MEDICINAL CHEMISTRY - III

UNIT 2 NOTES

ANTIBIOTICS

- BETA LACTAM ANTIBIOTICS
- AMINOGOYCOSIDES
- TETRACYCLINES

PRODRUGS

- BASIC CONCEPT
- APPLICATION

ANTIMALARIALS

- QUINOLINES
- BIGUANIDES
- ANTIMALARIALS

IMPERFECT PHARMACY

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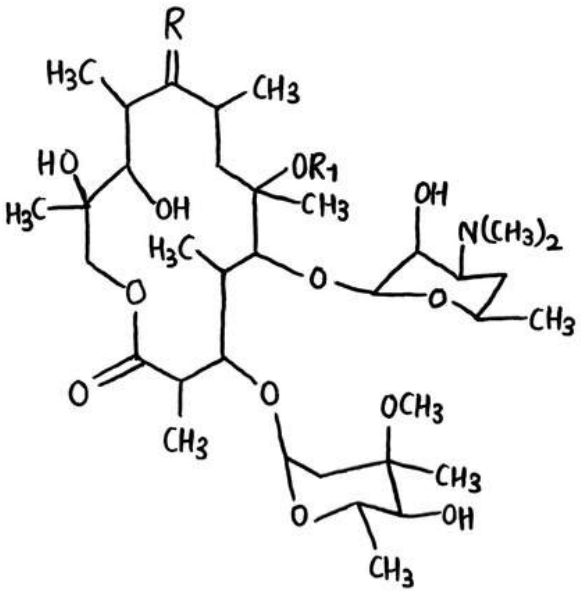
MACROLIDES

- Macrolides are class of bacteriostatic antibiotics derived from Streptomyces species, characterized by a macrocyclic lactone ring (14-16 membered) with attached sugars.
- The first macrolide discovered was Erythromycin.
- It was first used in 1952.
- Erythromycin was widely used as a substitute of penicillin in cases where patients were allergic to penicillin or had penicillin-resistant illness.

CHEMICAL STRUCTURE

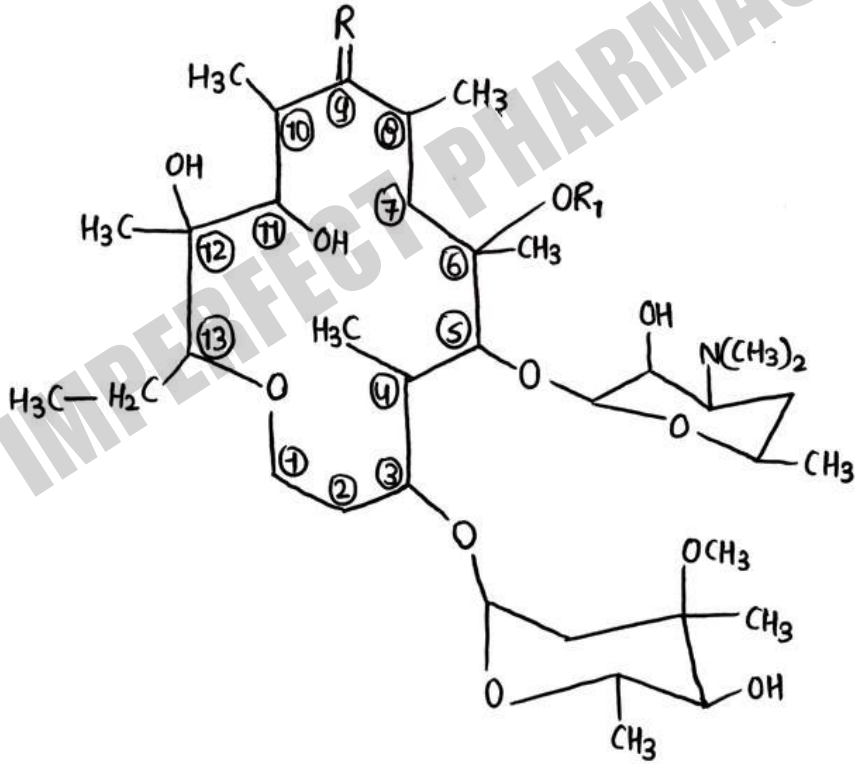
- It contains a large lactone ring along them Desosamine & Cladinose sugar.



MOA OF MACROLIDES

- Macrolides binds to the 50s subunit of the bacterial ribosome.
- They block the translocation i.e prevent the transfer of tRNA from A-site to the P-site on the ribosome.
- As a result, protein synthesis is halted, which prevent bacteria from producing essential proteins needed for growth & survival & leads to bacteriostatic effects.

SAR OF MACROLIDES



① Lactone Ring

- It is essential for activity.
- It is generally a 14, 15 or 16 membered lactone ring, 14 & 15 membered ring have better activity against Gram-positive bacteria.
- Larger ring sizes may improve spectrum & stability.

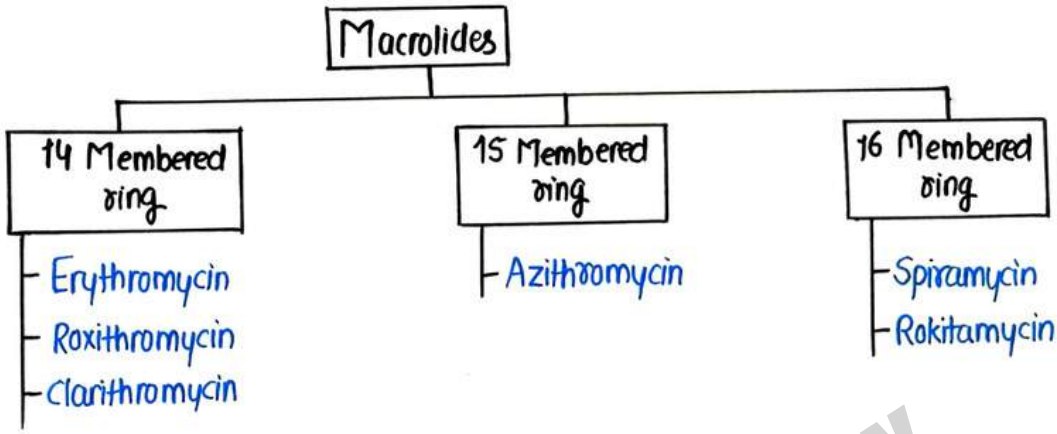
② Sugar Moietics

- Desosamine sugar at C_5 is critical for binding to the 50s ribosomal subunit.
- It's important for antibacterial activity.
- Cladinose sugar at C_3 enhances lipophilicity & oral absorption.

③ Substitution at C_9

- In erythromycin, a ketone group at C_9 can undergo acid catalyzed reactions, causing GI side effects.
- Removing this group, improves acid stability & tolerability (e.g. telithromycin).

