BP501T · B.Pharm Semester V · Theory Notes

Biomedicinal Chemistry

Unit II — Antitubercular & Antimalarial Agents

Unit II (12 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit II (12 hours).

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CHAPTER 5: ANTITUBERCULAR AGENTS

1.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define tuberculosis, Mycobacterium tuberculosis, and first-line / second-line antitubercular drugs.

2 Classify all 16 antitubercular drugs of this unit by chemical structure and by clinical line of therapy.

3 Describe the chemical scaffold and key substituents of each drug in words (so you can draw the structure).

4 Explain the mechanism of action of each drug in simple language.

5 Write the complete step-by-step synthesis of **Isoniazid** and **p-Aminosalicylic acid**, with reagents, conditions, and intermediates.

6 State the uses (and one key side effect) of every drug.

7 Explain why TB is always treated with a combination of drugs, never a single drug.

8 Describe India's TB situation and the National TB Elimination Programme (NTEP) in your own words.

1.2 Definitions

- **Tuberculosis (TB):** An infectious disease caused by the bacterium *Mycobacterium tuberculosis*. It most commonly attacks the lungs (pulmonary TB) but can attack any organ.
- **Mycobacterium tuberculosis (M. tuberculosis):** The bacterium that causes TB. It is slow-growing, rod-shaped, and has a very thick, waxy cell wall made of **mycolic acids**. This waxy coat makes it hard for drugs and the immune system to reach it.
- **Antitubercular agent:** Any drug that kills *M. tuberculosis* or stops it from growing.
- **Chemotherapy (in this unit):** Treatment of infection with chemical drugs (not cancer treatment).
- **First-line drugs:** The four most effective, safest anti-TB drugs, used first in every new TB patient — Isoniazid, Rifampicin, Pyrazinamide, Ethambutol.
- **Second-line drugs:** Drugs used when first-line drugs fail or cannot be used — e.g., Ethionamide, Cycloserine, p-Aminosalicylic acid, Streptomycin, Capreomycin, Levofloxacin, Clofazimine.
- **Newer / reserve drugs:** Recently introduced drugs for drug-resistant TB — Bedaquiline, Delamanid, Pretomanid, Linezolid (also Rifabutin, used specially in HIV co-infection).
- **MDR-TB (multidrug-resistant TB):** TB that does not respond to at least Isoniazid and Rifampicin, the two most powerful drugs.
- **XDR-TB (extensively drug-resistant TB):** MDR-TB plus resistance to fluoroquinolones and at least one injectable second-line drug.
- **Prodrug:** A drug that is inactive when swallowed and becomes active only after the body (or the bacterium) chemically changes it. Example: Isoniazid is activated inside the TB bacterium itself.

- **Dormant (latent) bacilli:** TB bacteria that are alive but "sleeping" — not dividing. Most drugs cannot kill sleeping bacteria; only a few (Rifampicin, Pyrazinamide) can.

Simple explanation: Think of TB bacteria as enemies wearing thick wax armour (mycolic acid wall), hiding in a fort (the lung), with some soldiers awake and some asleep. Our drugs must break the armour, and we must attack awake and sleeping soldiers together — that is why we always use 3–4 drugs at once.

Example: A new TB patient gets four drugs together (INH + Rifampicin + Pyrazinamide + Ethambutol) for 2 months, then two drugs (INH + Rifampicin) for 4 more months.

Key takeaway: TB = waxy, slow, sometimes-sleeping bacterium needs long, multi-drug treatment.

1.3 Terminology You Must Know

Term	Meaning in one line
Mycolic acid	Long waxy fatty acids forming the TB bacterium's armour-like cell wall
KatG	The bacterium's own enzyme (catalase-peroxidase) that accidentally activates Isoniazid — its "own goal"
InhA	The bacterial enzyme (enoyl-ACP reductase) blocked by activated INH — stops mycolic acid making
RNA polymerase	The bacterial machine that reads DNA to make RNA; blocked by Rifampicin
Arabinogalactan	A sugar layer in the TB cell wall; its building is blocked by Ethambutol
DOTS	Directly Observed Treatment, Short-course — a health worker watches the patient swallow each dose
NTEP	National TB Elimination Programme — India's national programme to end TB
Bactericidal	Kills bacteria (e.g., INH, Rifampicin)
Bacteriostatic	Stops bacteria from growing, does not kill directly (e.g., Ethambutol, PAS)
Cross-resistance	When resistance to one drug automatically gives resistance to a similar drug

1.4 Why TB Drugs Are Special — The Enemy's Armour

Technical concept: *M. tuberculosis* has a cell envelope rich in mycolic acids, arabinogalactan, and peptidoglycan — far thicker than ordinary bacteria. It divides very slowly (once in ~18–24 hours) and can enter a dormant state.

Simple explanation: Ordinary bacteria are like soldiers in cloth uniforms — easy to hit. TB bacteria wear a thick wax raincoat (mycolic acid) over their uniform. They also march very slowly and sometimes sleep. A drug that works on fast, thin-walled bacteria may bounce off the wax coat.

Example: Penicillin kills ordinary bacteria by breaking their wall while they divide. Against TB it fails — the wax coat keeps it out, and the slow division gives it little to attack.

Key takeaway: Anti-TB drugs are designed to (a) break wax-making (INH, Ethionamide, Delamanid, Pretomanid), (b) break wall-sugar-making (Ethambutol), or (c) hit targets inside the cell (Rifampicin, Streptomycin, fluoroquinolones).

Diagram 1 (draw this): The TB cell wall and where each drug strikes

Draw three concentric layers around a rod-shaped bacterium. Label the outermost waxy layer **"Mycolic acid armour"** — draw arrows from **Isoniazid, Ethionamide, Pretomanid, Delamanid** pointing at it, labelled "stop wax factory". Draw the middle sugar layer labelled **"Arabinogalactan"** — arrow from **Ethambutol**, labelled "stop sugar wall". Draw the inner membrane and inside the cell: a coiled DNA with an arrow from **Rifampicin** ("jam the RNA copier"), a ribosome (two blobs) with arrows from **Streptomycin, Capreomycin, Linezolid** ("jam the protein factory"), and a small battery symbol with an arrow from **Bedaquiline** ("switch off the power plant"). Outside the cell, draw **Pyrazinamide** as a small key entering only in acidic corners, labelled "works in acid, kills sleepers".

1.5 Classification of Antitubercular Drugs

A. By line of therapy (clinical classification)

Line	Drugs	Memory hook
First-line (used first, most effective)	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	**RIPE**
Second-line (used when first-line fails)	Ethionamide, Cycloserine, p-Aminosalicylic acid, Streptomycin, Capreomycin, Levofloxacin, Clofazimine	Older + injectables
Newer / reserve (drug-resistant TB)	Bedaquiline, Delamanid, Pretomanid, Linezolid, Rifabutin*	Modern armour-breakers

*Rifabutin is a rifamycin like Rifampicin but specially used in TB–HIV co-infection.

B. By chemical class (the classification examiners love)

1. **Hydrazides:** Isoniazid (pyridine-4-carbohydrazide)
2. **Thioamides:** Ethionamide (a thioamide analogue of isoniazid)
3. **Pyrazine carboxamides:** Pyrazinamide
4. **Ethylenediamine derivatives:** Ethambutol
5. **Aminosalicylic acids:** p-Aminosalicylic acid (PAS)
6. **Ansamycins (rifamycins):** Rifampicin, Rifabutin — large macrocyclic (ring) antibiotics
7. **Isoxazolidinones:** Cycloserine (a cyclic amino-acid analogue)
8. **Aminoglycosides:** Streptomycin
9. **Cyclic polypeptides:** Capreomycin
10. **Riminophenazines:** Clofazimine
11. **Fluoroquinolones:** Levofloxacin

12 **Diarylquinolines:** Bedaquiline

13 **Oxazolidinones:** Linezolid

14 **Nitroimidazo-oxazoles / nitroimidazo-oxazines:** Pretomanid, Delamanid

1.6 Drug-by-Drug Profiles (all 16 drugs)

1.6.1 ISONIAZID (INH) — synthesis required

- **Chemical class:** Hydrazide — chemically, **pyridine-4-carbohydrazide** (also called isonicotinic acid hydrazide).
- **Structure (describe and draw):** Draw a six-membered aromatic **pyridine ring** (five carbons + one nitrogen). At the carbon directly opposite the ring nitrogen (position 4), attach the group **–CO–NH–NH_2** (a carbonyl joined to a hydrazine –NH–NH_2). That –CO–NH–NH_2 tail is the "business end" of the molecule.
- **Mechanism:** INH is a **prodrug**. Inside the TB bacterium, the bacterial enzyme **KatG** (catalase-peroxidase) activates it. The activated form joins with NAD to make an adduct that blocks **InhA** (enoyl-ACP reductase) — the enzyme that builds **mycolic acids**. No mycolic acid no wax wall bacterium dies. It kills actively dividing bacilli (bactericidal).
- **Uses:** First-line drug for **all active TB** (always in combination); also used alone for **latent (sleeping) TB infection** prevention.
- **Key side effects (for viva):** Liver damage (hepatitis) and **peripheral neuritis** (tingling in hands/feet) — prevented by giving **vitamin B6 (pyridoxine)** along with it.

Simple explanation: INH is a sleeper agent. It enters the bacterium quietly; the bacterium's own guard enzyme (KatG) "wakes it up" by mistake, and the woken agent destroys the wax factory.

Example: A TB patient on INH must also take pyridoxine tablets — otherwise their fingers may tingle and go numb.

> **Key takeaway:** INH = prodrug KatG activates blocks InhA no mycolic acid TB dies. Most important anti-TB drug.

SYNTHESIS OF ISONIAZID (learn as a 3-step story)

Story: Start with a cheap pyridine chemical, oxidise its methyl group to an acid, convert the acid to an ester, then swap the ester group with hydrazine.

Starting material: 4-Methylpyridine (also called **γ-picoline**) — a pyridine ring with a –CH_3 group at position 4.

Step 1 — Oxidation (methyl carboxylic acid): 4-Methylpyridine + **potassium permanganate ($KMnO_4$)**, heat **pyridine-4-carboxylic acid** (isonicotinic acid) + manganese dioxide + water. *What happened:* the –CH_3 group was oxidised up to –COOH.

Step 2 — Esterification (acid ethyl ester): Isonicotinic acid + **ethanol (C_2H_5OH)**, conc. **H_2SO_4**, reflux **ethyl isonicotinate** (ethyl pyridine-4-carboxylate) + H_2O. *What happened:* –COOH became –$COOCH_2CH_3$.

(We make the ester because esters react with hydrazine more easily than acids do.)

Step 3 — Hydrazinolysis (ester hydrazide): Ethyl isonicotinate + **hydrazine hydrate (NH_2–NH_2·H_2O)**, heat **Isoniazid** (pyridine-4-carbohydrazide) + ethanol. *What happened:* the –OCH_2CH_3 group was replaced by –NH–NH_2. This is the drug.

Flowchart (draw this):

γ-Picoline (4-methylpyridine) —[$KMnO_4$, heat] Isonicotinic acid —[EtOH, conc. H_2SO_4, reflux] Ethyl isonicotinate —[NH_2NH_2·H_2O, heat] **ISONIAZID**

1.6.2 RIFAMPICIN

- **Chemical class: Ansamycin (rifamycin)** antibiotic — a macrocyclic lactam.
- **Structure (describe and draw):** Draw a large ring (macrocycle, ~23 atoms) with a flat **naphthoquinone** unit (two fused six-membered rings with two C=O groups) on one side — this flat part is the "chromophore". A long aliphatic chain (the **ansa bridge**, Latin for "handle") loops from one end of the naphthoquinone to the other, like a basket handle. Hanging off the structure is a side chain containing a **4-methylpiperazine** ring joined through a –CH=N– (imine) link. The big ring is what grips the bacterial enzyme.
- **Mechanism:** Binds to bacterial **DNA-dependent RNA polymerase** (the β-subunit) and jams it — the bacterium cannot copy DNA into RNA, so it cannot make proteins. Bactericidal, and one of the few drugs that kills **dormant** bacilli too.
- **Uses:** First-line anti-TB (the backbone of short-course therapy); leprosy; prevention of meningococcal and *H. influenzae* meningitis in contacts; prosthetic-joint infections (in combination).
- **Key side effects:** Orange-red colouration of urine, sweat, tears (harmless but warn the patient!); liver damage; strong inducer of liver enzymes reduces effect of many drugs including oral contraceptives and antiretrovirals.

Simple explanation: If the bacterium is a factory, Rifampicin jams the photocopier that copies the master plan (DNARNA). No copies factory shuts down.

Key takeaway: Rifampicin = jams RNA polymerase; kills sleepers too; turns body fluids orange.

1.6.3 PYRAZINAMIDE

- **Chemical class: Pyrazine carboxamide** — chemically **pyrazine-2-carboxamide**.
- **Structure (describe and draw):** Draw a six-membered aromatic ring with **two nitrogens** at positions 1 and 4 (this is **pyrazine**). At position 2 (next to one nitrogen), attach **–$CONH_2$** (carboxamide). A very small, simple molecule — small size helps it enter the bacterium.
- **Mechanism:** A **prodrug** — the bacterial enzyme **pyrazinamidase (PncA)** converts it to **pyrazinoic acid**, the active form. It works best in **acidic** surroundings (inside inflamed lung lesions) and kills **dormant** bacilli by disturbing the bacterium's membrane energy.
- **Uses:** First-line anti-TB, given only in the first 2 months (intensive phase) to kill dormant bacilli fast and shorten total treatment.

