BP501T · B.Pharm Semester V · Theory Notes

Biomedicinal Chemistry

Unit III — Antiprotozoals, Antivirals, Antifungals, Anthelmintics, UTI Agents, Antibiotics & Sulfa Drugs

Unit III (8 hours)

Pills & Python Notes

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

Syllabus coverage: Unit III (8 hours).

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B.Pharm Semester V | Unit III | Chapters 1–5 *Approved content draft — from-zero teaching notes in very simple English.* This unit studies two families of anti-infective drugs from the chemist's point of view: **antiprotozoals** (drugs that kill protozoa — single-celled parasites like the amoeba that causes dysentery) in Chapter 1, and **antivirals** (drugs that stop viruses — the tiny germs that cause flu, herpes, and HIV) in Chapter 2. For every drug you will learn three things: (1) its **chemical classification** — which structural family it belongs to, (2) its **structure** — described as a central scaffold plus the key substituents attached to it, and (3) its **uses** — what diseases it treats. SAR (structure–activity relationship) is presented as rule tables for the nitroimidazoles, the adamantanes, the nucleoside analogues, and the HIV protease inhibitors. For the two starred drugs (Metronidazole *and Acyclovir*) the full **synthesis** is given step by step, with every reagent, condition, and intermediate named.

CHAPTER 1: Antiprotozoals

1. Learning Objectives

After studying this chapter, you will be able to:

1 Define a protozoan infection and name the common protozoal diseases (amoebiasis, giardiasis, trichomoniasis, trypanosomiasis, leishmaniasis, Pneumocystis pneumonia).

2 Classify the ten syllabus antiprotozoal drugs into their chemical classes (nitroimidazoles, luminal amoebicides, diamidines, hydroxynaphthoquinones, ornithine analogues, aminoglycosides, nitrothiazoles).

3 Describe the chemical structure (scaffold + key substituents) of all ten antiprotozoal drugs.

4 Explain the mechanism of action of nitroimidazoles (nitro-group reduction by ferredoxin DNA damage) and the mechanisms of the other classes.

5 Write the complete synthesis of Metronidazole, naming every reagent, condition, and intermediate.

6 State the SAR rules of nitroimidazoles as a rule table.

7 Distinguish luminal amoebicides (Diloxanide, Iodoquinol, Paromomycin) from tissue amoebicides (Metronidazole, Tinidazole, Ornidazole).

8 State the therapeutic uses of each drug, with India-specific relevance (kala-azar, amoebic dysentery).

9 Draw the classification flowchart and the nitroimidazole activation flowchart.

2. Definitions

- **Protozoan.** A protozoan (plural: protozoa) is a **single-celled animal-like organism** — one cell that eats, moves, and multiplies like a tiny animal. Some protozoa live harmlessly in nature, but a few are parasites: they live inside the human body and cause disease. You cannot see them without a microscope.
- **Protozoal infection.** A disease caused by a parasitic protozoan multiplying inside the body. Examples: **amoebiasis** (bloody dysentery caused by *Entamoeba histolytica*), **giardiasis** (watery diarrhoea caused by *Giardia lamblia*), **trichomoniasis** (a sexually transmitted infection caused by *Trichomonas vaginalis*), **African trypanosomiasis** ("sleeping sickness" caused by *Trypanosoma brucei*), **leishmaniasis**

("kala-azar" or black fever in India, caused by *Leishmania donovani*), and **Pneumocystis pneumonia** (a lung infection in weak-immunity patients, caused by *Pneumocystis jirovecii*).