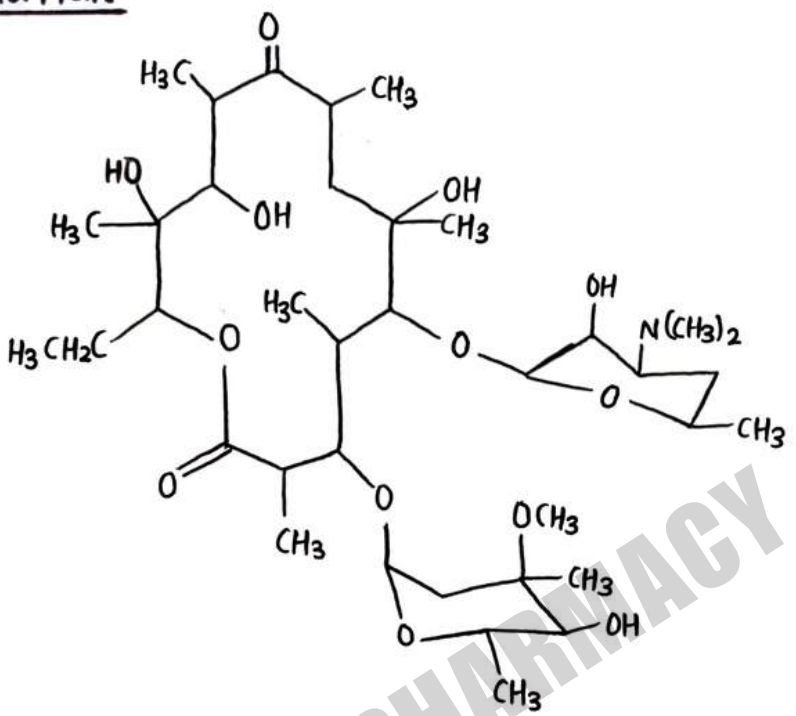
Classification



Drugs In Our Syllabus

- Erythromycin
- Clarithromycin
- Azithromycin

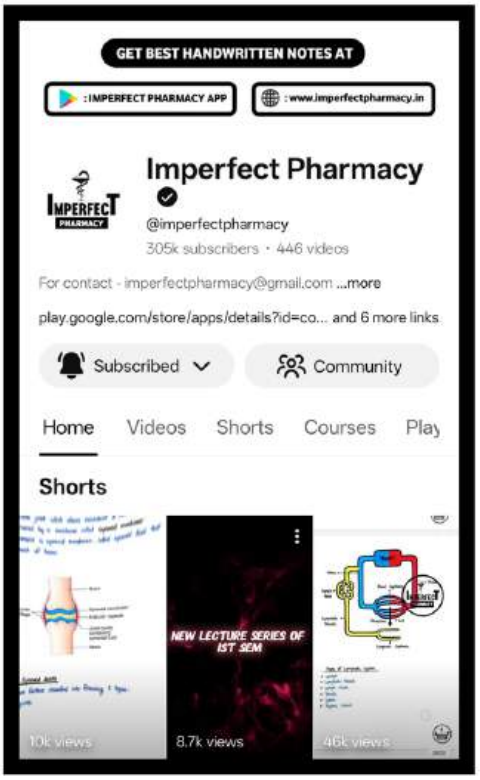
① ERYTHROMYCIN

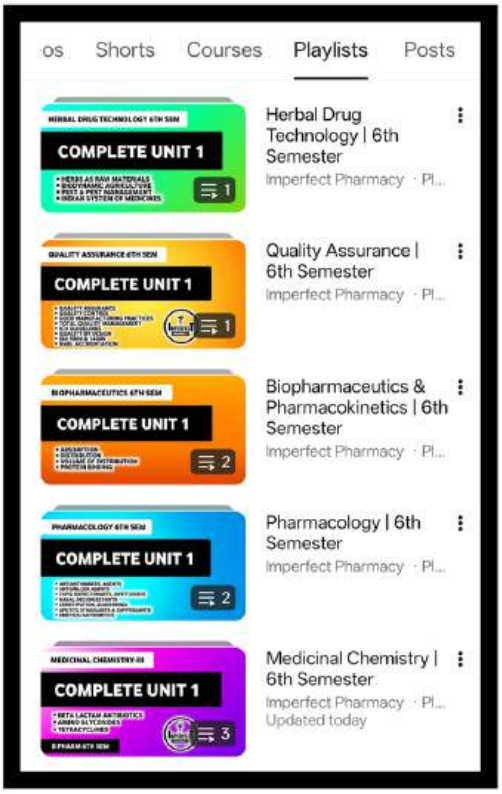


Uses

- Syphillis
- Gonnorrhea
- Pneumonia

FOR LECTURE VIDEOS VISIT OUR CHANNEL





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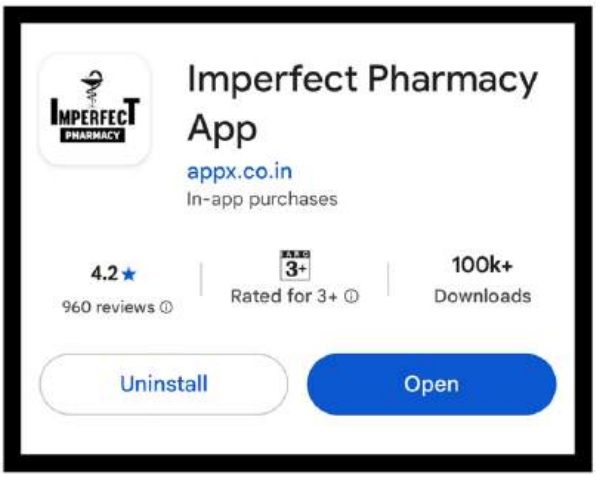
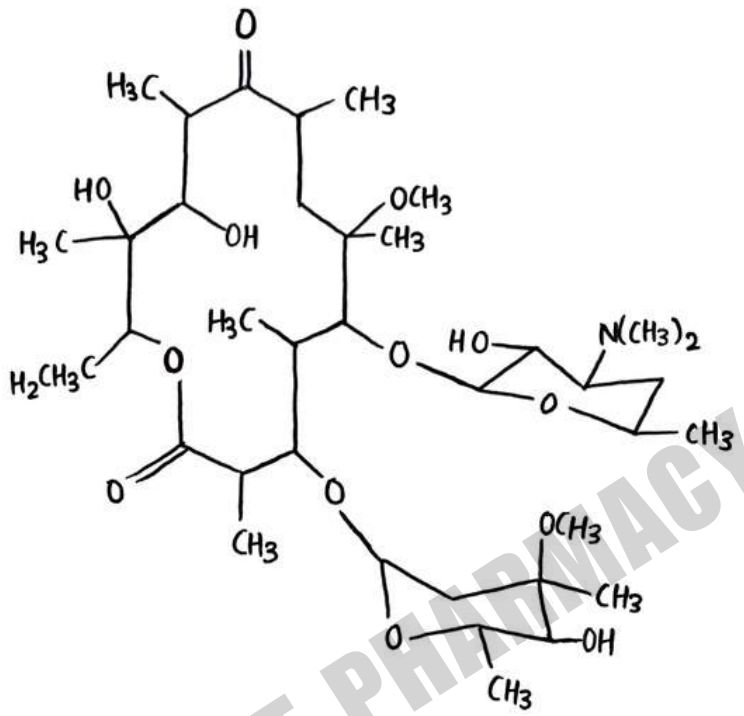