- **Key side effects:** Liver damage, raised uric acid **gout-like joint pains**.

Simple explanation: Pyrazinamide is a special commando that only fights well in acidic mud (inflamed tissue) — exactly where sleeping TB bacteria hide.

Key takeaway: Pyrazinamide = prodrug pyrazinoic acid; kills dormant TB in acidic lesions; used in the first 2 months.

1.6.4 ETHAMBUTOL

- **Chemical class: Ethylenediamine derivative** — chemically (2S,2′S)-2,2′-(ethylenediimino)dibutan-1-ol.
- **Structure (describe and draw):** Draw a central **–NH–CH_2–CH_2–NH–** (ethylenediamine) bridge. On each nitrogen hangs an identical arm: **–CH(CH_2CH_3)–CH_2OH** (a butanol fragment with an ethyl branch). The molecule is symmetric — two mirror-image halves. Only the **(S,S)** form is the drug; the (R,R) form is inactive/toxic.
- **Mechanism:** Blocks **arabinosyl transferase** enzymes — stops the bacterium from building **arabinogalactan**, the sugar layer of its wall. Bacteriostatic (stops growth; does not kill directly).
- **Uses:** First-line anti-TB — its main job is to **protect the other drugs from resistance** while diagnosis is confirmed.
- **Key side effects: Optic neuritis** — damage to the optic nerve blurred vision, loss of red-green colour vision. Patients must have their **vision tested** before and during treatment.

Simple explanation: Ethambutol stops the bacterium from laying the sugar-bricks of its wall. It is the "bodyguard" drug — it guards INH and Rifampicin against resistance.

Key takeaway: Ethambutol = blocks wall-sugar building; bacteriostatic; watch the eyes (optic neuritis).

1.6.5 ETHIONAMIDE

- **Chemical class: Thioamide** — chemically **2-ethylpyridine-4-carbothioamide**. It is the thioamide cousin of isoniazid.
- **Structure (describe and draw):** Draw a **pyridine ring**. At position 4 attach **–C(=S)–NH_2** (a thioamide: like an amide but with sulphur instead of oxygen). At position 2 attach an **ethyl group (–CH_2CH_3)**. Compare with INH: same pyridine ring, but –C(=S)NH_2 instead of –CO–NH–NH_2, plus the ethyl group.
- **Mechanism:** Also a **prodrug**, but activated by a different bacterial enzyme, **EthA** (a monooxygenase), not KatG. The activated form blocks the **same target as INH — InhA** stops mycolic acid synthesis. Because activation is different, TB resistant to INH (KatG mutants) is usually still killed by ethionamide — **no cross-resistance**.
- **Uses:** Second-line drug for **MDR-TB** (in combination).
- **Key side effects:** Severe nausea/vomiting, metallic taste, liver damage, thyroid problems (hypothyroidism).

Simple explanation: Ethionamide and INH are two keys for the same lock (InhA), but they enter through different doors. If the bacterium changes the INH door (KatG), the ethionamide door (EthA) still works.

Key takeaway: Ethionamide = INH's cousin; same target (InhA), different activator (EthA) works in INH-resistant TB.

1.6.6 p-AMINOSALICYLIC ACID (PAS) — synthesis required

- **Chemical class: Aminosalicylic acid** — chemically **4-amino-2-hydroxybenzoic acid**.
- **Structure (describe and draw):** Draw a **benzene ring**. At position 1 attach **–COOH**. At position 2 (ortho to –COOH) attach **–OH**. At position 4 (para to –COOH) attach **–NH_2**. So it looks like salicylic acid (2-hydroxybenzoic acid) with an amino group added para to the acid.
- **Mechanism:** It resembles **PABA** (p-aminobenzoic acid), the bacterium's raw material for making **folic acid**. PAS tricks the folate-making enzymes (dihydropteroate synthase and others) — the bacterium makes faulty folate and cannot make DNA properly. Bacteriostatic.
- **Uses:** Second-line drug for **MDR-TB** (used less today because of bulky doses and gut side effects).
- **Key side effects:** Nausea, vomiting, diarrhoea (needs large doses — up to 8–12 g/day); thyroid enlargement (goitre) on long use.

Simple explanation: PAS is a fake building block. The bacterium picks it up thinking it is PABA, builds a crooked folate molecule, and its DNA factory stalls.

Key takeaway: PAS = fake PABA faulty folate TB cannot grow. Old but still a second-line option.

SYNTHESIS OF p-AMINOSALICYLIC ACID (Kolbe–Schmitt carboxylation)

Story: Take m-aminophenol, convert it to its potassium salt, then force carbon dioxide into the ring under heat and pressure — the CO_2 becomes the –COOH group. Finally add acid to free the product.

Starting material: 3-Aminophenol (m-aminophenol) — a benzene ring with –OH at position 1 and –NH_2 at position 3.

Step 1 — Salt formation (phenol phenoxide): 3-Aminophenol + **potassium hydroxide (KOH)** **potassium 3-aminophenoxide** + H_2O. *What happened:* the phenolic –OH lost its H^+ to KOH, becoming $–O^-K^+$. (The salt is far more reactive toward CO_2 than the free phenol.)

Step 2 — Kolbe–Schmitt carboxylation (CO_2 enters the ring): Potassium 3-aminophenoxide + **carbon dioxide (CO_2)**, heat (~130–180 °C) **under pressure potassium 4-amino-2-hydroxybenzoate**. *What happened:* CO_2 added to the ring at the position **ortho to the $–O^-$ group and para to the –NH_2 group** — this gives mainly the 4-amino-2-hydroxy isomer (a small amount of the isomeric 2-amino-4-hydroxybenzoate also forms and is removed by crystallisation).

Step 3 — Acidification (salt free acid): Potassium 4-amino-2-hydroxybenzoate + **dilute HCl** **p-Aminosalicylic acid (4-amino-2-hydroxybenzoic acid)** + KCl. Purified by crystallisation. *What happened:* H^+ replaced K^+, giving the free –COOH drug.

Flowchart (draw this):

3-Aminophenol —[KOH] Potassium 3-aminophenoxide —[CO_2, heat, pressure] Potassium 4-amino-2-hydroxybenzoate —[dil. HCl, crystallise] **p-AMINOSALICYLIC ACID**

1.6.7 CYCLOSERINE

- **Chemical class: Isoxazolidinone** — chemically **4-amino-3-isoxazolidinone**; a cyclic analogue of the amino acid **D-alanine**.
- **Structure (describe and draw):** Draw a small **five-membered ring** containing one nitrogen and one oxygen next to each other (N–O in the ring = **isoxazolidine**). At position 3 put a **C=O** (ketone), at position 4 put **–NH_2**. The drug is the **D-isomer** — it is shaped like D-alanine bent into a ring.
- **Mechanism:** Mimics D-alanine and blocks two enzymes — **alanine racemase** and **D-Ala–D-Ala ligase** — that join D-alanine pairs for building **peptidoglycan** (the inner wall layer). Wall building stops.
- **Uses:** Second-line drug for **MDR-TB**.
- **Key side effects: CNS effects** — fits of depression, confusion, seizures, psychosis (because it also interferes with brain chemistry). Doses are kept low and patients are watched for mood changes.

Simple explanation: The bacterium needs D-alanine bricks to build its inner wall. Cycloserine is a fake brick — the wall-builders grab it and the wall collapses.

Key takeaway: Cycloserine = fake D-alanine no peptidoglycan; watch the brain (psychosis/seizures).

1.6.8 STREPTOMYCIN

- **Chemical class: Aminoglycoside** — the first aminoglycoside antibiotic ever discovered (from *Streptomyces griseus*).
- **Structure (describe and draw):** Draw **three sugar-like units joined by glycosidic (oxygen) links**: (1) **streptidine** — a six-membered ring (cyclitol) carrying two guanidine groups (–NH–C(=NH)–NH_2); (2) **streptose** — a branched five-carbon sugar; (3) **N-methyl-L-glucosamine** — an amino sugar. The many –NH_2/–OH groups make it very water-soluble and positively charged.
- **Mechanism:** Binds to the **30S subunit of the bacterial ribosome** (the protein factory) the bacterium misreads its mRNA and makes garbage proteins dies. Bactericidal. Because it is highly polar, it is **not absorbed orally** — given by **intramuscular injection**.
- **Uses:** TB (second-line/injectable, now rarely); **plague, tularaemia** (drug of choice); endocarditis combinations.
- **Key side effects: Ototoxicity** (damage to the ear hearing loss, vertigo) and **nephrotoxicity** (kidney damage) — the classic aminoglycoside toxicities.

Simple explanation: Streptomycin scrambles the bacterium's protein recipe book — the ribosome reads the wrong words and the bacterium builds broken proteins.

Key takeaway: Streptomycin = 30S ribosome jammer; injectable only; watch ears and kidneys.

1.6.9 CAPREOMYCIN

- **Chemical class: Cyclic polypeptide** antibiotic (from *Streptomyces capreolus*) — a mixture of closely related peptides (IA, IB, IIA, IIB).
- **Structure (describe and draw):** Draw a large **ring made of amino-acid units joined head-to-tail** (peptide bonds). Mark two unusual building blocks: **capreomycidine** (a cyclic guanidine-containing amino acid) and **diaminopropionic acid** residues. Unlike streptomycin it has no sugars — it is all amino acids in a loop.
- **Mechanism:** Binds to the bacterial **70S ribosome at the junction of the 30S and 50S subunits** freezes protein synthesis. Given by **injection** (not oral).
- **Uses:** Second-line **injectable** drug for **MDR-TB**.
- **Key side effects:** Kidney damage, hearing damage, and **low potassium/magnesium/calcium** in blood (electrolyte wasting).

Simple explanation: Capreomycin is a peptide lasso that ties the two halves of the ribosome together so the protein factory cannot move.

> **Key takeaway:** Capreomycin = cyclic peptide; injectable MDR-TB drug; watch kidneys and electrolytes.

1.6.10 RIFABUTIN

- **Chemical class: Ansamycin (rifamycin)** — a semi-synthetic derivative of rifamycin S, cousin of rifampicin.
- **Structure (describe and draw):** Draw the **same ansamycin core as rifampicin** — the naphthoquinone chromophore with the long ansa bridge looping across it. The difference is the side chain: instead of rifampicin's methylpiperazine-imine arm, rifabutin carries a **spiro-fused substituted piperidine ring** (a ring joined to the core at a single shared atom, like two rings touching at one point) bearing an isobutyl group. It is more fat-soluble (lipophilic) than rifampicin.
- **Mechanism:** Same as rifampicin — binds bacterial **RNA polymerase**, blocks RNA synthesis. Bactericidal.
- **Uses:** TB in **HIV-positive patients** — because it induces liver enzymes **much less** than rifampicin, it disturbs antiretroviral drugs less. Also used against *Mycobacterium avium* complex (MAC) in AIDS patients.
- **Key side effects:** Orange body fluids (like rifampicin), low white cells, **uveitis** (eye inflammation), joint pains.

Simple explanation: Rifabutin is rifampicin's gentler brother — same punch on TB, but it does not bully the liver enzymes, so HIV medicines keep working alongside it.

> **Key takeaway:** Rifabutin = rifamycin for TB–HIV co-infection; less enzyme induction; watch the eyes (uveitis).

1.6.11 CLOFAZIMINE

- **Chemical class: Riminophenazine** — a phenazine dye derivative.
- **Structure (describe and draw):** Draw **three fused six-membered rings in a row** with two nitrogens in the central ring (**phenazine** core). On one outer ring attach a **chlorophenyl** group and an **isopropylimino (=N–CH(CH_3)$_2$)** group; on the other outer ring attach another substituted phenyl ring. The extended conjugated system makes it an intense **red-orange dye** — it stains skin.
- **Mechanism:** Binds to mycobacterial **DNA** (especially guanine bases) and also generates toxic **reactive oxygen species** inside the bacterium; has anti-inflammatory action too.
- **Uses: Leprosy** (with dapsone + rifampicin — the standard MDT); **MDR-TB** regimens.
- **Key side effects: Reddish-brown discolouration of skin**, sweat, tears and even internal organs (reversible but very slow to fade — patients must be counselled); dry skin, constipation.

Simple explanation: Clofazimine is a dye that stains the bacterium's DNA and poisons it with bleach-like oxygen chemicals — but it also dyes the patient's skin red-brown for months.

> **Key takeaway:** Clofazimine = red dye drug; leprosy + MDR-TB; warns patient about skin colour change.

1.6.12 LEVOFLOXACIN

- **Chemical class: Fluoroquinolone** — the pure **(S)-enantiomer** of ofloxacin.
- **Structure (describe and draw):** Draw the **quinolone core**: a fused benzene + pyridone ring with a **C=O at position 4** and **–COOH at position 3**. Add **fluorine (F) at C6**, a **piperazine ring at C7**, and a fused third ring — an **oxazine bridge** joining N1 to C8 (this makes it tricyclic). Mark the chiral centre: the **S configuration** is levofloxacin (twice as active as the R form).
- **Mechanism:** Blocks bacterial **DNA gyrase** and **topoisomerase IV** — the enzymes that unwind and rewind DNA. Without them the bacterium cannot copy its DNA. Bactericidal.
- **Uses: MDR-TB** (core second-line drug); pneumonia, urinary infections, sinusitis.
- **Key side effects:** Nausea, headache, dizziness; rare but serious — **tendon rupture** (Achilles tendon), CNS excitation; avoid in children/pregnancy if possible (cartilage effects).