- **Antiprotozoal drug.** A medicine that kills protozoa or stops them from multiplying, without seriously harming the patient's own cells. Most antiprotozoals work by **attacking something the parasite has but human cells do not** (for example, the parasite's anaerobic energy system), or by **damaging the parasite's DNA**.
- **Amoebicide.** An antiprotozoal drug that kills *Entamoeba histolytica* (the amoeba of dysentery). **Luminal amoebicides** (Diloxanide, Iodoquinol, Paromomycin) act only inside the **gut tube (lumen)** and kill cysts and trophozoites there; **tissue amoebicides** (Metronidazole, Tinidazole, Ornidazole) are absorbed into the blood and reach amoebae in the **intestinal wall and liver**.
- **Nitroimidazole.** A chemical family whose members all contain an **imidazole ring** (a five-membered ring with two nitrogens) carrying a **nitro group (–NO_2)**. The nitro group is the "warhead": inside anaerobic parasites it is converted into toxic radicals that shred the parasite's DNA. Metronidazole, Tinidazole, and Ornidazole are nitroimidazoles.
- **Ferredoxin.** A small iron–sulphur protein found in anaerobic organisms (organisms that live without oxygen). Ferredoxin carries electrons and is the "switch" that activates nitroimidazole drugs inside the parasite — human cells lack this system, which is why the drug is selective.
- **SAR (Structure–Activity Relationship).** The study of how changing a part of a drug's structure changes its biological activity. SAR answers the question: "Which parts of this molecule are essential for killing the germ, and which parts can be changed?"

3. Terminology (word-by-word from zero)

Term	What it means in plain words
Scaffold	The central ring or carbon framework of a drug molecule — the "skeleton" to which substituents are attached. Example: the imidazole ring is the scaffold of metronidazole.
Substituent	A group of atoms attached to the scaffold, like decorations hung on a skeleton. Example: the –NO_2 group on metronidazole.
Anaerobe	An organism that lives and grows **without oxygen** (e.g., the amoeba in the gut, *Trichomonas*, anaerobic bacteria).
Trophozoite	The active, feeding, moving form of a protozoan (the form that causes disease symptoms).
Cyst	The tough, resting, sleeping form of a protozoan — it survives in soil and water and spreads the infection.
Luminal	Inside the hollow tube of the intestine (the lumen). A luminal drug stays in the gut and is not absorbed into blood.
Systemic	Throughout the body via the blood. A systemic drug is absorbed and reaches tissues and organs.
Prodrug	An inactive (or less active) form of a drug that the body converts into the active form.
Redox potential	A number that tells how easily a molecule accepts electrons. For nitroimidazoles, it decides how easily the nitro group is activated inside the parasite.

Term	What it means in plain words
Radical	A molecule fragment with an unpaired electron — extremely reactive and damaging; it tears apart DNA and proteins.
Selective toxicity	Killing the germ while sparing the patient — the central goal of all anti-infective drugs.
Isethionate	A salt form (2-hydroxyethanesulphonate) used to make a drug water-soluble for injection — as in pentamidine isethionate.
Chemoprophylaxis	Giving a drug to **prevent** a disease before it starts (rather than to treat it).
Relapse	The return of a disease after it seemed cured.

4. What Is a Protozoal Infection?

Technical concept. Protozoa are unicellular eukaryotes (single cells with a nucleus). Parasitic protozoa infect humans through contaminated water and food (amoeba, Giardia), insect bites (trypanosomes via the tsetse fly, Leishmania via the sandfly), sexual contact (*Trichomonas*), or weakened immunity (*Pneumocystis*). Antiprotozoal drugs exploit biochemical differences between parasite and host: anaerobic electron-transport proteins (nitroimidazoles), the kinetoplast DNA of trypanosomes (diamidines), mitochondrial respiration (atovaquone), polyamine synthesis (eflornithine), and ribosomal protein synthesis (paromomycin).

Simple explanation. Imagine your intestine as a long, dark, airless tunnel. Some tiny single-celled animals love exactly that environment — they eat the food you eat, multiply, and wound the tunnel walls, causing bloody dysentery. Other protozoa travel in the blood after an insect bite and attack the brain (sleeping sickness) or the internal organs (kala-azar). An antiprotozoal drug is a chemical that poisons something only the parasite has — like a lock that exists on the parasite's door but not on any human door.

Example. *Entamoeba histolytica* lives in the large intestine without oxygen. It has an electron-carrying protein (ferredoxin) that human cells do not use in the same way. Metronidazole enters the amoeba quietly, and ferredoxin hands electrons to its nitro group, converting it into toxic radicals that cut the amoeba's DNA into pieces. The amoeba dies; the patient's cells, which never activate the drug, are safe.

Key takeaway. Protozoa are single-celled parasites; antiprotozoals win by attacking chemistry the parasite has and we do not — anaerobic activation, parasite DNA, parasite mitochondria, or parasite polyamine synthesis.