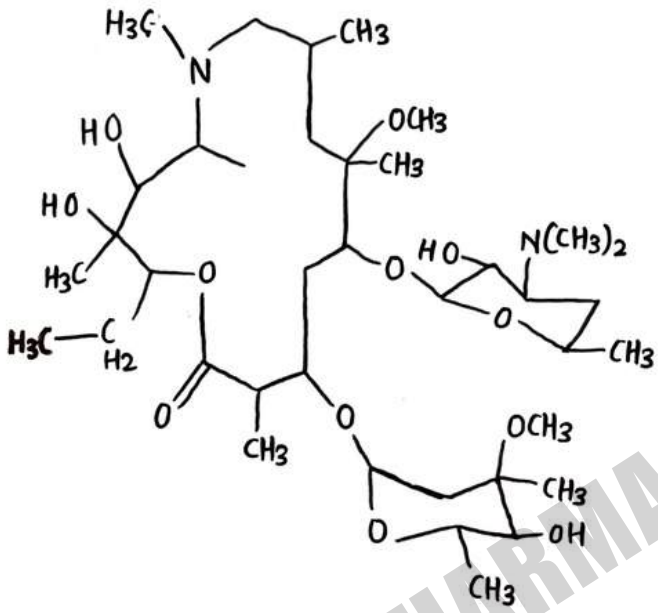
② CLARITHROMYCIN



Uses

- Pneumonia
- Sinusitis
- Bronchitis

③ AZITHROMYCIN



Uses

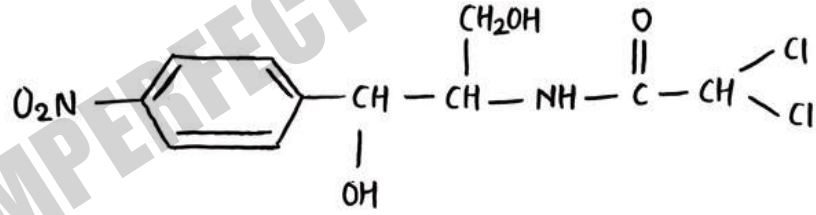
- Brochitis
- Chlamydia
- Typhoid
- Malaria
- COVID - 19

MISCELLANEOUS

CHLORAMPHENICOL

- Chloramphenicol is a broad - spectrum bacteriostatic antibiotic originally derived from Streptomyces venezuelae.
- It is now largely produced synthetically.
- It is effective against a wide range of Gram - positive and Gram-negative bacteria, as well as anaerobics.

Structure of Chloramphenicol

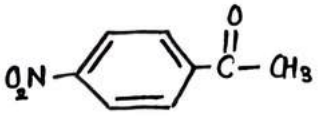


2,2 dichloro - N - [1,3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl] acetamide

MOA

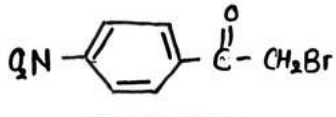
- It inhibits bacterial protein synthesis.
- Binds to the 50s ribosomal subunit.
- Prevents the formation of peptide bonds between amino acids during translation & leads to bacteriostatic effects.

SYNTHESIS



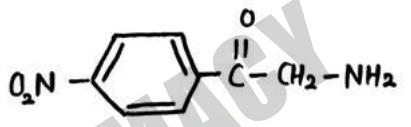
p- Nitroacetophenone

Br_2 / $-HBr$



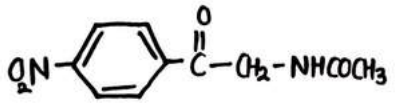
p- nitrophenacyl bromide

$(CH_2)_6N_4$ Hexamine / HCl / C_2H_5OH



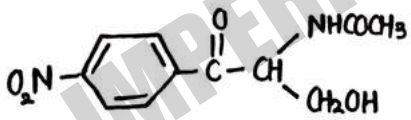
α- amino p- nitro acetophenone

Acetylation / $(CH_3CO)_2O$ / $-CH_3COOH$



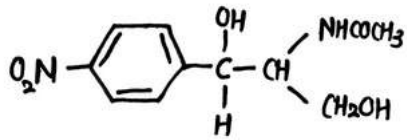
p-nitro acetamido -acetophenone

Na_2CO_3 / HCHO



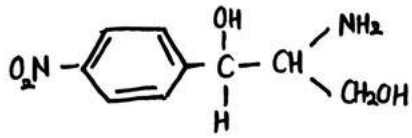
Hydroxmethyl Derivative

Reduction / Aluminium iso-propyl alcohol

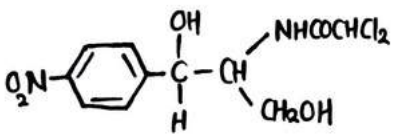


dl - form

HCl / $-CH_3COCl$



(i) Resolution / (ii) $Cl_2CHCOOCH_3$ Dichloromethylacetate / $-CH_3OH$



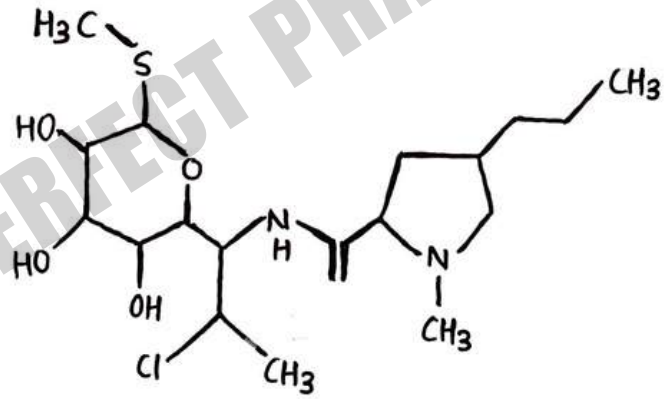
Chloramphenicol

CLINDAMYCIN

- Clindamycin is a lincosamide antibiotic used to treat various bacterial infections, particularly those caused by anaerobic bacteria & some Gram-positive cocci.

MOA

- Clindamycin binds to 50s ribosomal subunit of bacteria, inhibiting protein synthesis by preventing peptide bonds formation, which leads to bacteriostatic effect.



Clindamycin

Uses

- Skin & Soft tissue infections.
- Bone & Joint infections.
- Respiratory Tract infections.

PRODRUGS

- A prodrug is an inactive or less active precursor of a drug that requires biotransformation / metabolism (usually by enzymatic action in the body) to convert into its active pharmacological form.

IDEAL PROPERTIES

- Drug and the carrier linkage must be cleared in vivo.
- It should have not intristic pharmacologic activity.
- It should rapidly transform, chemically or enzymatically, into the active form where desired.
- The metabolic fragments, apart from the active drug, should be nontoxic.