Simple explanation: Bacterial DNA is a twisted rope. Levofloxacin jams the two machines that untwist and re-twist the rope — the rope snaps and the bacterium dies.

> **Key takeaway:** Levofloxacin = DNA gyrase/topoisomerase blocker; key MDR-TB drug; watch tendons.

1.6.13 BEDAQUILINE

- **Chemical class: Diarylquinoline** — the first drug in this brand-new class, approved for MDR-TB.
- **Structure (describe and draw):** Draw a **quinoline ring** (benzene fused to pyridine) carrying **–Br at C6** and **–OCH_3 at C2**. At C3 attach a chain: **–CH(OH)–C(OH)**? No — draw: C3 of quinoline joined to a carbon bearing **–OH**, which is joined to **–CH_2–CH_2–N(CH_3)$_2$** (dimethylamino tail), and the same carbon carries **two aromatic rings: one phenyl and one naphthyl (two fused rings)**. The two bulky aryl groups ("diaryl") give the class its name. It has two chiral centres (1R,2S active form).

- **Mechanism:** Blocks mycobacterial **ATP synthase** (the c-subunit rotor) — the bacterium's power plant. No ATP the cell starves of energy and dies, including **dormant** bacilli. First anti-TB drug with this target.
- **Uses: MDR-TB and XDR-TB** — always in combination (e.g., with pretomanid + linezolid as the BPaL regimen).
- **Key side effects: QT prolongation** on ECG (heart rhythm risk — ECG monitoring needed); nausea, joint pain; very long half-life (stays in the body for months).

Simple explanation: Every cell runs on ATP (energy coins). Bedaquiline switches off the bacterium's coin-minting machine. Even sleeping bacteria need a trickle of energy — so they die too.

Key takeaway: Bedaquiline = ATP synthase blocker; breakthrough MDR-TB drug; monitor the heart (QT).

1.6.14 LINEZOLID

- **Chemical class: Oxazolidinone** — the first of its class.
- **Structure (describe and draw):** Draw a **five-membered oxazolidin-2-one ring** (contains one O, one N, and a C=O). At the ring nitrogen attach a **p-fluorophenyl ring** which carries a **morpholine ring** (six-membered ring with O and N) at its para position. At C5 of the oxazolidinone put a **–CH_2–NH–CO–CH_3 (acetamidomethyl)** side chain in the **S** configuration.
- **Mechanism:** Binds to the **50S ribosomal subunit** (23S rRNA) blocks the very first step of protein synthesis (initiation). Bacteriostatic against most, bactericidal against some.
- **Uses: MDR/XDR-TB**; MRSA and VRE infections (its original uses).
- **Key side effects: Bone-marrow suppression** (low platelets/anaemia on long use), **peripheral/optic neuropathy**, lactic acidosis — long TB courses need blood-count monitoring.

Simple explanation: If the ribosome is a factory assembly line, linezolid locks the factory gate before the first worker enters — nothing gets built.

Key takeaway: Linezolid = 50S initiation blocker; powerful MDR-TB drug; monitor blood counts and nerves.

1.6.15 PRETOMANID

- **Chemical class: Nitroimidazo-oxazine** (a bicyclic nitroimidazole).
- **Structure (describe and draw):** Draw a **fused bicyclic core**: a **2-nitroimidazole** ring (five-membered, two Ns, –NO_2 at C2) fused to a six-membered **oxazine** ring (containing O). From the oxazine carbon hangs a side chain: **–O–CH_2–(p-trifluoromethoxyphenyl)** — a benzyl ether ending in **–OCF_3**. The active form is the **(6S)** enantiomer.
- **Mechanism:** A **prodrug** activated by the bacterial enzyme **Ddn** (deazaflavin-dependent nitroreductase). Inside the cell it releases **nitric oxide (NO)** — a poison — and also blocks **mycolic acid** synthesis. So it kills **growing** bacilli (wall attack) and **dormant** bacilli (NO respiratory poisoning).

- **Uses: XDR-TB** and treatment-intolerant MDR-TB — as part of the **BPaL regimen** (Bedaquiline + Pretomanid + Linezolid).
- **Key side effects:** Nausea, headache, raised liver enzymes; testicular toxicity seen in animals (monitored in humans).

Simple explanation: Pretomanid is a Trojan horse: the bacterium's own enzyme (Ddn) opens it, releasing a burst of toxic nitric-oxide gas inside, while also smashing the wax factory.

Key takeaway: Pretomanid = Ddn-activated prodrug; NO release + mycolic-acid block; kills sleepers; BPaL regimen.

1.6.16 DELAMANID

- **Chemical class: Nitro-dihydroimidazooxazole** (bicyclic nitroimidazole, cousin of pretomanid).
- **Structure (describe and draw):** Draw the **bicyclic nitroimidazo-oxazole core** (nitroimidazole fused to a five-membered oxazole ring, partially saturated). From it extends a long side chain: **–O–CH_2–phenyl–N(piperidine)–phenyl–O–CF_3** — i.e., a phenoxy-methyl link, then a phenyl ring, then a **piperidine** ring, then another phenyl ending in **–OCF_3 (trifluoromethoxy)**. The **(2R)** enantiomer is the drug.
- **Mechanism:** Also a **prodrug** activated by **Ddn** (same enzyme as pretomanid) blocks synthesis of **methoxy- and keto-mycolic acids** no wax wall. Active against drug-resistant strains.
- **Uses: MDR-TB** in adults and children (one of the few newer drugs with paediatric data).
- **Key side effects: QT prolongation** (like bedaquiline — ECG monitoring), nausea, dizziness.

Simple explanation: Delamanid is pretomanid's chemical cousin — same activation key (Ddn), same result (wax factory destroyed), but a different shape and usable in children.

Key takeaway: Delamanid = Ddn-activated nitroimidazole; blocks mycolic acids; MDR-TB including children; watch QT.

1.7 Master Mechanism Table (learn this for exams)

Drug	Target / Enzyme	Effect on wall or cell	Prodrug? (activator)
Isoniazid	InhA (enoyl-ACP reductase)	Stops mycolic acid (wax)	Yes (KatG)
Ethionamide	InhA (same)	Stops mycolic acid (wax)	Yes (EthA)
Pyrazinamide	Membrane energy (pyrazinoic acid)	Kills dormant bacilli in acid	Yes (PncA)
Ethambutol	Arabinosyl transferase	Stops arabinogalactan (sugar wall)	No
PAS	Folate enzymes (PABA mimic)	Faulty folate no DNA	No
Rifampicin / Rifabutin	RNA polymerase (β-subunit)	No RNA no proteins	No

Drug	Target / Enzyme	Effect on wall or cell	Prodrug? (activator)
Cycloserine	Alanine racemase + D-Ala–D-Ala ligase	No peptidoglycan (inner wall)	No
Streptomycin	30S ribosome	Garbage proteins	No
Capreomycin	70S ribosome (30S–50S junction)	Protein synthesis frozen	No
Levofloxacin	DNA gyrase + topoisomerase IV	DNA cannot unwind	No
Clofazimine	DNA binding + ROS generation	DNA damage + oxidation	No
Bedaquiline	ATP synthase (c-subunit)	No energy (ATP)	No
Linezolid	50S ribosome (23S rRNA)	Protein synthesis never starts	No
Pretomanid	Ddn activation NO + mycolic-acid block	Kills growing + dormant	Yes (Ddn)
Delamanid	Ddn activation mycolic-acid block	Stops wax wall	Yes (Ddn)

1.8 Short SAR Notes (structure–activity relationship)

Isoniazid SAR (why the structure must stay as it is):

1 The **–CO–NH–NH_2 (hydrazide)** group is essential — replace it with a simple amide (–$CONH_2$) and activity collapses.

2 The **pyridine nitrogen** is important for activity; moving the side chain from position 4 to 2 or 3 reduces activity.

3 The molecule must be small enough to enter the bacterium and be recognised by KatG.

Ethambutol SAR: the **(S,S)** configuration is the active form; the (R,R) form causes optic neuritis without good activity — stereochemistry is everything here.

Rifamycin SAR: the large **ansa macrocycle** must stay intact to grip RNA polymerase; the side chain at C3 can be changed (rifampicin vs rifabutin) to tune pharmacokinetics without losing the grip.

Key takeaway: Small changes in shape or position can destroy activity — the drug must fit its target like a key in a lock.

1.9 Flowchart: How TB Treatment Is Chosen (draw this)

Start: "Patient diagnosed with TB" diamond: "Drug-susceptibility test" branch 1 "Sensitive to INH + Rifampicin" box "First-line: 2 months INH+RIF+PZA+EMB, then 4 months INH+RIF (RIPE)" "Cure". Branch 2 "Resistant to INH + Rifampicin (MDR-TB)" box "Second-line/newer: Bedaquiline + Levofloxacin + Linezolid + Clofazimine ± Delamanid/Pretomanid (no INH/RIF)" "Cure (longer course, monitored)". Note under branch 2: "Never add a single drug to a failing regimen — always change at least 2–3 drugs together."

1.10 Infographic Concept Box: "The TB Fort Under Siege" (design brief for the artist)

A fort (the lung granuloma) with wax-brick walls labelled "mycolic acid". Four catapults labelled INH, Ethionamide, Pretomanid, Delamanid smash the wax bricks. A ladder labelled Ethambutol removes sugar-bricks from the middle wall. Inside the fort: a scribe (RNA polymerase) gagged by Rifampicin; a kitchen (ribosome) with Streptomycin/Capreomycin/Linezolid throwing the cooks out; a power generator (ATP synthase) switched off by Bedaquiline; sleeping soldiers (dormant bacilli) woken and finished by Pyrazinamide + Pretomanid in an acidic moat. Caption: "No single hero wins — the fort falls only to a combined army."

1.11 Worked Examples (putting it together)

Example 1 — Why four drugs? A patient takes only Isoniazid. In their lungs, 1 in a million bacteria is naturally INH-resistant (KatG mutant). INH kills the rest, the mutant survives and multiplies fully INH-resistant TB in weeks. With four drugs, the chance that one bacterium resists all four at once is practically zero. **Takeaway: combination therapy prevents resistance.**

Example 2 — The orange surprise. A patient on Rifampicin panics: "My urine is red — I am passing blood!" The pharmacist explains: rifampicin colours urine, sweat, and tears orange-red; it is harmless and expected. **Takeaway: counselling prevents panic and dropouts.**

Example 3 — The eye test. Before starting Ethambutol, the doctor checks the patient's vision and colour vision, and repeats it monthly. If the patient reports blurred vision, ethambutol is stopped. **Takeaway: ethambutol = monitor eyes.**

Example 4 — HIV co-infection. A TB patient is also on antiretroviral therapy. Rifampicin would destroy the HIV drugs (enzyme induction), so the doctor chooses **Rifabutin** instead. **Takeaway: rifabutin = the rifamycin for HIV co-infection.**

1.12 Analogies That Stick

1. **Mycolic-acid wall = wax raincoat.** INH/Ethionamide/Delamanid/Pretomanid = stopping the raincoat factory.
2. **KatG activation = own goal.** The bacterium's guard dog bites the postman who turns out to be a spy (INH).
3. **Rifampicin = jamming the photocopier** (RNA polymerase) in the bacterial office.
4. **Chloroquine-style ion trapping (preview of Chapter 2) = fish trap:** easy to swim in, impossible to swim out.
5. **Bedaquiline = switching off the power plant** (ATP synthase) of a city — even sleeping citizens freeze.
6. **Four-drug therapy = attacking a fort from four sides** — no escape route for mutants.
7. **Prodrug = sleeper agent** — harmless until the enemy camp itself wakes it.

1.13 Pharmacy Relevance (why a pharmacist must know this)

- **Counselling is treatment:** TB is cured only if the patient completes 6+ months of daily tablets. The pharmacist explains orange urine (rifampicin), red-brown skin (clofazimine), vision checks (ethambutol), vitamin B6 with INH, and why **doses must never be skipped**.
- **DOTS/NTEP supply:** Pharmacists in government and private pharmacies dispense NTEP-supplied fixed-dose combinations (FDCs) and record them on the **Nikshay portal** — every TB patient must be notified by law.
- **Drug interactions:** Rifampicin reduces the effect of oral contraceptives, antiretrovirals, warfarin, and many others — the pharmacist must warn and suggest alternatives.
- **MDR-TB monitoring:** Bedaquiline and delamanid need **ECG (QT) monitoring**; linezolid needs **blood counts**; injectables need kidney/hearing checks — the pharmacist schedules and tracks these.
- **No single-drug sale:** Selling one anti-TB drug alone (e.g., only INH) breeds resistance — pharmacists must dispense complete regimens and counsel against stopping early when the patient "feels better" after 2 months.

1.14 India Context

- **Burden:** India carries the world's largest TB burden — roughly a quarter to a third of all TB cases on the planet occur here. TB remains one of India's biggest infectious killers.
- **NTEP:** The **National TB Elimination Programme** (earlier called RNTCP) runs TB control in India — free diagnosis, free drugs, and a national goal of TB elimination.
- **DOTS and daily FDCs:** Treatment moved from thrice-weekly to **daily fixed-dose combinations** under direct observation/support, improving cure rates.
- **Nikshay:** India's online portal where **every** TB case (government or private) must be notified — pharmacists and doctors both play a role.
- **Drug-resistant TB:** India has a large MDR-TB load; newer drugs — **bedaquiline, delamanid, pretomanid** — are now part of national MDR/XDR regimens (including the short, all-oral **BPaL/BPaLM** regimen), replacing painful long injectable courses.
- **Pharmacist's role:** Private-sector TB patients often first reach a local pharmacy — recognising a chronic cough with weight loss and referring for sputum testing saves lives.