5. Classification of Antiprotozoals (Chemical)

Technical concept. The ten syllabus drugs fall into seven chemical classes:

Flowchart 1 — Chemical classification of the syllabus antiprotozoals (draw this as a tree).

"ANTIPROTOZOALS (10 drugs)" branches into seven boxes:

1 **Nitroimidazoles** Metronidazole*, Tinidazole, Ornidazole

2 **Luminal amoebicides — dichloroacetamides** Diloxanide (as furoate ester)

3 **Luminal amoebicides — 8-hydroxyquinolines** Iodoquinol

4 **Aromatic diamidines** Pentamidine isethionate

5 **Hydroxynaphthoquinones** Atovaquone

6 **Ornithine analogues (difluoromethyl amino acids)** Eflornithine

7 **Aminoglycosides** Paromomycin

8 **Nitrothiazoles (thiazolides)** Nitazoxanide

(Eight boxes, seven classes — the two luminal amoebicide groups are listed separately because their scaffolds differ.)

Simple explanation. Chemists group drugs by their "family skeleton." Three drugs share the nitro-imidazole skeleton (the M-T-O trio: Metro, Tinid, Ornid). Two are gut-only amoeba killers with different skeletons (diloxanide, iodoquinol). The rest are loners, each with its own unique skeleton: pentamidine (twin amidines), atovaquone (naphthoquinone), eflornithine (a fake amino acid), paromomycin (a sugar antibiotic), nitazoxanide (a nitro-thiazole).

Example. If you see "–nidazole" at the end of a drug name (metroNIDAZOLE, tiniDAZOLE, orniDAZOLE), you immediately know: nitroimidazole family, nitro group warhead, activated by anaerobic parasites. The name itself tells you the chemistry.

Key takeaway. Learn the class from the suffix: –nidazole = nitroimidazole; the rest are identified by their unique scaffolds (diamidine, naphthoquinone, aminoglycoside, nitrothiazole).

6. Mechanisms of Action (Class by Class)

Technical concept. Each chemical class kills protozoa by a different molecular attack:

6.1 Nitroimidazoles (Metronidazole, Tinidazole, Ornidazole) — reductive activation DNA damage

Step-by-step mechanism (Flowchart 2 — draw as a vertical chain):

"Drug enters the anaerobic parasite (unchanged, harmless)" "Parasite's ferredoxin (electron-carrier protein) donates electrons to the $–NO_2$ group" "Nitro group is reduced step by step: $–NO_2$ nitro radical anion nitroso hydroxylamine" "Toxic nitro radicals are formed INSIDE the parasite" "Radicals break the parasite's DNA strands and damage proteins" "Parasite dies."

Simple explanation. The drug is like a **sleeper agent**. It walks into the parasite quietly and does nothing — until the parasite's own machinery (ferredoxin) hands it electrons and "wakes it up" into a violent radical that shreds the parasite's DNA from inside. Human cells do not wake it up, because they lack this ferredoxin system — that is the selective toxicity.

Example. *Trichomonas vaginalis* and *Giardia* live without oxygen and carry ferredoxin-like proteins, so metronidazole is activated inside them. Your vaginal and intestinal cells are aerobic (use oxygen) and never reduce the nitro group, so they are spared.

Key takeaway. Nitroimidazoles are **prodrugs activated only inside anaerobes** — ferredoxin reduces $–NO_2$ to DNA-shredding radicals. No oxygen-using human cell performs this activation.

6.2 Luminal amoebicides (Diloxanide, Iodoquinol) — direct contact killing in the gut

Technical concept. These drugs are **poorly absorbed** from the intestine, so they stay in the gut lumen at high concentration and kill *Entamoeba* trophozoites and cysts by direct contact. Their exact molecular target is not fully known (diloxanide is a dichloroacetamide; iodoquinol is a halogenated 8-hydroxyquinoline that may act by chelating metal ions the parasite needs).

Simple explanation. Think of them as **disinfectant left inside the water pipe**: they never enter the bloodstream, they just sit in the intestine and poison the amoebae passing through. That is why they cure the gut infection (and stop cyst-shedding) but cannot treat a liver abscess — they never reach the liver.

Key takeaway. Luminal = stays in the gut, kills amoebae there, never reaches blood or liver. Always pair with a tissue amoebicide for invasive disease.