OBJECTIVES

They are designed with following objectives:

① Pharmaceutical Objectives:

- To improve water/ lipid solubility.
- To improve chemical stability.
- To alter organoleptic properties.
- To decrease irritation and paint at injection site.

② Pharmacokinetic Objectives

- To improve absorption.
- To reduce presystemic metabolism.
- To increase organ/tissue - selectivity.

③ Pharmacodynamic Objectives

- To decrease toxicity.
- To improve therapeutic index.

Designing Of Prodrug

- Prodrugs are chemically modified drug molecule that are inactive or less active in their administered form & require biotransformation in the body to release the active drug.
- Following factors needed to be considered while designing of prodrug structure :

① **Parent drug:**

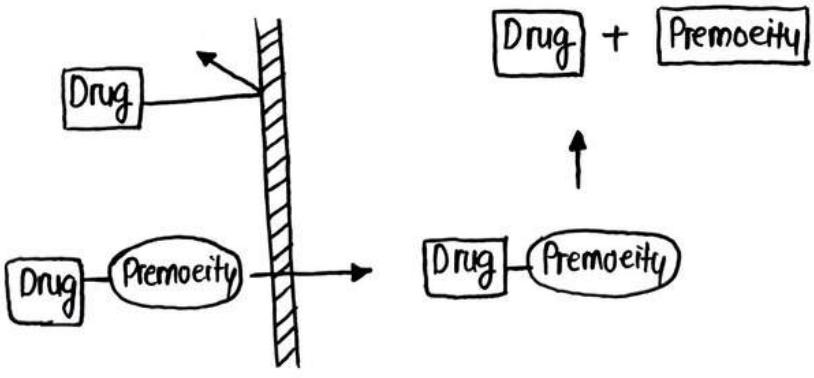
- In this functional groups are important as it helps in modifying drugs to make effective prodrugs.

② **Premoeity**

- This should ideally be safe & rapidly excreted from the body.
- The choice of premoeity should be considered with respect to the disease state, dose & duration of therapy.

③ **Parent & Prodrugs**

The absorption, distribution, metabolism & excretion need to be comprehensively understood.



Physiological barrier

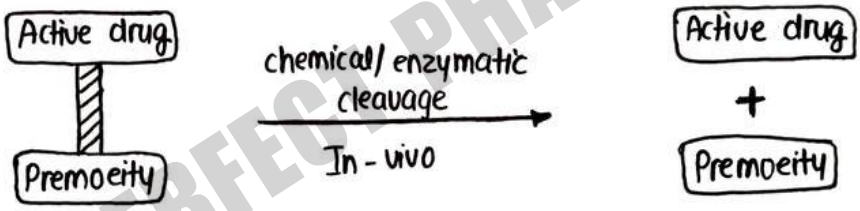
Classification Of Prodrug

Prodrugs are mainly classified into two types:

① Carrier - Linked prodrug
② Bioprecursors

① Carrier Linked Prodrugs

- These prodrugs are formed by attaching an active drugs to a non-toxic carrier (premoeity) via a chemical linkage.
- After administration, the linkage is enzymatically or chemically broken down, releasing the active drug.



- It is further divided into following subtypes:

① Double prodrugs
② Macromolecular Prodrugs
③ Site- specific Prodrugs
④ Mutual prodrugs

① Double Prodrugs

- A prodrug that turns into another prodrug before becoming the active drug.
- This two-step activation can improve targeting and control over drug release.

② Macromolecular Prodrugs

- In this drug attached to a big molecule (like a protein or polymer).
- This makes the drug stay longer in the body or go to a specific place (like a tumor).
- Example: Cancer drugs linked to antibodies to target tumors specifically.

③ Site-specific Prodrugs

- Designed to became active only in certain parts of the body (like liver or tumor cells) to avoid harming healthy tissues & reduce side effects.

④ Mutual Prodrugs

- In this two active drugs are combined into one.
- Each drug helps the other gets into the body better.
- Example: Ben Oxylate (Aspirin + Paracetamol) - combines pain relief & anti-inflammatory action.

② Bioprecursors

- They do not contain a carrier group. Instead the molecular structure itself is modified so that the drug becomes active undergoing metabolic transformation such as oxidation or reduction.
- Example : Prontosil ⟶ Sulfanilamide

Application Of Prodrug Design

① Improve Oral Bioavailability

- Better absorption.
- Example = Valacyclovir ⟶ Acyclovir

② Enhance Solubility

- Useful for IV use.
- Example = Fosphenytoin ⟶ Phenytoin

③ Prolong Drug Action

- Sustained / Controlled release.
- Example : Lisdexamfetamine ⟶ Dextroamphetamine

④ Reduce Toxicity / Side effects

- Safer delivery
- Example = Aspirin ⟶ Salicyclic Acid

⑤ Targeted Drug delivery

- Activated in specific tissues.
- Example: Capecitabine ⟶ 5- Fluorouracil (activated in tumors).

⑥ Mask taste / Odor

- Better patient compliance
- Example: chloramphenicol palmitate ⟶ Chloramphenicol

⑦ Improve stability

- Protect drug from degradation
- Example: Enalapril ⟶ Enalaprilat

⑧ Enhance CNS Delivery

- Crosses blood-brain barrier
- Example: Levodopa ⟶ Dopamine

ANTIMALARIALS

Antimalarial drugs are used to prevent, treat or eradicate malaria, a disease caused by Plasmodium parasites, which are transmitted to humans through the bite of infected Anopheles Mosquitoes (female mosquitoes).

MALARIA

- Malaria is life-threatening infectious disease caused by Plasmodium parasites.
- It is transmitted to human through the bite of female Anopheles mosquito.

CAUSATIVE AGENTS

- Plasmodium falciporum — Most severe and deadly
- Plasmodium vivax — Causes recurring malaria & mainly affects the liver.
- Plasmodium ovale — Similiar to vivax, less common
- Plasmodium malarie — less severe but chronic
- Plasmodium knowlesi — Usually infects monkeys, but it can also infect humans.

TYPES OF MALARIA

It can be classified into two types:

① Uncomplicated Malaria
② Complicated Malaria

① Uncomplicated Malaria

- It can be caused by any malaria paraties species
- Symptoms include :
  - Fever
  - Headache
  - Sweating
  - Nausea
- No sign of organ failure
- Usually treatable with oral medicines.

② Complicated Malaria

- It is most often caused by Plasmodium falciporum.
- It involves serious symptoms like :
  - Siezures
  - Severe Anemia
  - Kidney failure
  - Breathing problems
  - Coma
- It is a medical emergency and need immediate treatment, often with IV medicines.