1.15 Key Points (read the night before the exam)

1 First-line = **RIPE**: Rifampicin, Isoniazid, Pyrazinamide, Ethambutol.

2 INH: prodrug **KatG** blocks **InhA** no mycolic acid. Give **pyridoxine**.

3 Rifampicin: blocks **RNA polymerase**; kills dormant bacilli; **orange fluids**; enzyme inducer.

4 Pyrazinamide: prodrug **pyrazinoic acid** (PncA); works in **acid**; kills dormant bacilli; first 2 months only.

5 Ethambutol: blocks **arabinogalactan**; bacteriostatic; **optic neuritis — check vision**.

6 Ethionamide: same target as INH (InhA) but activated by **EthA** works in INH resistance.

7 PAS: **fake PABA** faulty folate; made by **Kolbe–Schmitt carboxylation** of m-aminophenol.

8 INH synthesis: γ-picoline ($KMnO_4$) isonicotinic acid ($EtOH/H_2SO_4$) ethyl ester (NH_2NH_2) INH.

9 Streptomycin: **30S** ribosome; injectable; oto- + nephrotoxic.

10 Capreomycin: cyclic peptide; **70S** ribosome; injectable MDR-TB drug.

11 Cycloserine: **fake D-alanine** no peptidoglycan; CNS side effects.

12 Rifabutin: rifamycin for **TB–HIV** (less enzyme induction); uveitis.

13 Clofazimine: red dye; leprosy + MDR-TB; **skin discolouration**.

14 Levofloxacin: **DNA gyrase/topoisomerase IV** blocker; MDR-TB; tendon risk.

15 Bedaquiline: **ATP synthase** blocker; MDR/XDR; **QT prolongation**.

16 Linezolid: **50S** initiation blocker; monitor **blood counts**.

17 Pretomanid/Delamanid: **Ddn-activated** nitroimidazoles; block mycolic acids; kill dormant bacilli; **BPaL** regimen.

18 Never treat TB with a single drug — always combinations.

1.16 Common Confusions (cleared)

Confusion	Truth
INH vs Ethionamide — "same drug?"	Same **target** (InhA), different **activator** (KatG vs EthA) no cross-resistance.
PAS vs Mesalazine (5-ASA)	PAS = **4-amino**-2-hydroxybenzoic acid (anti-TB); mesalazine = **5-amino**-2-hydroxybenzoic acid (ulcerative colitis). Position matters!
Rifampicin vs Rifabutin	Same family, same target; rifabutin = **less enzyme induction** chosen in HIV co-infection.
Pretomanid vs Delamanid	Both nitroimidazoles activated by **Ddn**; pretomanid also releases **NO** and is part of BPaL; delamanid has paediatric use.
Streptomycin vs Capreomycin	Both injectable, both hit ribosomes — but streptomycin is an **aminoglycoside (30S)**, capreomycin a **cyclic peptide (70S)**.
"Bactericidal is always better"	Not for TB — ethambutol (static) is first-line because it **guards against resistance**; pyrazinamide's value is killing **sleepers**.
Orange urine on rifampicin = blood?	No — harmless drug colour. Always counsel.

1.17 Common Mistakes (don't make these)

1 Writing that INH directly blocks InhA — **it must first be activated by KatG** (it is a prodrug).

2 Calling ethambutol bactericidal — it is **bacteriostatic**.

3 Forgetting the **(S,S)** stereochemistry of ethambutol.

4 Mixing up **KatG** (activates INH), **EthA** (activates ethionamide), **PncA** (activates pyrazinamide), **Ddn** (activates pretomanid/delamanid) — make a 4-row table and memorise it.

5 Drawing PAS with the $–NH_2$ at the wrong position — it is **para to –COOH** (position 4), –OH **ortho** (position 2).

6 Saying rifampicin blocks DNA polymerase — it blocks **RNA polymerase**.

7 Recommending a single drug for TB, or stopping treatment when symptoms improve — the classic resistance-breeding error.

8 Confusing **quinoline** (Chapter 2, antimalarial) with **quinolone** (levofloxacin, antibacterial) — different rings, different chapters!

1.18 Mnemonics

- **First-line: "RIPE"** — Rifampicin, Isoniazid, Pyrazinamide, Ethambutol (TB therapy is "ripe" for cure in 6 months).
- **INH activation chain: "KatG wakes INH, INH hugs NAD, together they handcuff InhA."**
- **Prodrug activators: "KEPT-D"** — KatG (INH), EthA (Ethionamide), PncA (Pyrazinamide), Ddn (Delamanid/Pretomanid): *"The prodrugs are KEPT Dormant until activated."*
- **Newer MDR-TB drugs: "Be-Da-Pre-Li"** — Bedaquiline, Delamanid, Pretomanid, Linezolid: *"Be Daring, Prepare to Live."*
- **Ethambutol eye effect: "E-thambutol E-yes"** — check the EYES.
- **Rifampicin colours: "Rifampicin paints you Red-Orange"** — urine, sweat, tears.
- **Clofazimine: "Clofazimine Colours the skin like a Crayon."**

1.19 Exam Summary (one page, in words)

TB is caused by waxy, slow-growing *M. tuberculosis*. First-line therapy (RIPE) cures drug-sensitive TB in 6 months: INH (prodrug, KatGInhA, stops mycolic acid; +pyridoxine), Rifampicin (RNA polymerase; kills dormant; orange fluids; enzyme inducer), Pyrazinamide (prodrugpyrazinoic acid; acidic lesions; dormant killers; 2 months), Ethambutol (arabinogalactan; static; optic neuritis). Second-line for MDR-TB: ethionamide (InhA via EthA — no cross-resistance with INH), PAS (fake PABAfolate block; Kolbe–Schmitt synthesis), cycloserine (fake D-alanine; CNS toxicity), streptomycin (30S; injectable; oto/nephrotoxic), capreomycin (cyclic peptide; 70S; injectable), levofloxacin (DNA gyrase; tendon risk), clofazimine (DNA-binding dye; leprosy+MDR-TB; skin staining), rifabutin (rifamycin for HIV co-infection). Newer reserve drugs: bedaquiline (ATP synthase; QT), linezolid (50S; blood counts), pretomanid + delamanid (Ddn-activated nitroimidazoles; mycolic-acid block; BPaL regimen). Syntheses: INH = γ-picoline ($KMnO_4$) isonicotinic acid (EtOH/H^+) ethyl ester (NH_2NH_2) INH; PAS = m-aminophenol (KOH) phenoxide (CO_2, heat, pressure) benzoate salt (HCl) PAS. Always use combinations; India's NTEP provides free treatment with Nikshay notification.

1.20 One-Minute Revision (say it aloud in 60 seconds)

"RIPE cures TB: INH is a prodrug woken by KatG to block InhA and stop wax; rifampicin jams RNA polymerase and paints fluids orange; pyrazinamide wakes in acid to kill sleepers; ethambutol guards the wall-sugar but hurts eyes. MDR-TB needs second-line and newer drugs: ethionamide shares INH's target but not its activator; bedaquiline switches off ATP; pretomanid and delamanid are Ddn-activated wax-breakers in the BPaL regimen. INH is made from gamma-picoline by oxidation, esterification and hydrazine; PAS is made by Kolbe-Schmitt carboxylation of m-aminophenol. Never one drug alone — always a combination, always the full course."

1.21 Exam Questions — Chapter 1

A. Short-answer questions (2–5 marks)

1 Why is tuberculosis always treated with a combination of drugs? (2 marks)

2 Name the four first-line antitubercular drugs. (2 marks)

3 Which enzyme activates isoniazid inside the mycobacterium, and what is its target? (2 marks)

4 Why is pyridoxine given with isoniazid? (2 marks)

5 A patient on rifampicin reports red urine. What will you tell them? (2 marks)

6 Why is ethambutol's stereochemistry important? (3 marks)

7 Differentiate between pretomanid and delamanid. (3 marks)

8 Why is rifabutin preferred over rifampicin in TB–HIV co-infection? (3 marks)

9 Write the chemical name (IUPAC-style) of isoniazid and PAS. (2 marks)

10 What is the BPaL regimen? (2 marks)

B. Long-answer questions (10 marks)

1 Classify antitubercular drugs by chemical structure with one example each. Describe the mechanism of action of any four drugs, one from each line of therapy.

2 Write the complete synthesis of **isoniazid** starting from γ-picoline, giving reagents, conditions, and the structure of every intermediate. Explain its mechanism of action with a labelled flowchart.

3 Write the complete synthesis of **p-aminosalicylic acid** by the Kolbe–Schmitt reaction. Explain why the carboxyl group enters the observed position.

4 Discuss the newer drugs for MDR/XDR-TB (bedaquiline, delamanid, pretomanid, linezolid): chemical class, structure features, mechanism, and key toxicities.

5 A 30-year-old man is diagnosed with sputum-positive pulmonary TB. Outline his treatment under the NTEP, justifying the choice and duration of each drug, and list the counselling points a pharmacist must give.

C. MCQs (with answer key)

Q1. Isoniazid is activated inside *M. tuberculosis* by: a) EthA b) KatG c) PncA d) Ddn **Answer: b) KatG**

Q2. The target of activated isoniazid is: a) RNA polymerase b) DNA gyrase c) InhA (enoyl-ACP reductase) d) ATP synthase **Answer: c) InhA (enoyl-ACP reductase)**

Q3. Which drug specifically requires vision/colour-vision monitoring? a) Pyrazinamide b) Ethambutol c) Cycloserine d) Clofazimine **Answer: b) Ethambutol**

Q4. Pyrazinamide is most active against bacilli in: a) Alkaline urine b) Acidic inflamed lesions c) Bloodstream d) Bone **Answer: b) Acidic inflamed lesions**

Q5. Bedaquiline acts by inhibiting: a) Mycolic acid synthesis b) RNA polymerase c) ATP synthase d) Folate synthesis **Answer: c) ATP synthase**

Q6. The starting material for isoniazid synthesis is: a) m-Aminophenol b) γ-Picoline c) Pyrazine-2-carboxamide d) 3-Chloroaniline **Answer: b) γ-Picoline**

Q7. PAS is synthesised by which named reaction? a) Gould–Jacobs b) Kolbe–Schmitt c) Mannich d) Friedel–Crafts **Answer: b) Kolbe–Schmitt**

Q8. Which pair shares the same target (InhA) but different activating enzymes? a) INH + Rifampicin b) INH + Ethionamide c) PZA + Ethambutol d) Streptomycin + Capreomycin **Answer: b) INH + Ethionamide**

Q9. Orange-red discolouration of urine and tears is caused by: a) Clofazimine b) Rifampicin c) Bedaquiline d) Linezolid **Answer: b) Rifampicin**

Q10. Pretomanid is activated by the mycobacterial enzyme: a) KatG b) EthA c) Ddn d) PncA **Answer: c) Ddn**

Q11. Linezolid binds to: a) 30S ribosomal subunit b) 50S ribosomal subunit c) RNA polymerase d) DNA gyrase **Answer: b) 50S ribosomal subunit**

Q12. The BPaL regimen consists of: a) Bedaquiline + Pyrazinamide + Levofloxacin b) Bedaquiline + Pretomanid + Linezolid c) Bedaquiline + PAS + INH d) Bedaquiline + Rifampicin + Ethambutol **Answer: b) Bedaquiline + Pretomanid + Linezolid**

D. Viva questions (with model answers)

1. **Why is INH called a prodrug?** Because it is inactive until the bacterial enzyme KatG converts it into the active INH–NAD adduct.
2. **Which anti-TB drug colours the skin?** Clofazimine — reddish-brown discolouration.
3. **Name two drugs that kill dormant TB bacilli.** Rifampicin and pyrazinamide (also bedaquiline and pretomanid).
4. **What is the chemical name of PAS?** 4-Amino-2-hydroxybenzoic acid.
5. **Why can't streptomycin be given orally?** It is highly polar (many $–NH_2$/–OH groups) and not absorbed from the gut — given IM.
6. **What does DOTS stand for?** Directly Observed Treatment, Short-course.
7. **Which drug needs ECG monitoring and why?** Bedaquiline (and delamanid) — QT prolongation risk.
8. **How does ethionamide escape INH resistance?** It hits the same target (InhA) but is activated by EthA, not KatG.

E. Application-based questions

1. **Case:** A TB patient on standard RIPE therapy stops all medicines after 2 months saying "I feel completely fine." As the pharmacist, explain (a) what will likely happen biologically, and (b) what you will tell the patient. *(Expected: surviving dormant bacilli + possible resistant mutants regrow relapse, possibly MDR-TB; counsel on full 6-month course, DOTS support, Nikshay follow-up.)*
2. **Case:** An HIV-positive patient on efavirenz-based antiretroviral therapy is diagnosed with TB. The doctor avoids rifampicin. Which rifamycin is chosen and why? *(Expected: rifabutin — same anti-TB action, much weaker enzyme induction, so antiretroviral levels are preserved.)*

3 **Case:** A patient on an MDR-TB regimen containing bedaquiline complains of palpitations. Which investigation will you arrange, and what is the pharmacological reason? *(Expected: ECG for QT prolongation — bedaquiline blocks cardiac potassium channels at high exposure; dose review/cardiology referral.)*

4 **Prescription check:** A prescription reads "Isoniazid 300 mg alone for active pulmonary TB." Identify the error and correct it. *(Expected: monotherapy breeds resistance — must be a full combination regimen per NTEP.)*

1.22 References — Chapter 1

- Kar, A. *Medicinal Chemistry*. New Age International.
- Williams, D. A., Lemke, T. L., and Roche, V. F. *Foye's Principles of Medicinal Chemistry*. Lippincott Williams & Wilkins.
- Wilson, Beale, and Block. *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*. Lippincott Williams & Wilkins.
- Lednicer, D. *The Organic Chemistry of Drug Synthesis*. Wiley.
- Li, J. J. *Modern Drug Synthesis*. Wiley.
- Brunton, L. L. et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. McGraw-Hill.
- Vogel's *Textbook of Practical Organic Chemistry*. Pearson.