6.3 Aromatic diamidine (Pentamidine) — DNA minor-groove binding

Technical concept. Pentamidine is a long molecule with a positively charged amidine group at each end. It slides into the **minor groove of DNA**, preferring AT-rich regions, and jams DNA replication and RNA/protein synthesis. It also interferes with polyamine synthesis and mitochondrial function in trypanosomes.

Simple explanation. Imagine DNA as a spiral staircase. Pentamidine is a rod that wedges itself into the narrow groove of the staircase, so the parasite's copying machinery cannot climb the stairs — no copying, no multiplication, parasite dies.

Key takeaway. Pentamidine = twin-charged rod that wedges into parasite DNA's minor groove and blocks replication.

6.4 Hydroxynaphthoquinone (Atovaquone) — mitochondrial electron-transport blockade

Technical concept. Atovaquone blocks the **cytochrome bc_1 complex (Complex III)** of the parasite's mitochondrial electron-transport chain — the parasite's "power station." Without electron flow, the parasite cannot make energy (ATP) and cannot make pyrimidines for DNA.

Simple explanation. Every cell runs a tiny power station (mitochondria). Atovaquone throws a wrench into the parasite's power station at one specific gear (Complex III). The lights go out — the parasite cannot make energy or DNA building blocks, and it starves.

Key takeaway. Atovaquone = wrench in the parasite's mitochondrial power station (cytochrome bc_1, Complex III).

6.5 Ornithine analogue (Eflornithine) — suicide inhibition of polyamine synthesis

Technical concept. Eflornithine looks like the amino acid **ornithine**, so the parasite's enzyme **ornithine decarboxylase** grabs it — but the difluoromethyl group then **permanently (irreversibly) locks** the enzyme. Without this enzyme the parasite cannot make **polyamines** (small molecules essential for cell division), so trypanosomes stop multiplying.

Simple explanation. It is a **fake key that breaks inside the lock**. The parasite's enzyme mistakes eflornithine for its natural raw material (ornithine), swallows it, and gets permanently jammed. No polyamines no cell division the sleeping-sickness parasite cannot multiply.

Key takeaway. Eflornithine = fake ornithine that permanently jams ornithine decarboxylase polyamine starvation trypanosomes cannot divide.

6.6 Aminoglycoside (Paromomycin) — ribosomal protein-synthesis blockade

Technical concept. Paromomycin binds the **30S subunit of the parasite's ribosome** (the protein-making factory), causing misreading of the genetic code and stopping protein production. In the gut it acts as a luminal amoebicide; given by injection it reaches *Leishmania* parasites.

Simple explanation. The ribosome is the parasite's protein factory, reading an instruction tape (mRNA). Paromomycin scrambles the reading head — the factory produces garbage proteins and shuts down.

Key takeaway. Paromomycin = aminoglycoside that jams the parasite's 30S ribosome faulty proteins death. Luminal in the gut; injectable for kala-azar.

6.7 Nitrothiazole (Nitazoxanide) — PFOR inhibition

Technical concept. Nitazoxanide blocks **pyruvate:ferredoxin oxidoreductase (PFOR)**, an enzyme anaerobic parasites use to convert pyruvate into energy. Like nitroimidazoles, its nitro group is also reduced in anaerobes, adding a second killing mechanism.

Simple explanation. Anaerobic parasites run a special energy furnace (PFOR) that human cells do not have. Nitazoxanide jams that furnace — no energy, parasite dies. It also carries a nitro "warhead" like metronidazole for extra damage.

Key takeaway. Nitazoxanide = jams the anaerobe-only energy enzyme PFOR (+ nitro warhead) — broad anti-protozoal action.

7. Structure Diagrams (Describe Textually — Draw These)

Diagram 1 — The nitroimidazole "family skeleton" (common to Metronidazole, Tinidazole, Ornidazole). Draw a five-membered ring: positions 1 and 3 are nitrogen atoms (N), positions 2, 4, 5 are carbons. At **C5** attach a **–NO_2 (nitro) group** — label it "WARHEAD (activated in anaerobes)." At **C2** attach a **–CH_3 (methyl) group** — label "activity booster." At **N1** attach a variable side chain R — label "R decides which drug it is: –CH_2CH_2OH = Metronidazole; –$CH_2CH_2SO_2CH_2CH_3$ = Tinidazole; –$CH_2CH(OH)CH_2Cl$ = Ornidazole." Number the ring 1–5.