LIFE CYCLE OF MALARIA

The life cycle of malaria involves two hosts :

- The female Anopheles mosquito (Asexual stage)
- A Human (Sexual stage)

① IN HUMAN (Asexual stage)

a.) Sporozoite stage

- The infected mosquito bites a human & injects sporozoites into the bloodstream.
- These sporozoites travel to the liver.

b.) Liver (Exo - erythrocytic) Stage

- In liver cells, sporozoites mature into merozoites.
- The liver cells burst, releasing merozoites into the blood.

c.) Blood (Erythrocytic) Stage

- Merozoites infects Red blood cells (RBCs), multiply, and burst the cells.
- This cycle causes malaria symptoms (fever, chills, anemia).
  Some merozoites develop into gametocytes (sexual forms).

② In Mosquito (Sexual stage)

a) Gametocyte uptake

- A mosquito bites an infected human and ingests gametocytes.

b) Sexual Reproduction

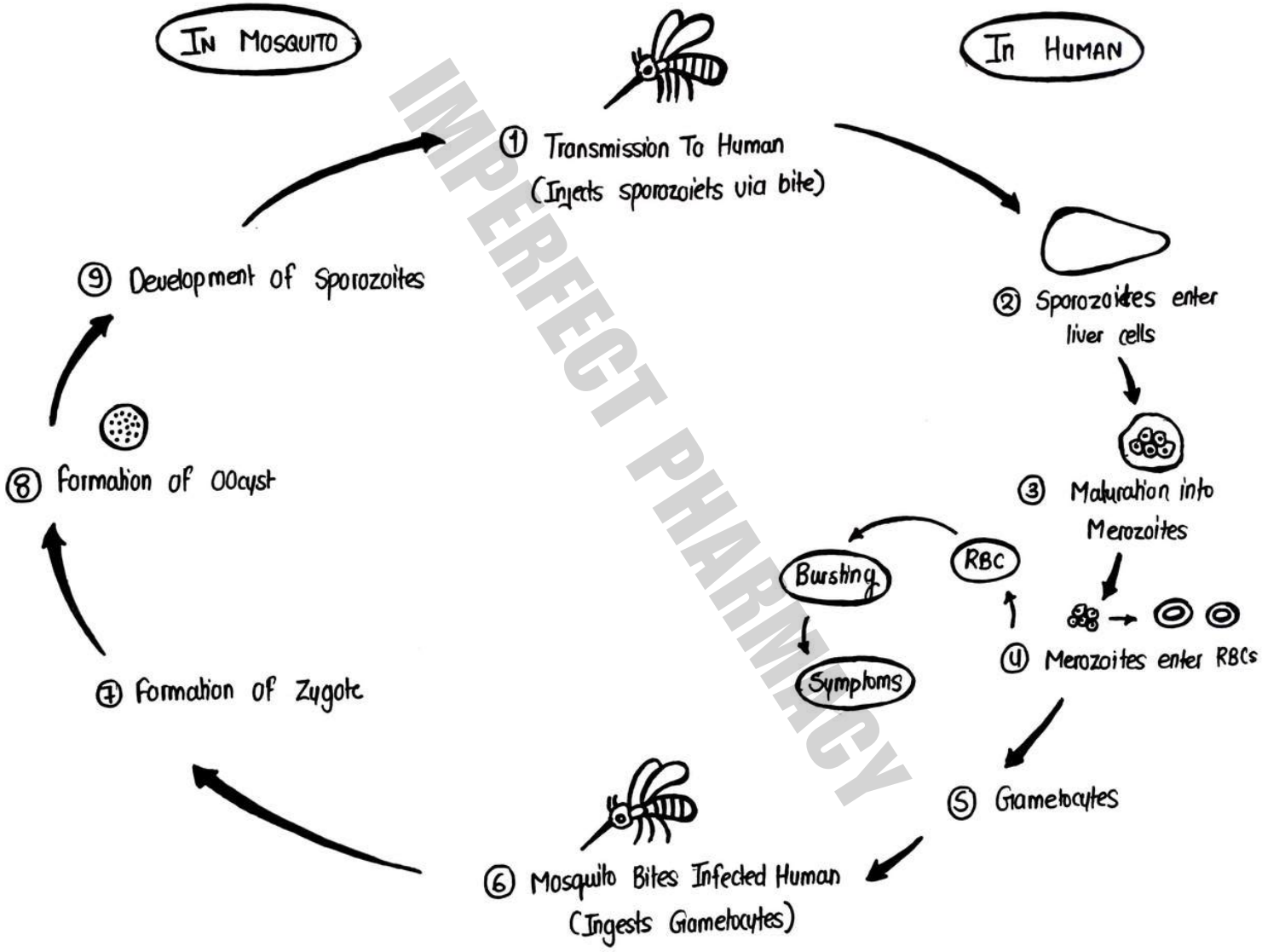
- In the mosquito's gut, gametocytes mature into gametes and fuse to form a zygote.
- The zygote becomes a motile ookinete, which penetrates the gut wall and forms an oocyst.

c) Sporozoite Formation

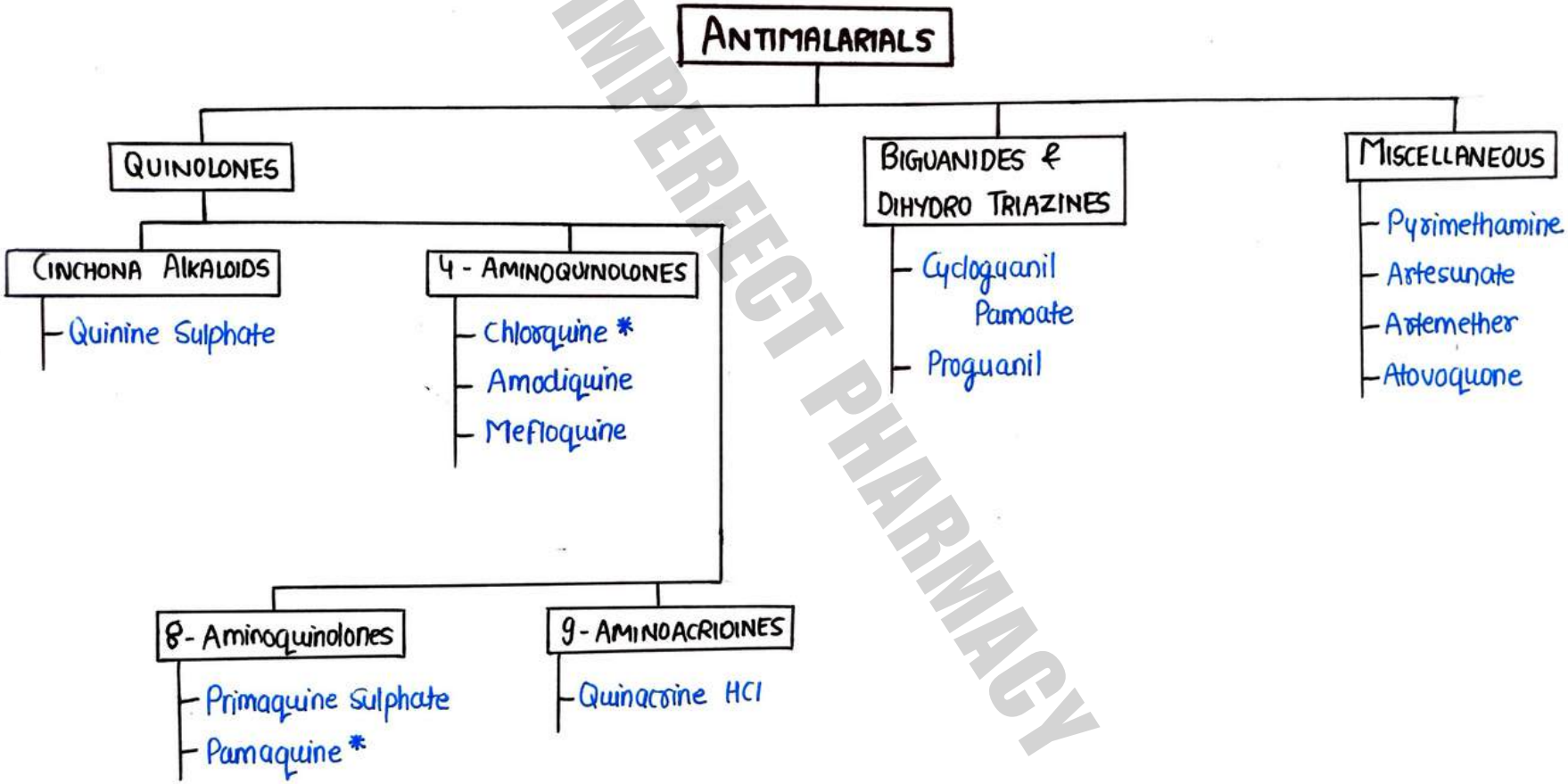
- Inside the oocyst, sporozoites develop.
- When the oocyst bursts, sporozoites migrate to the mosquito's salivary Glands.