CHAPTER 6: ANTIMALARIAL AGENTS

2.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define malaria, the *Plasmodium* species infecting humans, and the stages of the parasite life cycle.

2 Classify all 13 antimalarial drugs of this unit by chemical structure and by the parasite stage they kill.

3 Describe the chemical scaffold and key substituents of each drug in words (so you can draw the structure).

4 Explain how each drug kills the parasite, especially the **heme-detoxification** mechanism of quinolines.

5 State the **SAR rules of quinoline antimalarials** as a rule table and apply them.

6 Write the complete step-by-step synthesis of **Chloroquine**, with reagents, conditions, and intermediates.

7 Choose the right drug for *P. vivax* vs *P. falciparum* malaria and justify the choice.

8 Describe India's malaria control programme and drug policy in your own words.

2.2 Definitions

- **Malaria:** A mosquito-borne infectious disease caused by *Plasmodium* parasites, characterised by recurring high fever with chills and sweating.
- ***Plasmodium*:** The parasite genus causing malaria. Four species infect humans: ***P. falciparum*** (most dangerous, causes cerebral malaria), ***P. vivax*** (most common in India; forms sleeping liver forms), *P. ovale*, and *P. malariae*.
- **Vector:** The female *Anopheles* mosquito, which carries the parasite from person to person.
- **Blood schizonticide:** A drug that kills the parasite stage living inside red blood cells (the stage that causes fever). Example: chloroquine.
- **Tissue schizonticide:** A drug that kills the parasite stage in the **liver**. Example: primaquine.
- **Hypnozoite:** A sleeping liver form of *P. vivax*/*P. ovale* that can wake up months later and cause relapse. Only 8-aminoquinolines (primaquine) kill it — this is called **radical cure**.
- **Gametocytocide:** A drug that kills gametocytes (the sexual forms taken up by mosquitoes) — stops spread. Example: primaquine.
- **Hemozoin (malaria pigment):** The parasite eats haemoglobin and releases toxic free **heme**; to protect itself it converts heme into harmless dark crystals called hemozoin — the parasite's "garbage bins".
- **ACT (Artemisinin-based Combination Therapy):** Treatment combining a fast artemisinin drug with a longer-acting partner (e.g., artemether + lumefantrine).
- **Prodrug (recap):** Proguanil is inactive until the liver converts it to **cycloguanil**.

Simple explanation: The malaria parasite is a thief that breaks into red blood cells, eats the haemoglobin, and hides its poisonous garbage (heme) in dustbins (hemozoin). Most antimalarial drugs either smash the dustbins (quinolines), poison the thief's kitchen (folate blockers), or blow up the thief with chemical bombs (artemisinins).

Example: A patient with *P. vivax* malaria needs **two** drugs: chloroquine (kills blood forms stops fever) + primaquine for 14 days (kills sleeping liver forms prevents relapse months later).

> **Key takeaway:** Know the parasite's address (blood vs liver vs mosquito stomach) — each drug works at one address.

2.3 Terminology You Must Know

Term	Meaning in one line
Schizont	The parasite form that divides into many daughters inside RBCs/liver
Food vacuole	The parasite's stomach inside the RBC, where haemoglobin is digested (acidic)
Ion trapping	A weak-base drug enters the acidic vacuole easily but cannot leave once protonated — it gets trapped and concentrated
DHFR	Dihydrofolate reductase — the folate-pathway enzyme blocked by proguanil/cycloguanil/pyrimethamine

Term	Meaning in one line
Endoperoxide	The –O–O– bridge in artemisinin — a chemical "bomb" that explodes on contact with iron
Radical cure	Killing hypnozoites (sleeping liver forms) so vivax malaria never relapses — primaquine's job
Suppressive cure / prophylaxis	Preventing blood-stage infection — e.g., mefloquine, doxycycline, Malarone
G6PD deficiency	A common enzyme deficiency; primaquine can burst RBCs in these patients — test before 14-day primaquine

2.4 The Parasite's Journey (learn the life cycle first — drugs make sense only after this)

Technical concept: Mosquito bite sporozoites liver (tissue schizonts; hypnozoites in vivax) merozoites red blood cells (blood schizonts fever) gametocytes mosquito.

Simple explanation: The mosquito injects the parasite into blood; it first hides in the **liver** (1–2 weeks, no symptoms), then storms the **red blood cells**, bursting them in waves — each burst = a fever attack. Some parasites turn into **gametocytes**, waiting to be sucked up by the next mosquito.

Flowchart (draw this):

Mosquito bite **Liver stage** (tissue schizonts; *vivax* also makes sleeping **hypnozoites**) — killed by **primaquine** **Blood stage** (RBC schizonts fever bursts) — killed by **chloroquine, quinine, mefloquine, artemisinins, atovaquone–proguanil, pyrimethamine** **Gametocytes** (taken by mosquito) — killed by **primaquine** Mosquito stomach (sporogony) — blocked by **pyrimethamine** (sporontocide).

Key takeaway: Liver = primaquine's territory; Blood = almost every other drug's territory.

Diagram 2 (draw this): How quinolines kill — the dustbin story

Draw a red blood cell containing a parasite with an acidic **food vacuole** (a round stomach). Inside the vacuole: haemoglobin free **heme** (draw as toxic red stars) hemozoin **dustbins** (dark crystals). Now draw **chloroquine** molecules as small boats sailing in from the blood, entering the vacuole easily (neutral form), then getting a "+" charge in the acid and being unable to sail out (ion trapping — draw a one-way gate). The trapped chloroquine sits on the heme stars and **blocks dustbin-making**; toxic heme piles up and poisons the parasite. Caption: "Block the dustbin drown in your own garbage."

2.5 Classification of Antimalarial Drugs

A. By chemical class

Class	Drugs
Quinoline derivatives — 4-aminoquinolines	Chloroquine , Amodiaquine

Class	Drugs
Quinoline derivatives — quinoline methanols	Quinine, Mefloquine
Quinoline derivatives — 8-aminoquinolines	Primaquine, Pamaquine
Acridine derivatives	Quinacrine (mepacrine)
Biguanides	Proguanil (prodrug of cycloguanil)
Diaminopyrimidines	Pyrimethamine
Sesquiterpene lactone endoperoxides	Artesunate, Artemether
Hydroxynaphthoquinones	Atovaquone
(Repository salt)	Cycloguanil pamoate

B. By parasite stage (clinical classification)

Stage killed	Drugs
Blood schizonticides (stop the fever)	Chloroquine, Quinine, Mefloquine, Amodiaquine, Quinacrine, Pyrimethamine, Artesunate, Artemether, Atovaquone
Tissue schizonticides (liver forms)	Primaquine, Pamaquine
Hypnozoitocides (radical cure of vivax)	Primaquine (only reliable one)
Gametocytocides (stop transmission)	Primaquine
Sporontocides (in mosquito)	Pyrimethamine, Proguanil

Mnemonic for chemical classes: "Queen And Brave Princes Ate Apples Nightly" — **Qu**inoline, **A**cridine, **B**iguanide, **P**yrimidine, **A**rtemisinin, **N**aphthoquinone.

2.6 Drug-by-Drug Profiles (all 13 drugs)

2.6.1 QUININE

- **Chemical class: Quinoline methanol** — a natural alkaloid from the bark of the *Cinchona* tree.
- **Structure (describe and draw):** Draw a **quinoline ring** (benzene fused to pyridine) with a **–OCH_3 (methoxy)** group at C6′. At C4′ attach a **–CH(OH)–** bridge going to a bulky bicyclic amine: **quinuclidine** (a cage-like structure — two fused rings sharing a nitrogen at the bridgehead) carrying a **vinyl (–CH=CH_2)** group. Quinine has four chiral centres; its diastereomer quinidine is the heart drug.
- **Mechanism:** Like chloroquine, it concentrates in the food vacuole and **blocks hemozoin formation** toxic heme accumulates. Also intercalates DNA at high doses.
- **Uses: Severe chloroquine-resistant falciparum malaria** (IV quinine when artesunate is unavailable); babesiosis (with clindamycin). Historically the first antimalarial (from Cinchona bark — the reason "tonic water" contains quinine).
- **Key side effects: Cinchonism** — ringing in ears (tinnitus), headache, blurred vision, nausea; low blood sugar (stimulates insulin); can disturb heart rhythm in overdose.

Simple explanation: Quinine is nature's own antimalarial — tree bark that taught us the quinoline shape all later drugs copied.

Key takeaway: Quinine = natural quinoline methanol; reserve drug for severe resistant malaria; cinchonism (tinnitus).

2.6.2 CHLOROQUINE — synthesis required

- **Chemical class: 4-Aminoquinoline** — the most famous synthetic antimalarial.
- **Structure (describe and draw):** Draw a **quinoline ring**. At **C7** put **–Cl** (this chlorine is the single most important atom for activity). At **C4** put **–NH–** joined to the side chain: **–CH(CH_3)–CH_2–CH_2–CH_2–N(CH_2CH_3)$_2$** — i.e., a 4-carbon chain with a methyl branch at the top and a **diethylamino** group (–N(Et)$_2$) at the bottom end. Full name: N^4-(7-chloroquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine. Note the two basic nitrogens (quinoline N + side-chain N) — these drive ion trapping.
- **Mechanism:** A **weak base** — crosses membranes easily in neutral form, but inside the **acidic food vacuole** it picks up protons, becomes charged, and **cannot escape (ion trapping)** concentrates ~1000-fold. There it binds **free heme** and **blocks its polymerisation into hemozoin** toxic heme builds up and kills the blood-stage parasite. Blood schizonticide.
- **Uses: P. vivax malaria** (still effective where sensitive); extraintestinal amoebiasis (liver abscess, with metronidazole); **rheumatoid arthritis and SLE** (disease-modifying anti-rheumatic drug — long-term low doses).
- **Key side effects:** Nausea, itching (common in dark-skinned patients), headache; **retinopathy** (retina damage) on long-term high doses — needs eye checks; safe in pregnancy (important!).

Simple explanation: Chloroquine is a fish that swims into the parasite's acidic stomach, then grows too big to swim out. Trapped inside, it sits on the garbage (heme) and stops the dustbin factory — the parasite drowns in its own poison.

Example: A traveller returning with vivax malaria gets chloroquine for 3 days (fever gone) + primaquine for 14 days (no relapse).

Key takeaway: Chloroquine = 7-chloro-4-aminoquinoline; ion trapping + heme binding; blood schizonticide; resistance is now widespread in falciparum.

SYNTHESIS OF CHLOROQUINE (learn as three parts: ring side chain joining)

PART A — Making 4,7-dichloroquinoline (the ring half), by the Gould–Jacobs reaction

Starting material: 3-Chloroaniline (m-chloroaniline) — a benzene ring with –NH_2 at position 1 and –Cl at position 3.

Step 1 — Condensation: 3-Chloroaniline + **diethyl ethoxymethylenemalonate** (EMME: CH_3CH_2O–CH=C($COOEt$)$_2$) **diethyl [(3-chlorophenyl)amino]methylenemalonate** + ethanol. *What happened:* the aniline nitrogen attacked the ethoxymethylene carbon, throwing out ethanol — the two pieces are now linked.

Step 2 — Cyclisation (Gould–Jacobs ring closure): Heat the product in **boiling diphenyl ether (~250 °C)** **ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate** + ethanol. *What happened:* the ring closed to form the quinoline skeleton. (Two isomers are possible — the **7-chloro** isomer forms predominantly because cyclisation away from the –Cl is less crowded — and it is the isomer we need.)

Step 3 — Hydrolysis: Ethyl ester + **NaOH**, then acidify → **7-chloro-4-hydroxyquinoline-3-carboxylic acid**. *What happened:* –COOEt became –COOH.

Step 4 — Decarboxylation: Heat (~250–270 °C) → **7-chloro-4-hydroxyquinoline** (exists mainly as the **4-quinolone** tautomer) + CO_2. *What happened:* the –COOH left as carbon dioxide.

Step 5 — Chlorination: 7-Chloro-4-hydroxyquinoline + **$POCl_3$ (phosphorus oxychloride)**, reflux → **4,7-dichloroquinoline**. *What happened:* the –OH at C4 (activated position) was replaced by –Cl. The C4–Cl bond is highly reactive toward nucleophiles — exactly what we need for the next part.

PART B — Making novoldiamine [4-amino-1-diethylaminopentane] (the side-chain half)

Starting material: Ethyl acetoacetate (CH_3–CO–CH_2–COOEt) — the classic active-methylene compound.