Diagram 2 — Metronidazole full structure. Draw the 5-nitroimidazole ring with: N1 bearing **–CH_2–CH_2–OH** (2-hydroxyethyl chain — two carbons ending in an alcohol; this –OH makes the drug water-soluble), C2 bearing **–CH_3**, C5 bearing **–NO_2**. Below, write the name: 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol.

Diagram 3 — Diloxanide furoate. Draw a benzene ring (left). On it: at para position, an **–O–CO–(2-furyl)** ester group (the furoate part — a five-membered furan ring with oxygen, attached via C=O); at the other para position, an **–N(CH_3)–CO–$CHCl_2$** group (the dichloroacetamide part — nitrogen carrying a methyl and a –CO–$CHCl_2$ dichloroacetyl group). Label: "Furoate ester = prodrug mask (removed in gut); dichloroacetamide = active part."

Diagram 4 — Iodoquinol. Draw a **quinoline** system: a benzene ring fused to a pyridine ring (two fused six-membered rings, one nitrogen in the second ring). On the pyridine part: **–OH at position 8** (next to the ring nitrogen — label "chelating pair: N···OH"). On the benzene part: **iodine atoms at positions 5 and 7** (two big I atoms — label "heavy halogens; drug poorly absorbed, stays in gut").

Diagram 5 — Pentamidine. Draw a horizontal molecule: left benzene ring with **–C(=NH)NH_2 (amidine)** at para position **–O– –$(CH_2)_5$–** (five-carbon chain) **–O–** right benzene ring with para **–C(=NH)NH_2**. Label the two ends "positively charged amidines (grip DNA)" and the middle "flexible 5-carbon + ether spacer (spans the DNA groove)."

Diagram 6 — Atovaquone. Draw a **1,4-naphthoquinone**: two fused six-membered rings; the right ring has **C=O at positions 1 and 4** (quinone) and **–OH at position 3** (label "hydroxyquinone — redox-active head"). At position 2 attach a **cyclohexane ring** (six-membered saturated ring), and on the far side of that cyclohexane a **para-chlorophenyl group** (–C_6H_4–Cl). Label the tail "bulky lipophilic tail (anchors into mitochondrial membrane)."

Diagram 7 — Eflornithine. Draw a straight five-carbon amino-acid chain: **HOOC–C(NH_2)(CHF_2)–CH_2–CH_2–CH_2–NH_2**. Label: "Looks exactly like ornithine (an amino acid) EXCEPT the

α-carbon carries a –CHF_2 (difluoromethyl) group — label 'the trap: this group permanently jams the enzyme.'"

Diagram 8 — Paromomycin (simplified). Draw a central six-membered ring labelled **"2-deoxystreptamine (aminocyclitol core)"** with **–NH_2** and **–OH** groups. From it, draw three sugar rings branching off, each labelled with its amino/hydroxy groups: "Ring A: 2-amino-2-deoxy-glucose," "Ring B: ribose," "Ring C: diamino-dideoxy-idose." Label the whole: "Aminoglycoside = amino sugars on a central core — many –NH_2/–OH groups (very water-soluble, poorly absorbed from gut)."

Diagram 9 — Nitazoxanide. Draw a benzene ring (left) bearing **–O–CO–CH_3 (acetoxy)** at ortho position and **–CO–NH–** at the adjacent position; the –NH– connects to a **thiazole ring** (five-membered: S at 1, N at 3) bearing **–NO_2 at position 5**. Label: "Left = salicylate-like half; right = 5-nitrothiazole warhead (nitro group = anaerobic activation)."

8. Flowcharts

Flowchart 3 — Synthesis of Metronidazole (see full details in Section 13). "2-Methylimidazole" —(conc. HNO_3 + conc. H_2SO_4, heat; nitration) "2-Methyl-4(5)-nitroimidazole" —(ethylene oxide, base; N-hydroxyethylation) "Metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole]."

Flowchart 4 — Choosing the right amoebicide (clinical logic from chemistry). "Patient has amoebiasis" "Is it ONLY in the gut (cysts, mild diarrhoea)?" YES "Luminal amoebicide: Diloxanide furoate or Iodoquinol or Paromomycin (oral)." NO (invasive: bloody dysentery / liver abscess) "Tissue amoebicide: Metronidazole / Tinidazole / Ornidazole" then "FOLLOW with a luminal amoebicide to clear gut cysts and prevent relapse." Add note: "Tissue drugs are absorbed; luminal drugs are not — chemistry decides the reach."