d) Transmission

- The mosquito bites another human, injecting the sporozoites, and the cycle repeats.



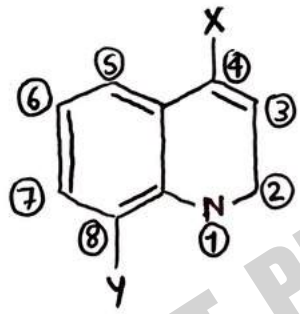
Classification Of Antimalarials



QUINOLINES

- Quinolines are class of organic compounds derived from Quinine (an alkaloid) which was isolated from the bark of cinchona tree.
- Quinine was first known antimalarial.

SAR OF QUINOLINES



① Basic Quinoline Core

- The fused benzene - pyridine system is essential for activity.
- The nitrogen atom in quinolone is at 1- position, hence sometimes refferred to as 1- azanapthalene.

② Substitution at position 4 (4- Aminoquinolines)

- Amino group at position 4 is critical for antimalarial activity.
- A long basic side chain helps drug reach inside parasites food vacuole.
- 7 - chloro group increases binding to parasite's heme & improve activity.

③ Substitution at 8 (8 - Aminoquinolones)

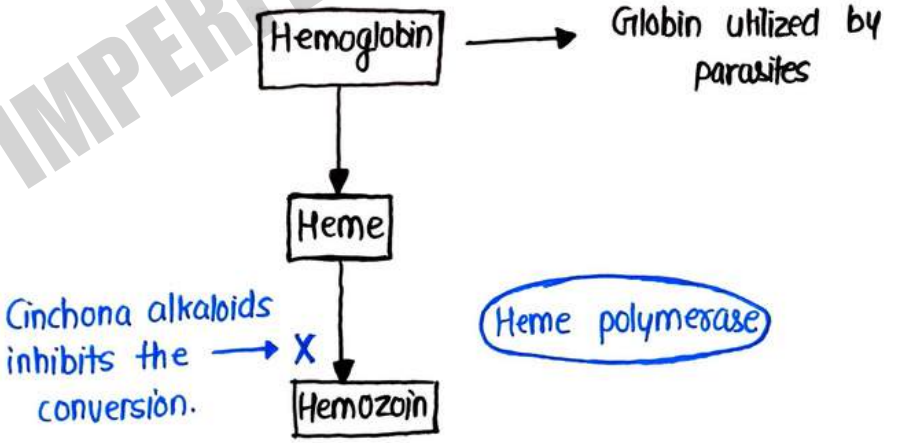
- Amino group at position 8 gives activity against liver & dormant malaria stages.
- Good for relapsing malaria like P. vivax & ovale.
- Alky side chain is neccessary for better absorption & targetting.

Cinchona Alkaloids

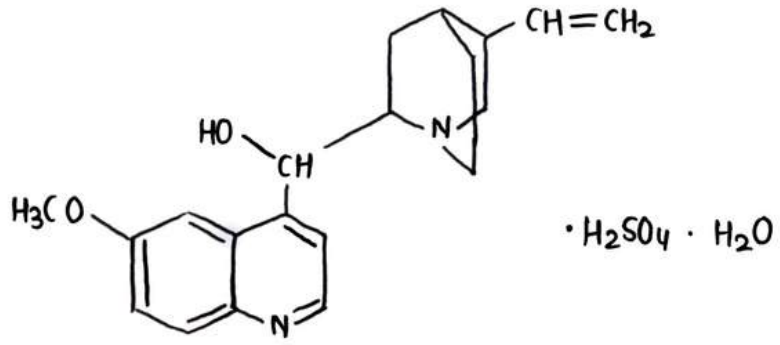
- Cinchona Alkaloids are natural antimalarial compounds extracted from the bark of the Cinchona tree.
- They are among the oldest known treatments for malaria.

MOA

- The malaria parasites utilizes haemoglobin as a source of Amino acid.
- After utilizing haemoglobin, Heme is released which is highly toxic for malaria parasites so they convert it into a non-toxic product - Hemozoin.
- Cinchona Alkaloids binds to Heme & inhibits its conversion into Hemozoin.
- This leads to buildup of free Heme, which causes oxidative damage, & membrane lysis, ultimately killing the parasites.



@ Quinine Sulphate



Uses

- Malaria
- Artheritis
- Leg Cramps (Nocturnal)

② 4 - AMINOQUINOLONES

- 4- Aminoquinolones are a class of Antimalarial drugs that have a quinolone ring with amino group ~~of~~ at 4th position.
- They act on blood (Erythrocytic stage).

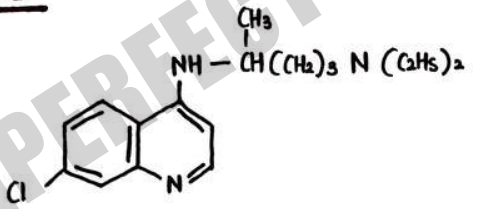
MOA

Same as mentioned in Cinchona Alkaloids.