Step 1 — Alkylation: Ethyl acetoacetate + **NaOEt** (to make the enolate) + **2-chloroethyldiethylamine** [Cl–CH_2–CH_2–$N(Et)_2$] → **ethyl 2-(2-diethylaminoethyl)acetoacetate** + NaCl. *What happened:* the acidic –CH_2– between the two carbonyls attacked the chloroethyl compound, extending the chain by –$CH_2CH_2N(Et)_2$.

Step 2 — Hydrolysis + decarboxylation: Heat with dilute acid/alkali → the ester hydrolyses to a β-keto acid, which **loses CO_2 on heating** → **5-(diethylamino)pentan-2-one** [CH_3–CO–CH_2–CH_2–CH_2–$N(Et)_2$] + CO_2 + ethanol. *What happened:* the –COOEt group was removed as CO_2, leaving a simple ketone with the diethylamino tail.

Step 3 — Reductive amination: 5-(Diethylamino)pentan-2-one + **NH_3, H_2 / Raney nickel** (catalytic hydrogenation) → **novoldiamine** [CH_3–$CH(NH_2)$–CH_2–CH_2–CH_2–$N(Et)_2$] + H_2O. *What happened:* the ketone C=O became CH–NH_2 — a primary amine at one end, tertiary diethylamino at the other. (Sodium cyanoborohydride, $NaCNBH_3$, with NH_3 is the modern lab alternative.)

PART C — Joining the two halves (nucleophilic aromatic substitution)

Step 1 — Coupling: 4,7-Dichloroquinoline + novoldiamine, **heat** (often in phenol as solvent/catalyst) → **Chloroquine base** + HCl. *What happened:* the **primary –NH_2** of novoldiamine displaced the **C4–Cl** of the quinoline ring (SNAr — the C4 position is strongly activated by the ring nitrogen). The C7–Cl stays untouched. The product is usually converted to **chloroquine diphosphate** (phosphate salt) for tablets — the salt is stable and water-soluble.

Master flowchart (draw this):

Ring half: 3-Chloroaniline —[EMME] anilino-methylenemalonate —[Ph_2O, 250 °C] ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate —[NaOH, then H^+] carboxylic acid —[heat, –CO_2] 7-chloro-4-hydroxyquinoline —[$POCl_3$] **4,7-dichloroquinoline Side-chain half:** Ethyl acetoacetate —[NaOEt; $ClCH_2CH_2NEt_2$] alkylated acetoacetate —[hydrolysis, heat, –CO_2] 5-(diethylamino)pentan-2-one —[NH_3, H_2/Ni] **novoldiamine Join:** 4,7-dichloroquinoline + novoldiamine —[heat] **CHLOROQUINE** (diphosphate salt)

2.6.3 AMODIAQUINE

- **Chemical class: 4-Aminoquinoline** (Mannich base) — chloroquine's close cousin.
- **Structure (describe and draw):** Draw the **7-chloroquinolin-4-yl** unit (same as chloroquine's ring). At C4, instead of chloroquine's alkyl chain, attach **–NH–** to a **phenol ring**: the phenol has **–OH** and, ortho to it, a **–CH_2–$N(Et)_2$** (diethylaminomethyl) group — this –CH_2–NR_2 next to a phenol is the **Mannich base** feature. Full name: 4-[(7-chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol.

- **Mechanism:** Same as chloroquine — food-vacuole accumulation, **heme binding, hemozoin blockade**. Effective against some chloroquine-resistant strains.
- **Uses:** With **artesunate** as the ACT **ASAQ** (artesunate + amodiaquine) for uncomplicated falciparum malaria.
- **Key side effects:** Nausea, vomiting; rare but serious — **liver damage and agranulocytosis** (low white cells) on prolonged/prophylactic use not used alone for prophylaxis.

Simple explanation: Amodiaquine is chloroquine wearing a phenol hat — same dustbin-smashing job, slightly different shape, so some resistant parasites still fall for it.

Key takeaway: Amodiaquine = 4-aminoquinoline Mannich base; partner drug in ASAQ combination.

2.6.4 PRIMAQUINE

- **Chemical class: 8-Aminoquinoline**.
- **Structure (describe and draw):** Draw a **quinoline ring** with **–OCH_3 at C6**. At **C8** (next to the ring nitrogen, on the benzene side) attach **–NH–CH(CH_3)–CH_2–CH_2–CH_2–NH_2** — a 4-carbon chain with a methyl branch and a **primary amine** at the far end. Note the difference from chloroquine: the side chain is at **C8, not C4**, and there is a **6-methoxy** group.
- **Mechanism:** The exact target is still debated; its metabolites generate **reactive oxygen species** that damage parasite mitochondria — kills **liver stages, hypnozoites, and gametocytes**. Not a good blood schizonticide.
- **Uses: Radical cure of P. vivax / P. ovale** (14 days, kills hypnozoites); **gametocytocidal** single dose in falciparum (blocks transmission).
- **Key side effects: Haemolysis in G6PD-deficient patients** (RBCs burst) — screen/test or counsel before the 14-day course; nausea, abdominal pain; methaemoglobinaemia in overdose.

Simple explanation: Primaquine is the only soldier that enters the liver's deep bunkers and shoots the sleeping parasites (hypnozoites) — without it, vivax malaria keeps coming back like a bad dream.

Key takeaway: Primaquine = 8-aminoquinoline; the ONLY reliable hypnozoite killer; check G6PD; 14-day radical cure.

2.6.5 PAMAQUINE

- **Chemical class: 8-Aminoquinoline** — the older predecessor of primaquine.
- **Structure (describe and draw):** Same **6-methoxyquinolin-8-yl** core as primaquine. The side chain at C8 is **–NH–CH(CH_3)–CH_2–CH_2–CH_2–N(Et)$_2$** — identical carbon skeleton to primaquine's, but ending in a **diethylamino (tertiary amine)** instead of a primary –NH_2.
- **Mechanism / Uses:** Same tissue-schizonticidal and gametocytocidal actions as primaquine, but **more toxic** (haemolysis, methaemoglobinaemia at lower doses).
- **Status:** Largely **replaced by primaquine** — asked in exams as "the first 8-aminoquinoline, now obsolete".

Key takeaway: Pamaquine = primaquine's older, more toxic brother; replaced by primaquine.

2.6.6 QUINACRINE (MEPACRINE)

- **Chemical class: Acridine** derivative.
- **Structure (describe and draw):** Draw **three six-membered rings fused in a row** with a **nitrogen in the central ring** (**acridine** core). On one outer ring put **–Cl** and **–OCH_3** substituents; at C9 (central ring carbon) attach the familiar basic side chain **–NH–CH(CH_3)–CH_2–CH_2–CH_2–N($Et)_2$** (same as chloroquine's tail).
- **Mechanism: Intercalates into parasite DNA** (slides between base pairs) and also blocks hemozoin formation. Blood schizonticide.
- **Uses:** Historical antimalarial (World War II era); later used for **giardiasis** and lupus skin lesions. Now obsolete as an antimalarial.
- **Key side effects:** Yellow discolouration of skin, nausea, CNS effects on long use.

Simple explanation: Quinacrine is a flat yellow dye molecule that slips between the rungs of the parasite's DNA ladder and jams it.

Key takeaway: Quinacrine = acridine dye; DNA intercalator; historically important, now obsolete.

2.6.7 MEFLOQUINE

- **Chemical class: Quinoline methanol**.
- **Structure (describe and draw):** Draw a **quinoline ring** with **–CF_3 (trifluoromethyl)** groups at **C2 and C8** (these make it very fat-soluble and long-acting). At **C4** attach **–CH(OH)–** joined to a **piperidine ring** (six-membered saturated ring with one N) at its C2′ position. Two chiral centres — used as the racemate.
- **Mechanism:** Blood schizonticide — binds heme and blocks hemozoin formation (quinoline-methanol family action).
- **Uses: Prophylaxis and treatment of chloroquine-resistant falciparum malaria** (weekly dosing for prophylaxis — very convenient for travellers).
- **Key side effects: Neuropsychiatric effects** — vivid dreams, anxiety, dizziness, rarely psychosis/seizures; avoid in epilepsy or psychiatric history; nausea.

Simple explanation: Mefloquine is chloroquine's long-distance cousin — the CF_3 groups make it stay in the body for weeks, so one tablet a week protects a traveller.

Key takeaway: Mefloquine = 2,8-bis(trifluoromethyl) quinoline methanol; weekly prophylaxis; watch the brain (neuropsychiatric effects).

2.6.8 PROGUANIL

- **Chemical class: Biguanide** — chemically N^1-(4-chlorophenyl)-N^5-isopropylbiguanide.

- **Structure (describe and draw):** Draw a **p-chlorophenyl ring** (benzene with –Cl para). Attach **–NH–C(=NH)–NH–C(=NH)–NH–CH(CH_3)$_2$**: two **guanidine units** (C(=NH)–NH–) joined in a row — this double-guanidine chain is the **biguanide** backbone — ending in an **isopropyl** group.
- **Mechanism:** A **prodrug** — liver enzymes cyclise it into **cycloguanil**, which blocks **dihydrofolate reductase (DHFR)** the parasite cannot make folate cannot make DNA. Slow blood schizonticide; also kills liver stages of falciparum (causal prophylaxis).
- **Uses:** With **atovaquone** as **Malarone** (atovaquone + proguanil) — first-choice **traveller's prophylaxis** and treatment of uncomplicated falciparum malaria.
- **Key side effects:** Very safe — mild nausea, mouth ulcers; safe in pregnancy at prophylactic doses.

Simple explanation: Proguanil is a folded paper crane; the liver unfolds and refolds it into a dart (cycloguanil) that hits the parasite's folate factory.

Key takeaway: Proguanil = biguanide prodrug cycloguanil DHFR block; partner in Malarone.

2.6.9 CYCLOGUANIL PAMOATE

- **Chemical class: Dihydrotriazine** (the active metabolite of proguanil), given as the **pamoate (embonate) salt**.
- **Structure (describe and draw):** Draw a **1,3,5-triazine ring** (six-membered with three Ns) partially saturated: **1-(p-chlorophenyl)-4,6-diamino-2,2-dimethyl-1,2-dihydro-1,3,5-triazine** — the biguanide chain of proguanil cyclised into a ring, with two –NH_2 groups and two methyls. Then note: it is paired with **pamoic acid** (a large, insoluble dicarboxylic acid) as the salt — the pamoate makes it **insoluble**.
- **Mechanism:** Same as proguanil's active form — **DHFR inhibition**.
- **Uses:** Historical **repository (depot) prophylaxis** — a single **intramuscular injection** of the insoluble pamoate salt released drug slowly for weeks/months. Now obsolete (resistance + better options).
- **Key point for exams:** The pamoate salt trick — making an insoluble salt for a long-acting injection — is the concept being tested, not current use.

Simple explanation: Cycloguanil pamoate is a "slow-release capsule" injected into muscle — the insoluble salt dissolves drop by drop for weeks.

Key takeaway: Cycloguanil = active form of proguanil; pamoate salt = insoluble depot injection (historical).

2.6.10 PYRIMETHAMINE

- **Chemical class: Diaminopyrimidine** — chemically 5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine.
- **Structure (describe and draw):** Draw a **pyrimidine ring** (six-membered, two Ns at 1 and 3). Put **–NH_2 at C2 and C4** (the "diamino" part), a **p-chlorophenyl** group at C5, and an **ethyl** group at C6. It looks like a fake folate building block — that is the whole trick.
- **Mechanism:** Directly blocks **DHFR** (no activation needed) — parasite folate DNA synthesis stops. Slow blood schizonticide; also **sporontocidal** (kills stages in the mosquito).

- **Uses:** With **sulfadoxine** as **Fansidar** (sulfadoxine + pyrimethamine, "SP") for falciparum malaria (now limited by resistance; still used in intermittent preventive treatment in pregnancy in Africa); with **sulfadiazine** for **toxoplasmosis**.
- **Key side effects:** Nausea, rash; **megaloblastic anaemia** on long use (folate block affects human cells too — give folinic acid, not folic acid, as rescue).

Simple explanation: Pyrimethamine is a counterfeit key that jams the parasite's folate lock — but it can also jam human locks slightly, so long courses need a rescue vitamin (folinic acid).

Key takeaway: Pyrimethamine = diaminopyrimidine; direct DHFR blocker; Fansidar (SP) partner; toxoplasmosis combo.

2.6.11 ARTESUNATE

- **Chemical class: Sesquiterpene lactone endoperoxide** — a semi-synthetic derivative of **artemisinin** (from the plant *Artemisia annua*, sweet wormwood).
- **Structure (describe and draw):** Draw the **artemisinin skeleton**: a complex fused ring system (three fused rings + a lactone) containing the critical **–O–O– (endoperoxide) bridge** — mark this bridge with a star: it is the "bomb". In artesunate, the lactone carbonyl region is modified: dihydroartemisinin esterified with **succinic acid** a **hemisuccinate ester (–O–CO–CH_2–CH_2–COOH)**. The free –COOH makes it **water-soluble** (can be given IV).
- **Mechanism:** Inside the parasite, iron (from heme) **snaps the endoperoxide bridge**, generating **carbon-centred free radicals** — chemical shrapnel that shreds parasite proteins and membranes. The **fastest-acting** blood schizonticide known — clears parasites within hours.
- **Uses: Severe falciparum malaria — IV artesunate is the first-choice, life-saving drug**; oral artesunate is the artemisinin component of ACTs (ASAQ, etc.).
- **Key side effects:** Generally safe; transient low reticulocyte count; rare delayed haemolysis after IV cure (monitor).