9. Infographic Concept Box

ANTIPROTOZOALS AT A GLANCE The enemies: Single-celled parasites — amoeba (bloody dysentery), Giardia (watery diarrhoea), Trichomonas (STI), trypanosomes (sleeping sickness), Leishmania (kala-azar), Pneumocystis (pneumonia in weak immunity). **The star weapon — nitroimidazoles (M-T-O):** Metronidazole*, Tinidazole, Ornidazole. Shared skeleton: 5-nitroimidazole ring; –NO_2 at C5 = warhead; –CH_3 at C2 = booster; N1 side chain = the name-giver. They are **sleeper agents**: harmless until the parasite's ferredoxin wakes the nitro group into DNA-shredding radicals. Human cells never wake them. **Gut-only killers (luminal):** Diloxanide furoate, Iodoquinol, Paromomycin (oral) — never absorbed, disinfect the intestine, cannot treat liver abscess. **Rule: tissue infection nitroimidazole first, THEN a luminal drug to mop up cysts. The specialists:** Pentamidine (twin amidines wedge into parasite DNA — sleeping sickness, PCP); Atovaquone (wrench in parasite mitochondrial Complex III — PCP, malaria); Eflornithine (fake ornithine that permanently jams polyamine synthesis — sleeping sickness); Nitazoxanide (jams the anaerobe-only PFOR furnace — Cryptosporidium, Giardia). **Name tricks:** "–nidazole" = nitroimidazole. **Star synthesis:** Metronidazole = 2-methylimidazole (nitration) nitroimidazole (ethylene oxide) hydroxyethyl side chain added. **India notes:** Metronidazole is among the most used (and misused — self-medicated for every diarrhoea) drugs in India; Paromomycin injection is a key kala-azar drug in Bihar.

10. Master Table — Chapter 1 Drugs

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Metronidazole*	Nitroimidazole	5-nitroimidazole ring + 2-methyl + N1-(2-hydroxyethyl)	Amoebiasis (intestinal + liver abscess), giardiasis, trichomoniasis, anaerobic bacterial infections, bacterial vaginosis, H. pylori regimens
Tinidazole	Nitroimidazole	5-nitroimidazole ring + 2-methyl + N1-[2-(ethylsulphonyl)ethyl]	Same as metronidazole; longer half-life (single-dose options), bacterial vaginosis, giardiasis
Ornidazole	Nitroimidazole	5-nitroimidazole ring + 2-methyl + N1-(3-chloro-2-hydroxypropyl)	Amoebiasis, giardiasis, trichomoniasis, anaerobic infections (popular in Indian fixed-dose combinations)
Diloxanide (furoate)	Dichloroacetamide (luminal amoebicide)	p-(N-methyl-dichloroacetamido)phenyl furoate ester	Asymptomatic intestinal amoebiasis (cyst passers); follow-up after tissue amoebicide
Iodoquinol	8-Hydroxyquinoline (luminal amoebicide)	5,7-diiodo-8-hydroxyquinoline	Intestinal amoebiasis; Dientamoeba, Blastocystis infections
Pentamidine isethionate	Aromatic diamidine	Bis(4-amidinophenoxy)pentane (twin amidines + 5-carbon ether spacer), isethionate salt	Pneumocystis pneumonia (treatment/prophylaxis), early African trypanosomiasis, visceral leishmaniasis (alternative)
Atovaquone	Hydroxynaphthoquinone	3-hydroxy-1,4-naphthoquinone + 2-[4-(4-chlorophenyl)cyclohexyl] tail	Pneumocystis pneumonia, toxoplasmosis; with proguanil for malaria (prophylaxis/treatment); babesiosis
Eflornithine	Ornithine analogue (difluoromethyl amino acid)	α-difluoromethyl-ornithine (fake amino acid with $–CHF_2$ trap)	African trypanosomiasis (late-stage, CNS; with nifurtimox); hirsutism (topical cream)
Paromomycin	Aminoglycoside	2-deoxystreptamine core + 3 amino-sugar rings	Intestinal amoebiasis (luminal), giardiasis, cryptosporidiosis; visceral leishmaniasis/kala-azar (injection)
Nitazoxanide	Nitrothiazole (thiazolide)	N-(5-nitrothiazol-2-yl) salicylamide (acetoxy ortho + nitrothiazole warhead)	Cryptosporidiosis, giardiasis; broad antiparasitic

