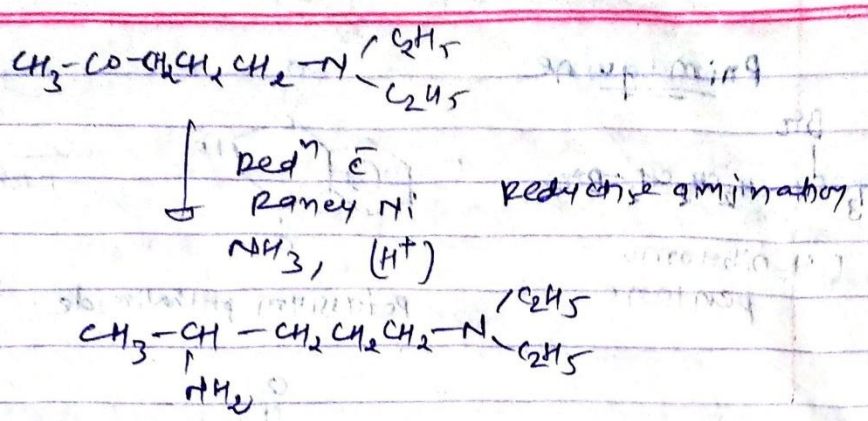
chloroquine

Step-I Synthesis of quinoline moiety



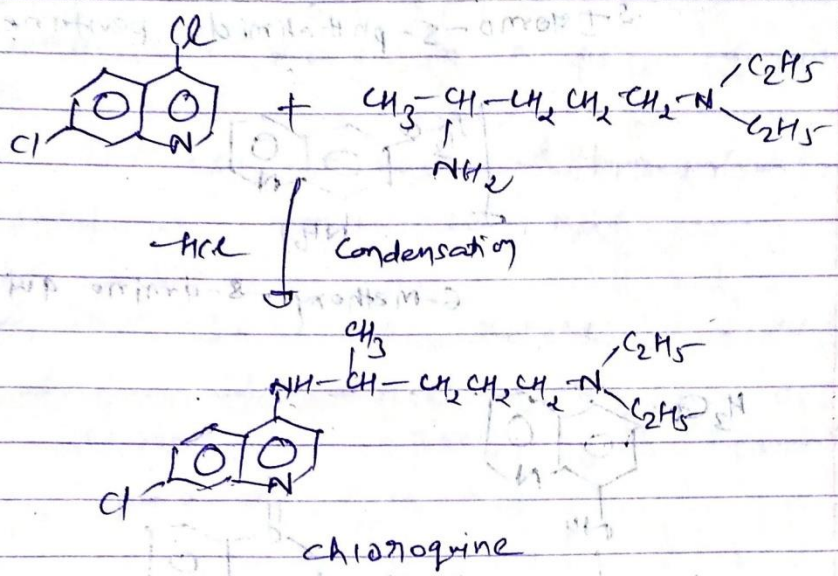
Step-II Synthesis of side chain





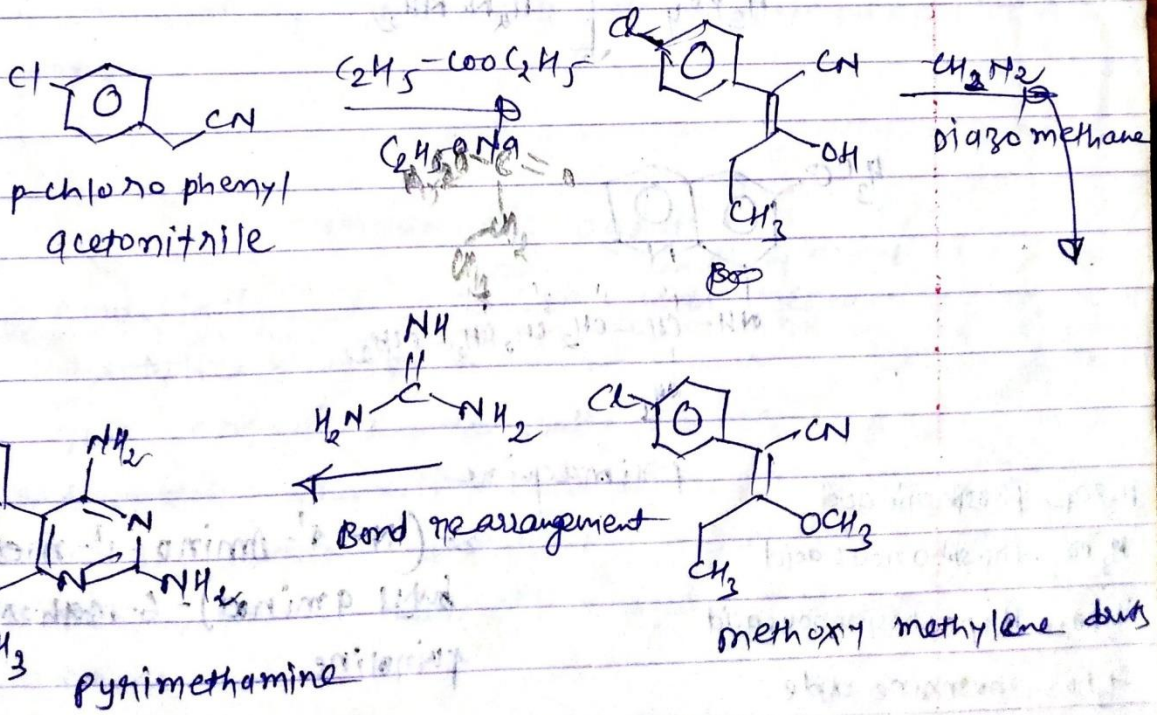
(B)