Simple explanation: Artesunate is a tiny bomb with an –O–O– fuse. The parasite's own iron lights the fuse — the explosion happens inside the parasite, not in us.

Key takeaway: Artesunate = water-soluble artemisinin hemisuccinate; fastest killer; IV drug of choice for severe malaria.

2.6.12 ARTEMETHER

- **Chemical class: Sesquiterpene lactone endoperoxide** — the **methyl ether** of dihydroartemisinin.
- **Structure (describe and draw):** Same artemisinin skeleton with the starred **endoperoxide bridge**. The difference from artesunate: at the hemiacetal position there is **–O–CH_3 (methyl ether)** instead of the hemisuccinate. No free –COOH **lipid-soluble** (oil-soluble), not water-soluble.
- **Mechanism:** Identical to artesunate — iron-triggered **free-radical** damage; fast blood schizonticide.
- **Uses:** With **lumefantrine** as **Coartem** (artemether + lumefantrine) — the world's most widely used ACT for uncomplicated falciparum malaria; also IM oily injection.

- **Artesunate vs Artemether (exam favourite):** Artesunate = hemisuccinate ester **water-soluble** IV/oral; Artemether = methyl ether **lipid-soluble** oral/IM oily. Same bomb, different coating.

Key takeaway: Artemether = lipid-soluble methyl ether; Coartem partner; same endoperoxide bomb as artesunate.

2.6.13 ATOVAQUONE

- **Chemical class: Hydroxynaphthoquinone** — chemically 2-hydroxy-3-[4-(4-chlorophenyl)cyclohexyl]naphthalene-1,4-dione.
- **Structure (describe and draw):** Draw a **1,4-naphthoquinone** (two fused rings with two C=O at 1 and 4). At C2 put **–OH**; at C3 attach a **cyclohexane ring** which carries a **p-chlorophenyl** group at its 4-position. The bulky cyclohexyl-chlorophenyl tail mimics ubiquinone (coenzyme Q).
- **Mechanism:** Mimics **ubiquinone** and jams the parasite's **mitochondrial electron transport chain** at the **cytochrome bc_1 complex** the mitochondrion cannot make energy parasite dies. Blood schizonticide (slow).
- **Uses:** With **proguanil** as **Malarone** (atovaquone + proguanil) — prophylaxis and treatment of falciparum malaria; alternative for **Pneumocystis pneumonia (PCP)** in sulfa-allergic patients.
- **Key side effects:** Nausea, headache, raised liver enzymes; resistance develops fast if used alone — always combined.

Simple explanation: The parasite's mitochondrion is a power station running on ubiquinone fuel. Atovaquone is fake fuel — the power station chokes and the parasite blacks out.

Key takeaway: Atovaquone = ubiquinone mimic; blocks mitochondrial bc_1 complex; Malarone partner; never alone.

2.7 SAR of Quinoline Antimalarials — The Rule Table (memorise this)

Technical concept: Structure–activity relationship (SAR) = which parts of the molecule are essential for killing the parasite and which can be changed.

Diagram 3 (draw this): Annotated chloroquine SAR map

Draw chloroquine large. Circle the **Cl at C7** and label "Rule 1: keep me". Draw a box around the **–NH– at C4** and label "Rule 2: secondary amine linker". Bracket the **4-carbon chain** and label "Rule 3: 2–4 carbons between nitrogens, 4 is best". Circle the **$–N(Et)_2$** and label "Rule 4: basic tertiary amine — the trapping engine". Draw the quinoline **ring N** and label "Rule 5: needed for vacuole entry". Put a cross on C2 and label "Rule 6: don't substitute here".

#	Structural feature	SAR rule	Example / explanation
1	**7-Chloro on quinoline**	A chloro (or similar electron-withdrawing) group at **C7** gives the best activity	Chloroquine (7-Cl) >> des-chloro analogues; 6-Cl or 8-Cl less active

#	Structural feature	SAR rule	Example / explanation
2	**Basic side chain at C4**	A **4-amino** linkage (secondary amine) joining the side chain is essential	Replacing –NH– with –O– or $–CH_2–$ kills activity
3	**Chain length**	**2–4 carbon atoms** between the two nitrogens; the 4-carbon chain (chloroquine) is optimal	Shorter/longer chains lose potency
4	**Terminal tertiary amine**	A **dialkylamino** group (e.g., $–N(Et)_2$) at the chain end is required — it drives **ion trapping** in the food vacuole	Primary amine endings are weaker
5	**Quinoline ring nitrogen**	The ring N (basic) helps the drug cross membranes and concentrate in the acidic vacuole	Quinoline other heterocycles usually lose activity
6	**C2 substitution**	Bulky groups at **C2** reduce antimalarial activity	Keep C2 free (H) in 4-aminoquinolines
7	**8-Aminoquinolines** (primaquine type)	Need the **6-methoxy** group + the **8-(aminoalkyl)amino** side chain for tissue-schizonticidal action	Removing 6-OCH_3 weakens liver-stage activity
8	**Quinoline methanols** (quinine/mefloquine type)	The **–CH(OH)–** bridge between quinoline and the basic amine is essential; **2,8-bis(CF_3)** (mefloquine) boosts lipophilicity and duration	Esterifying the –OH reduces activity
9	**Stereochemistry**	Activity often differs between enantiomers (e.g., quinine vs quinidine)	Use the correct isomer

Simple explanation: Think of chloroquine as a key with four teeth: the **7-Cl tooth**, the **4-NH tooth**, the **4-carbon shaft**, and the **basic tail tooth**. File down any tooth and the key no longer opens the parasite's lock.

Example: If you move the –Cl from C7 to C6, activity drops sharply — examiners love asking "which position of chlorine is optimal?" Answer: **C7**.

Key takeaway: 7-chloro + 4-(dialkylaminoalkyl)amino + quinoline N = the winning formula.

2.8 Master Mechanism Table — Antimalarials

Drug	Chemical class	Parasite stage	Mechanism in one line
Quinine	Quinoline methanol	Blood	Blocks hemozoin formation; DNA effects
Chloroquine	4-Aminoquinoline	Blood	Ion trapping binds heme blocks hemozoin
Amodiaquine	4-Aminoquinoline	Blood	Same as chloroquine
Mefloquine	Quinoline methanol	Blood	Binds heme blocks hemozoin

Drug	Chemical class	Parasite stage	Mechanism in one line
Quinacrine	Acridine	Blood	DNA intercalation + hemozoin block
Primaquine	8-Aminoquinoline	Liver, hypnozoite, gametocyte	ROS damage via metabolites
Pamaquine	8-Aminoquinoline	Liver, gametocyte	Same as primaquine (more toxic)
Proguanil	Biguanide (prodrug)	Blood, liver (falciparum)	Cycloguanil DHFR block
Cycloguanil pamoate	Dihydrotriazine salt	(Prophylaxis, historical)	DHFR block; depot injection
Pyrimethamine	Diaminopyrimidine	Blood; mosquito stages	Direct DHFR block
Artesunate	Endoperoxide	Blood (fastest)	Iron free radicals shred parasite
Artemether	Endoperoxide	Blood (fastest)	Same as artesunate
Atovaquone	Hydroxynaphthoquinone	Blood	Blocks mitochondrial bc_1 complex

Diagram 4 (draw this): The folate pathway and its blockers

Draw a pipeline: **PABA** —(dihydropteroate synthase) **dihydrofolate** —(**DHFR**) **tetrahydrofolate** DNA building blocks. Draw **PAS** (Chapter 1) as a fake PABA entering the first machine. Draw **cycloguanil** and **pyrimethamine** as padlocks on the DHFR machine. Draw **sulfadoxine/sulfadiazine** (sulfa drugs, partner drugs) as padlocks on the first machine. Caption: "Two locks, two keys — that is why pyrimethamine is always paired with a sulfa drug (double blockade)."

2.9 Flowchart: Choosing the Right Antimalarial (draw this)

Start: "Malaria diagnosed — which species?" Branch A "**P. vivax**" box "Chloroquine 3 days (blood forms) + **Primaquine 14 days** (hypnozoites — radical cure). Check G6PD." Branch B "**P. falciparum, uncomplicated**" box "**ACT**: Artemether + Lumefantrine (or Artesunate + Amodiaquine / + SP per policy)" Branch C "**Severe falciparum** (cerebral, etc.)" box "**IV Artesunate** immediately (quinine only if artesunate unavailable)". Note at bottom: "Primaquine single dose may be added in falciparum to kill gametocytes and stop spread."

2.10 Infographic Concept Box: "The Parasite's Three Addresses" (design brief for the artist)

A three-panel strip. **Panel 1 — LIVER (the hideout):** a liver-shaped bunker with sleeping parasites (hypnozoites drawn as "Zzz" bubbles); primaquine depicted as a commando with a flashlight labelled "radical cure — only I go in here". **Panel 2 — BLOOD (the battlefield):** red blood cells bursting; chloroquine boats trapped in a stomach-shaped vacuole sitting on heme stars; artesunate drawn as tiny bombs exploding on contact with iron sparks; atovaquone as fake fuel choking a mitochondrion power station. **Panel 3 — MOSQUITO (the getaway car):** a mosquito with gametocytes inside; primaquine and pyrimethamine as roadblocks labelled "transmission stops here". Caption: "Right drug, right address — that is antimalarial therapy."

2.11 Worked Examples

Example 1 — Vivax relapse. A patient took chloroquine for 3 days, felt fine, skipped primaquine. Four months later the fever returns. Why? Chloroquine killed blood forms but the **hypnozoites slept on** in the liver. **Takeaway: vivax needs primaquine 14 days — radical cure.**

Example 2 — Traveller's prophylaxis. A student travels to a chloroquine-resistant falciparum area for a month. Options: **mefloquine weekly** or **Malarone (atovaquone + proguanil) daily**. Mefloquine is avoided if they have anxiety/epilepsy history. **Takeaway: match prophylaxis to resistance and patient history.**

Example 3 — Severe malaria. A child arrives unconscious with confirmed falciparum malaria. The life-saving drug is **IV artesunate** — it clears parasites fastest. Quinine IV is the backup. **Takeaway: severe = IV artesunate, no delay.**

Example 4 — The G6PD check. Before starting 14-day primaquine, the doctor asks about dark urine or jaundice after certain foods/drugs (fava beans) — clues to **G6PD deficiency**, where primaquine bursts RBCs. **Takeaway: primaquine + G6PD deficiency = haemolysis risk.**

2.12 Analogies That Stick

1. **Hemozoin dustbins:** the parasite eats haemoglobin and hides toxic garbage in dustbins — quinolines smash the dustbins.
2. **Ion trapping = fish trap:** chloroquine swims into the acidic stomach easily, gets charged, and can't swim out.
3. **Artemisinin = a bomb with an iron fuse:** the parasite's own iron lights it.
4. **Hypnozoites = sleeping terrorists in a bunker:** only primaquine's commando reaches them.
5. **Proguanil = folded paper crane dart:** the liver refolds it into cycloguanil.
6. **Atovaquone = fake fuel:** the mitochondrion chokes on counterfeit ubiquinone.
7. **Pyrimethamine + sulfadoxine = double padlock** on the folate pipeline.

2.13 Pharmacy Relevance

- **Species first:** The pharmacist must check the prescription matches the species — vivax without primaquine = guaranteed relapse; severe falciparum needs IV artesunate, not tablets.
- **Primaquine counselling:** 14 days is long — patients stop early. Explain *why* (sleeping liver forms), warn about dark urine/abdominal pain (possible haemolysis), and ask about G6PD/fava-bean history.
- **ACT adherence:** Artemether–lumefantrine must be taken with **fatty food/milk** (lumefantrine absorbs poorly on an empty stomach) — a classic counselling point.
- **Prophylaxis timing:** Mefloquine starts 2 weeks before travel; Malarone 1–2 days before — the pharmacist plans the traveller's calendar.
- **Resistance awareness:** Never dispense chloroquine alone for falciparum in resistant areas; report treatment failures — they signal resistance.
- **Quinine cinchonism:** Warn about tinnitus and blurred vision so patients don't panic.

2.14 India Context

- **Burden:** Malaria remains endemic in several Indian states, especially forested, tribal, and north-eastern regions; *P. vivax* is the commonest species nationally, while *P. falciparum* dominates in high-burden pockets and causes most deaths.
- **Programme:** The **National Vector Borne Disease Control Programme (NVBDCP)** — now the **National Center for Vector Borne Diseases Control (NCVBDC)** — runs malaria control: bed nets, indoor spraying, rapid diagnostic kits, and free drugs.
- **Drug policy:** India follows **ACT** for *P. falciparum* (artemether–lumefantrine is the national first-line; artesunate + sulfadoxine–pyrimethamine was used earlier), **chloroquine + primaquine** for *P. vivax*, and **IV artesunate** for severe malaria — pharmacists must follow the current national drug policy, not old habits.
- **Radical cure challenge:** The 14-day primaquine course for vivax has poor completion — pharmacists are the adherence safety net.
- **Elimination goal:** India has committed to malaria elimination — every case must be diagnosed (microscopy/RDT), treated per policy, and reported.

2.15 Key Points (read the night before the exam)

1 Four human species: **falciparum** (deadliest), **vivax** (hypnozoites relapse), ovale, malariae.

2 Quinolines kill blood stages by **blocking hemozoin** (heme detox) after **ion trapping** in the food vacuole.

3 Chloroquine = **7-chloro-4-aminoquinoline**; SAR: 7-Cl optimal, 4-carbon basic side chain, terminal tertiary amine.

4 Chloroquine synthesis: **Gould–Jacobs** (3-chloroaniline + EMME cyclise hydrolyse decarboxylate $POCl_3$ 4,7-dichloroquinoline) + **novoldiamine** (acetoacetate alkylation decarboxylation reductive amination) heat coupling chloroquine (diphosphate salt).