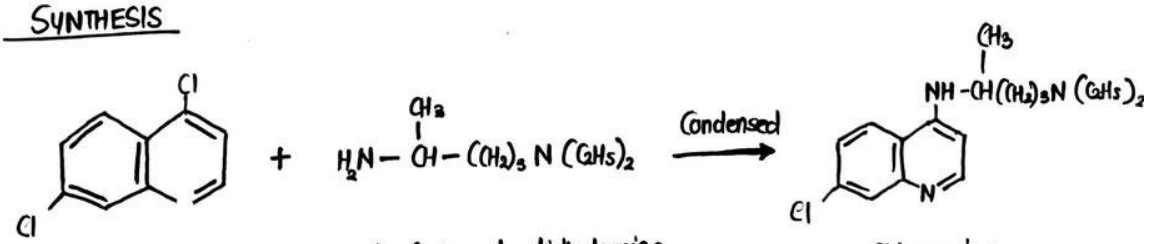
Drugs in Our Syllabus

- Chloroquine*
- Amodiaquine
- Mefloquine

③ CHLOROQUINE *



SYNTHESIS



4,7- Dichloroquinoline

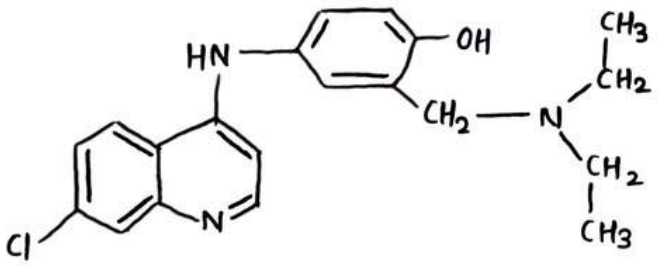
4- Amino - 1- diethylamino pentane

Chloroquine

Uses

- Treatment of Malaria

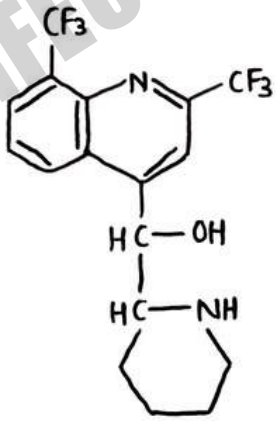
ⓑ AMODIAQUINE



Uses

- Autoimmune disease
- Malaria
- COVID -19

© MEFLOQUINE



Uses

- Malaria
- Chloroquine - resistance
- Prophylaxis

③ 8-AMINOQUINOLONES

- 8- Aminoquinolones are a class of synthetic compounds derived from quinidine, charactarized by having an amino group at 8th position.

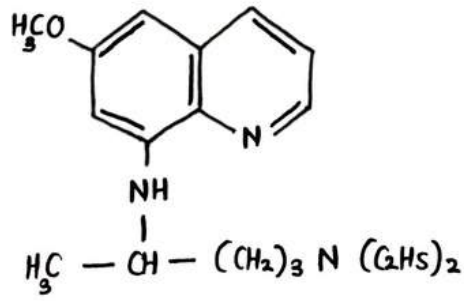
MOA

- 8- Aminoquinolones distrupt the parasites's mitochondrial electron transport chain, leading to generation of reactive oxygen species (ROS) that damage parasite cells.
- They are unique in their ability to eliminate hyponozoites the dormant liver stages of P. vivax & ovale, which prevents relapse.

Drugs in Our Syllabus

- Pamaquine *
- Primaquine Sulphate

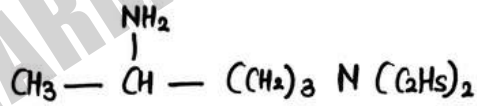
@ PAMAQUINE *



SUNTHESIS

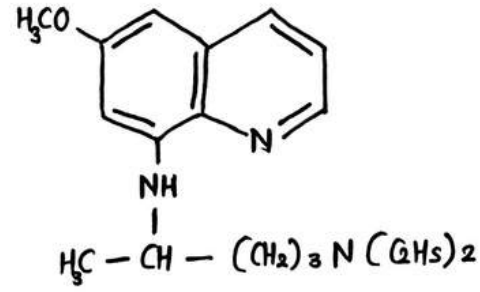
8 - amino - 6 methoxy quinoline

+



3 - Amino - 1 - diethylamino butane

$-NH_3$ ↓ Condensed

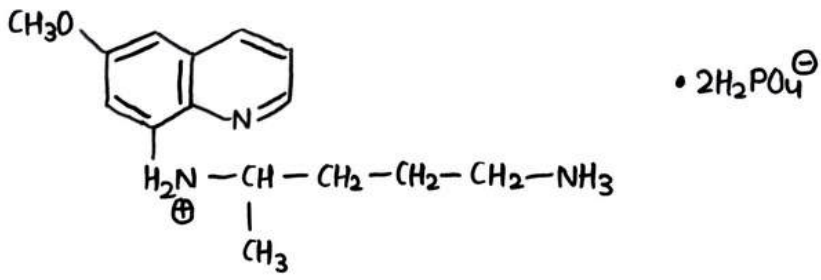


Pamaquine

Uses

- Treatment of Malaria.

ⓑ PRIMAQUINE PHOSPHATE



Uses

- Malaria
- Pneumonia

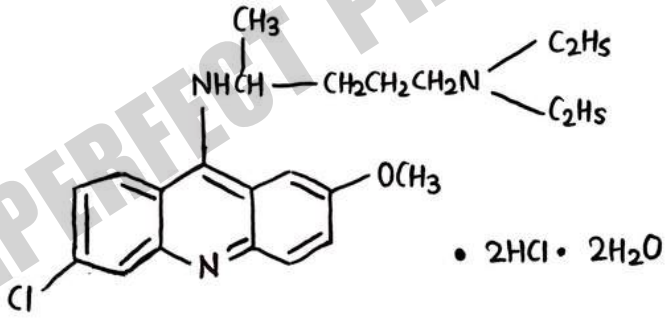
④ 9 - AMINOACRIDINES

- 9- Aminoacridines are a class of chemical compounds derived from Acridine, with an amino group ($-NH_2$) attached at 9th position of acridine ring system.

MOA

- They insert themselves b/w DNA base pairs.
- They block DNA replication & RNA transcription.
- This leads to stops cell growth as they can't devide or make proteins.