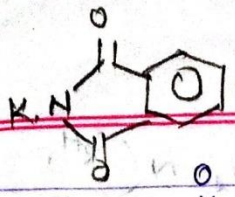
→ Condensation of (A) + (B)



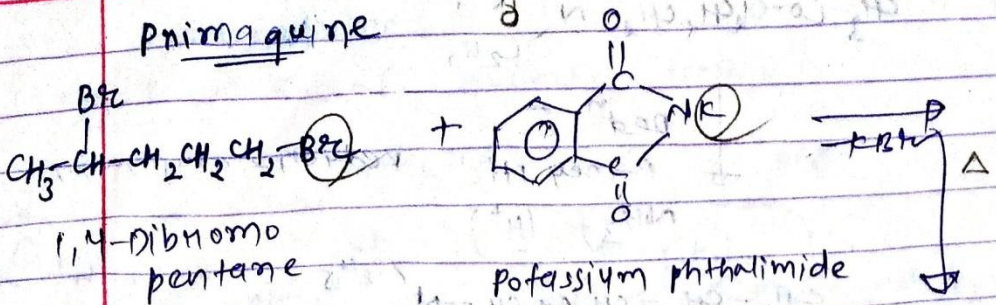
Chloroquine

(2) Pyrimethamine



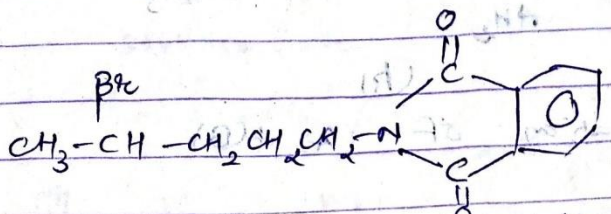


Primaquine

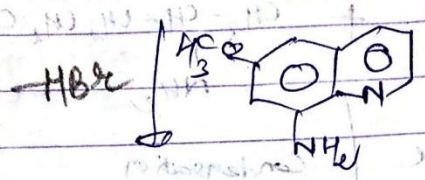


1,4-Dibromo pentane

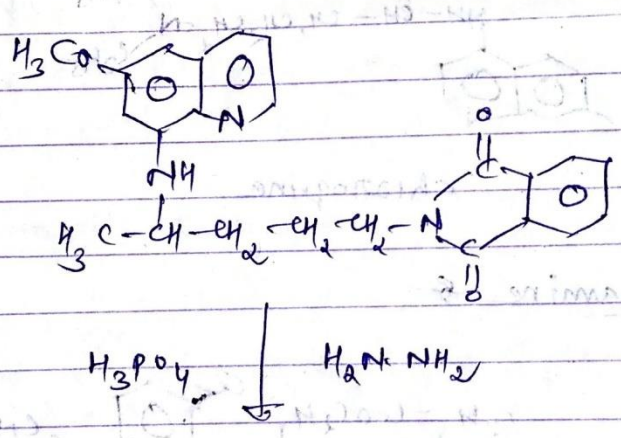
Potassium phthalimide

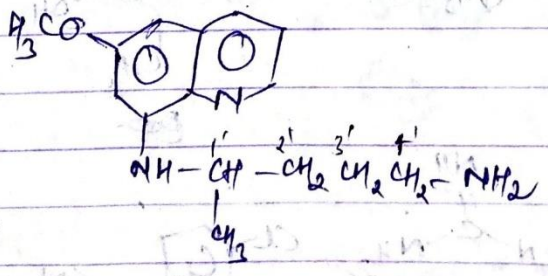


2-Bromo-5-phthalimido pentane



6-methoxy-8-amino quinoline





Primaquine

H_3PO_4 - Phosphoric acid
H_3PO_3 - Phosphorous acid
H_3PO_2 - Hypophosphorous acid
H_3PO - Phosphine oxide

8-(N-4'-Amino-1'-methyl butyl amino)-6-methoxy quinoline

chloroquine-Heme complex

Quinine drug → chloroquine

Host Hb $\xrightarrow{\text{Parasite Protease Enzyme}}$ Heme (Ferriprotoporphyrin-IX) $\xrightarrow{\text{Heme crystallization / polymerization}}$ Haemazoin

Heme: toxic to parasite

Haemazoin: Non toxic to parasite

- Plasmodia (Malaria causing parasite) derived their nutrition by digesting host Hb. and degrade that Hb.
- Chloroquine enters in to RBCs & concentrated there
- Conc^{n} of CQ is higher in infected RBC compared to non infected RBC
- Compd. is basic in nature. By accumulating in RBC, they enhance the pH of cell that ultimately interferes with degradation of Hb. by parasitic lysosomes.
- Polymerization of toxic heme generated from degradation of Hb to non toxic hemazoin is inhibited by formation of chloroquine-heme complex.