5 Primaquine = **8-aminoquinoline**; ONLY drug for **hypnozoite radical cure** + gametocytocidal; G6PD caution.

6 Quinine = natural **quinoline methanol**; severe resistant malaria; **cinchonism** (tinnitus).

7 Mefloquine = **2,8-bis(CF_3)** quinoline methanol; weekly prophylaxis; neuropsychiatric effects.

8 Amodiaquine = 4-aminoquinoline **Mannich base**; ASAQ partner.

9 Quinacrine = **acridine**; DNA intercalator; obsolete.

10 Proguanil (liver) **cycloguanil** **DHFR** block; Malarone partner.

11 Pyrimethamine = **diaminopyrimidine**; direct DHFR block; **Fansidar (SP)**; toxoplasmosis.

12 Artesunate = **water-soluble** hemisuccinate; artemether = **lipid-soluble** methyl ether; both = **endoperoxide bombs**, fastest killers; IV artesunate for severe malaria.

13 Atovaquone = **ubiquinone mimic**; blocks **bc_1 complex**; Malarone partner; never alone.

2.16 Common Confusions (cleared)

Confusion	Truth
Chloroquine vs Hydroxychloroquine	Same family; hydroxychloroquine has an extra –OH (not in this syllabus). Don't mix them.
Quinoline vs **quinolone**	Quinoline = antimalarial ring (this chapter); quinolone = antibacterial ring (levofloxacin, Chapter 1). Different drugs!
Primaquine vs Pamaquine	Same 8-aminoquinoline family; **primaquine** = safer, current; pamaquine = older, toxic, obsolete.
Proguanil vs Cycloguanil	Proguanil = **prodrug**; cycloguanil = its **active metabolite**. Cycloguanil pamoate = insoluble depot salt (historical).
Artesunate vs Artemether	Same bomb (endoperoxide); artesunate = **water-soluble** (IV), artemether = **lipid-soluble** (oral/IM).
"Chloroquine cures all malaria"	No — widespread **falciparum resistance**; and chloroquine alone never kills **hypnozoites**.
Artemisinin = antibiotic?	No — antimalarial **endoperoxide**; its trick is iron-triggered free radicals.

2.17 Common Mistakes (don't make these)

1. Saying chloroquine kills hypnozoites — **only primaquine** does (radical cure).
2. Forgetting **ion trapping** when explaining chloroquine's concentration in the food vacuole.
3. Drawing the chloroquine –Cl at the wrong position — it must be **C7**.
4. Calling proguanil directly active — it is a **prodrug** of cycloguanil.
5. Mixing up **Fansidar** (sulfadoxine + pyrimethamine) with **Malarone** (atovaquone + proguanil).
6. Writing the Gould–Jacobs starting material as aniline — it is **3-chloroaniline** (the –Cl becomes the 7-Cl).
7. Saying artemisinins are slow — they are the **fastest** blood schizonticides.
8. Prescribing primaquine 14 days without mentioning **G6PD** screening/counselling.

2.18 Mnemonics

- **Chemical classes: "Queen And Brave Princes Ate Apples Nightly"** — Quinoline, Acridine, Biguanide, Pyrimidine, Artemisinin, Naphthoquinone.
- **Quinoline SAR: "Lucky 7, Four-midable tail"** — Cl at 7, basic side chain at 4.
- **Vivax needs two: "Chloroquine clears the blood, Primaquine puts the liver to sleep — permanently."**
- **Malarone = "Ato + Pro"** — Atovaquone + Proguanil, the traveller's pair.
- **Fansidar = "SP"** — Sulfadoxine + Pyrimethamine.
- **Coartem = "AL"** — Artemether + Lumefantrine.
- **Primaquine's jobs: "Liver, Late-relapse, and the Last mosquito meal"** — tissue schizonts, hypnozoites, gametocytes.

2.19 Exam Summary (one page, in words)

Malaria (*Plasmodium*, *Anopheles* mosquito): liver stage → blood stage (fever) → gametocytes. Quinolines (chloroquine, amodiaquine, quinine, mefloquine) concentrate in the acidic food vacuole by ion trapping, bind heme, and block hemozoin formation — blood schizonticides. Chloroquine SAR: 7-Cl optimal; 4-(dialkylaminoalkyl)amino side chain with 2–4 carbons; terminal tertiary amine; free C2. Chloroquine synthesis = Gould–Jacobs 4,7-dichloroquinoline (3-chloroaniline + EMME → cyclisation → hydrolysis → decarboxylation → $POCl_3$) + novoldiamine (acetoacetate alkylation → decarboxylation → reductive amination) → SNAr coupling → diphosphate salt. Primaquine (8-aminoquinoline, 6-methoxy) is the only hypnozoite killer (radical cure, 14 days; G6PD caution) and gametocytocide; pamaquine is its obsolete predecessor; quinacrine is an obsolete acridine DNA intercalator. Folate blockers: proguanil (prodrug cycloguanil) and pyrimethamine block DHFR; cycloguanil pamoate was a depot injection. Artemisinins (artesunate = water-soluble hemisuccinate; artemether = lipid-soluble methyl ether) are endoperoxide bombs — fastest killers; IV artesunate saves severe malaria. Atovaquone mimics ubiquinone, blocking the mitochondrial bc_1 complex (Malarone with proguanil). India: NCVBDC programme, ACT for falciparum, chloroquine + primaquine for vivax, IV artesunate for severe disease.

2.20 One-Minute Revision (say it aloud in 60 seconds)

"Malaria's parasite hides in liver, then bursts red cells. Quinolines trap themselves in its acidic stomach and smash its heme dustbins — chloroquine needs 7-chloro and a basic four-carbon tail; it's built by Gould-Jacobs ring-making plus a reductive-amination side chain. Primaquine alone reaches the liver's sleeping hypnozoites — fourteen days, watch G6PD. Folate blockers proguanil and pyrimethamine jam DHFR. Artemisinins are iron-triggered bombs — artesunate dissolves in water for IV rescue, artemether in oil for Coartem. Atovaquone fakes the mitochondrion's fuel in Malarone. Vivax gets chloroquine plus primaquine; falciparum gets ACT; severe gets IV artesunate."

2.21 Exam Questions — Chapter 2

A. Short-answer questions (2–5 marks)

1 Define blood schizonticide, tissue schizonticide, and hypnozoite with one example each. (3 marks)

2 Why is primaquine essential in *P. vivax* malaria even after the fever subsides? (2 marks)

3 What is ion trapping? Explain its role in chloroquine's action. (3 marks)

4 Name the two artemisinin derivatives in the syllabus and state one structural difference and its consequence. (3 marks)

5 What are Malarone, Fansidar, and Coartem made of? (3 marks)

6 Why is G6PD status important before primaquine therapy? (2 marks)

7 State two SAR rules for 4-aminoquinoline antimalarials. (2 marks)

8 Why is atovaquone never used alone? (2 marks)

9 Differentiate quinoline from quinolone with one drug example each. (2 marks)

10 Which drug would you choose for severe falciparum malaria, and by which route? (2 marks)

B. Long-answer questions (10 marks)

1 Write the complete synthesis of **chloroquine**, covering (a) 4,7-dichloroquinoline by the Gould–Jacobs reaction, (b) novoldiamine, and (c) the final coupling. Give reagents, conditions, and every intermediate.

2 Explain the **SAR of quinoline antimalarials** with a labelled diagram of chloroquine. How does each structural feature contribute to activity?

3 Describe the life cycle of the malaria parasite and classify antimalarial drugs by the stage they attack, with mechanisms.

4 Compare and contrast: (a) chloroquine vs primaquine, (b) artesunate vs artemether, (c) proguanil vs pyrimethamine — covering class, structure, mechanism, and uses.

5 A 25-year-old is diagnosed with *P. vivax* malaria and a 40-year-old traveller with severe *P. falciparum* malaria. Write the complete treatment plan for each as per India's drug policy, with pharmacist counselling points.

C. MCQs (with answer key)

Q1. Chloroquine accumulates in the parasite's food vacuole by: a) Active transport b) Ion trapping c) Pinocytosis d) Facilitated diffusion **Answer: b) Ion trapping**

Q2. The optimal position of chlorine in chloroquine for antimalarial activity is: a) C5 b) C6 c) C7 d) C8 **Answer: c) C7**

Q3. The only drug in the syllabus that kills hypnozoites (radical cure) is: a) Chloroquine b) Primaquine c) Mefloquine d) Quinine **Answer: b) Primaquine**

Q4. The Gould–Jacobs reaction in chloroquine synthesis starts from: a) Aniline b) 3-Chloroaniline c) 4-Chloroaniline d) m-Aminophenol **Answer: b) 3-Chloroaniline**

Q5. Novoldiamine is prepared from 5-(diethylamino)pentan-2-one by: a) Oxidation b) Reductive amination c) Hydrolysis d) Decarboxylation **Answer: b) Reductive amination**

Q6. Artesunate differs from artemether in being: a) Lipid-soluble methyl ether b) Water-soluble hemisuccinate c) A quinoline d) A prodrug of quinine **Answer: b) Water-soluble hemisuccinate**

Q7. The endoperoxide bridge of artemisinins is cleaved by: a) Calcium b) Iron (heme) c) Zinc d) Magnesium **Answer: b) Iron (heme)**

Q8. Malarone consists of: a) Atovaquone + proguanil b) Sulfadoxine + pyrimethamine c) Artemether + lumefantrine d) Quinine + clindamycin **Answer: a) Atovaquone + proguanil**

Q9. Pyrimethamine acts by inhibiting: a) DNA gyrase b) Dihydrofolate reductase c) ATP synthase d) Heme polymerase **Answer: b) Dihydrofolate reductase**

Q10. Which adverse effect is characteristic of mefloquine? a) Orange urine b) Neuropsychiatric effects c) Skin staining d) Tendon rupture **Answer: b) Neuropsychiatric effects**

Q11. Cycloguanil pamoate was used as: a) An oral tablet b) A depot intramuscular injection c) An IV infusion d) An inhaler **Answer: b) A depot intramuscular injection**

Q12. Atovaquone blocks the parasite's: a) Folate synthesis b) Mitochondrial electron transport (bc_1 complex) c) Protein synthesis d) Cell wall synthesis **Answer: b) Mitochondrial electron transport (bc_1 complex)**

D. Viva questions (with model answers)

1 **Why is chloroquine a weak base important?** The two basic nitrogens let it enter the acidic food vacuole neutral and get trapped protonated — ion trapping concentrates it ~1000-fold.

2 **What is hemozoin?** Harmless crystals the parasite makes from toxic free heme; quinolines block their formation.

3 **Artesunate or artemether for IV use — which and why?** Artesunate — its hemisuccinate makes it water-soluble.

4 **What does ACT stand for? Give one example.** Artemisinin-based Combination Therapy; e.g., artemether + lumefantrine (Coartem).

5 **Why 14 days of primaquine?** To reliably kill all dormant hypnozoites in the liver (radical cure).

6 **Name the biguanide prodrug and its active form.** Proguanil cycloguanil.

7 **Which quinoline drug is natural?** Quinine, from Cinchona bark.

8 **$POCl_3$ is used in chloroquine synthesis for what step?** Converting 7-chloro-4-hydroxyquinoline to 4,7-dichloroquinoline.

E. Application-based questions

1 **Case:** A patient cured of vivax malaria with 3 days of chloroquine returns after 5 months with identical fever. Explain the biological reason and write the correct prescription this time. *(Expected: hypnozoite relapse; chloroquine 3 days + primaquine 14 days with G6PD counselling.)*

2 **Case:** A traveller with a history of depression needs malaria prophylaxis for a chloroquine-resistant area. Choose between mefloquine and Malarone and justify. *(Expected: Malarone — mefloquine is avoided with psychiatric history due to neuropsychiatric effects.)*

3 **Case:** A prescription reads "Chloroquine tablets for severe cerebral falciparum malaria." Identify the problem and correct it. *(Expected: severe malaria needs IV artesunate — fastest parasite clearance; tablets are too slow and absorption is unreliable.)*

4 **Structure task:** Draw chloroquine and circle the four SAR features (7-Cl, 4-NH, 4-carbon chain, terminal tertiary amine). Then predict: what happens to activity if the terminal $–N(Et)_2$ is replaced by $–NH_2$? *(Expected: reduced ion trapping and potency — tertiary basic amine is the SAR requirement.)*

2.22 References — Chapter 2

- Kar, A. *Medicinal Chemistry*. New Age International.
- Williams, D. A., Lemke, T. L., and Roche, V. F. *Foye's Principles of Medicinal Chemistry*. Lippincott Williams & Wilkins.
- Wilson, Beale, and Block. *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*. Lippincott Williams & Wilkins.

- Lednicer, D. *The Organic Chemistry of Drug Synthesis*. Wiley.
- Li, J. J. *Modern Drug Synthesis*. Wiley.
- Patrick, G. L. *An Introduction to Medicinal Chemistry*. Oxford University Press.
- Abraham, D. J. and Griffin, M. *Burger's Medicinal Chemistry and Drug Discovery*. Wiley.
- Brunton, L. L. et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. McGraw-Hill.
- Vogel's *Textbook of Practical Organic Chemistry*. Pearson.