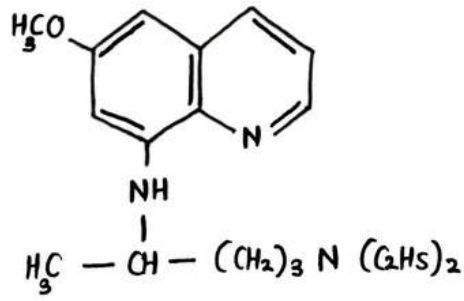
⑤ QUINACRINE HYDROCHLORIDE



Uses

- Malaria
- Rheumatoid Arthiritis
- Tapeworm

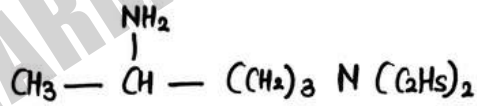
@ PAMAQUINE *



SUNTHESIS

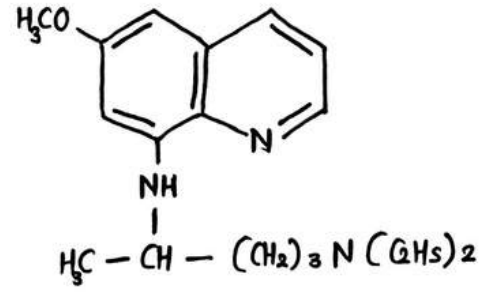
8 - amino - 6 methoxy quinoline

+



3 - Amino - 1 - diethylamino butane

$-NH_3$ ↓ Condensed



Pamaquine

Uses

- Treatment of Malaria.

BIGUANIDES & DIHYDROTRIAZINES

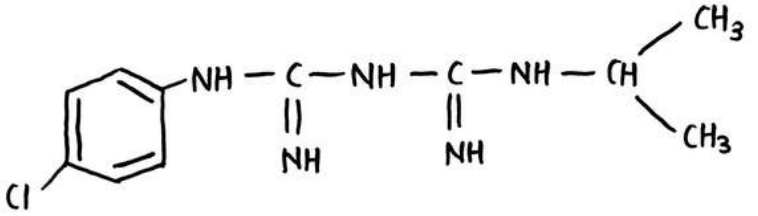
BIGUANIDES

- Biguanides are a class of compounds that contain two linked guanidine groups.
- Example : Proguanil

MOA

- Biguanides block the DHFR (Dihydro Folate Reductase) enzyme in plasmodium parasites.
- DHFR is essential for converting DHF to THF , which is needed to make DNA.
- Without THF , parasite can't produce DNA , RNA or proteins , hence they stop growing or multiplying & ultimately died.

@ PROGUANIL



Uses

- Malaria
- Chloroquine - resistance
- Relapse - prevention

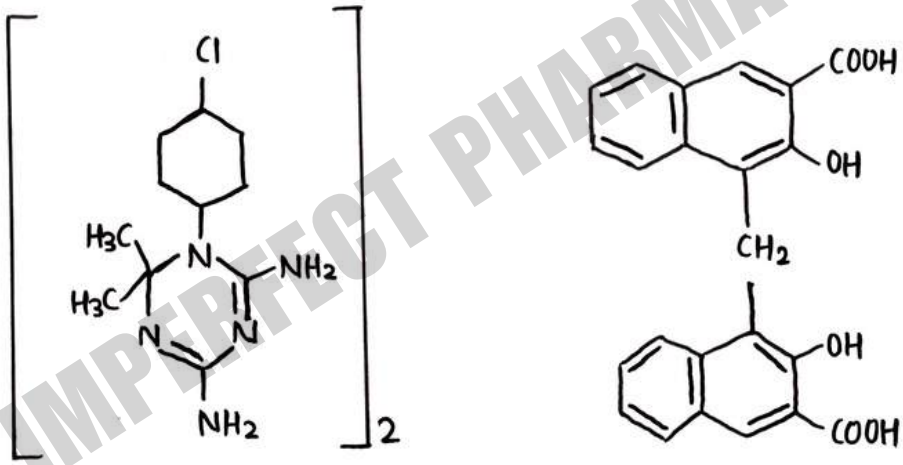
② Dihydro Triazenes

- Dihydrotriazenes are derivatives of triazine rings (a six membered ring with three nitrogen atoms).
- Example: Cycloguanil Pamoate

MOA

Same as biguanides.

Cycloguanil Pamoate



Uses

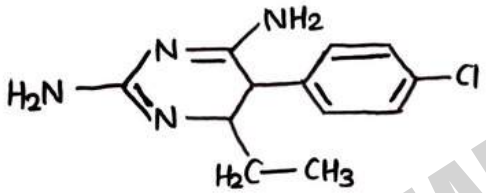
- Prophylaxis
- Malaria
- Relapse - prevention

MISCELLANEOUS

① PYRIMETHAMINE

MOA

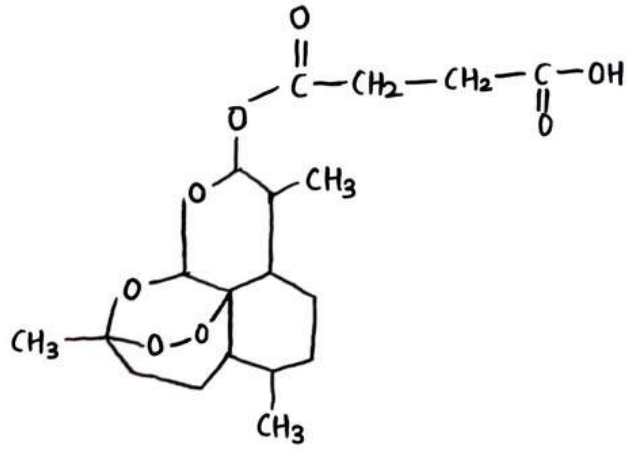
Inhibits DHFR in parasites, leading to parasite death.



Uses

- Used as immunosupperesive agents
- Malaria

② ARTESUNATE



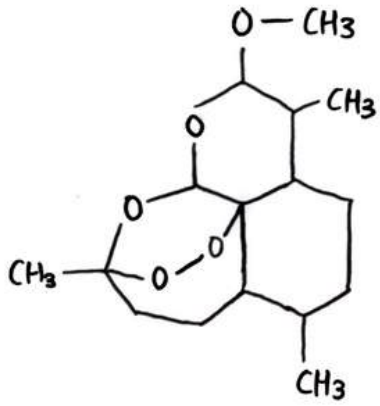
MOA

- Generate free radicals inside parasites, which damage, protein & membrane, especially in blood stage.

Uses

- Malaria & Severe - Malaria
- Cancer
- COVID - 19
- Leukemia

③ ARTEMETHER



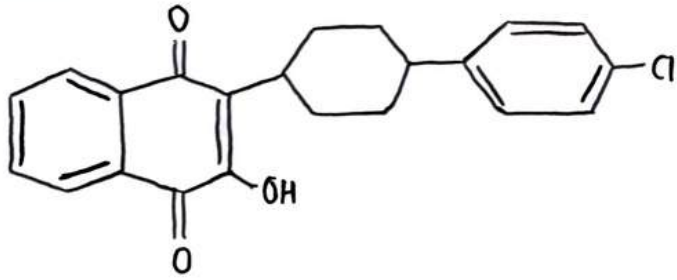
MOA

- Generates reactive oxygen species that damage protein, lipids & DNA in parasites.

Uses

- Malaria
- Chloroquine resistance
- Severe Malaria

④ ATOVAQUONE



MOA

- Inhibits mitochondrial ETC, distrupts ATP production, leading to parasite death.

Uses

- Malaria
- Pneumonia
- Antiparasitic
- Antiprotozoal

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

IMPERFECT PHARMACY

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