11. Drug-by-Drug Profiles — Structure and Uses

A. NITROIMIDAZOLES

1. Metronidazole*

- **Chemical classification:** Nitroimidazole (5-nitroimidazole) — the prototype of the class.
- **Structure:** Scaffold = **imidazole ring** (five-membered, N at 1 and 3). Key substituents: **$–NO_2$ at C5** (the warhead — reduced inside anaerobes to DNA-damaging radicals), **$–CH_3$ at C2** (boosts activity), and

–CH_2CH_2OH (2-hydroxyethyl) at N1 (gives water solubility for oral/IV use). Chemical name: 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol.

- **Uses: Intestinal amoebiasis and amoebic liver abscess**; **giardiasis**; **trichomoniasis** (including the partner, single dose); **anaerobic bacterial infections** (intra-abdominal, pelvic, dental, *C. difficile* colitis); **bacterial vaginosis**; part of **H. pylori** eradication regimens; surgical prophylaxis for colorectal surgery.
- **Synthesis:** see Section 13 (starred — full steps, reagents, conditions, intermediates).

2. Tinidazole

- **Chemical classification:** Nitroimidazole (second generation).
- **Structure:** Same 5-nitroimidazole + 2-methyl scaffold as metronidazole; the N1 side chain is **–CH_2CH_2–SO_2–CH_2CH_3** [2-(ethylsulphonyl)ethyl]. The sulphone (–SO_2–) group is electron-withdrawing and bulky — it slows metabolism, giving a **longer half-life (~12–14 h vs ~8 h for metronidazole)**.
- **Uses:** Same spectrum as metronidazole — **amoebiasis, giardiasis, trichomoniasis, bacterial vaginosis, anaerobic infections**; preferred where single-dose or short-course therapy is wanted (e.g., single 2 g dose for trichomoniasis/giardiasis).

3. Ornidazole

- **Chemical classification:** Nitroimidazole.
- **Structure:** Same 5-nitroimidazole + 2-methyl scaffold; N1 side chain is **–CH_2–CH(OH)–CH_2Cl** (3-chloro-2-hydroxypropyl). The side chain carries both a **chlorine** and a **hydroxyl group** — the –OH aids solubility, the –Cl tunes the redox behaviour.
- **Uses: Amoebiasis, giardiasis, trichomoniasis, anaerobic bacterial infections**; very widely used in India, often in fixed-dose combinations (e.g., with ofloxacin for mixed diarrhoea — a combination pharmacists must counsel on carefully).

B. LUMINAL AMOEBICIDES

4. Diloxanide (used as Diloxanide furoate)

- **Chemical classification:** Dichloroacetamide — luminal amoebicide.
- **Structure:** Scaffold = a **para-disubstituted benzene**. Substituents: at one end **–N(CH_3)–CO–$CHCl_2$** (N-methyl-dichloroacetamide — the active amoeba-killing part); at the other end **–O–CO–(2-furyl)** (furoate ester). The furoate ester is a **prodrug mask**: gut esterases clip it off, releasing active diloxanide in the lumen. The drug is poorly absorbed, so it stays in the intestine.
- **Uses: Asymptomatic intestinal amoebiasis (cyst passers)** — the drug of choice for eradicating luminal cysts; **follow-up therapy after metronidazole** for invasive amoebiasis (to prevent relapse from surviving gut cysts).

5. Iodoquinol (diiodohydroxyquinoline)

- **Chemical classification:** Halogenated 8-hydroxyquinoline — luminal amoebicide.

- **Structure:** Scaffold = **quinoline** (benzene fused to pyridine). Key substituents: **–OH at C8** (adjacent to the ring nitrogen — together they form a metal-chelating pair) and **two iodine atoms at C5 and C7**. The heavy iodines make the molecule poorly absorbed — it remains in the gut lumen.
- **Uses: Intestinal (luminal) amoebiasis**; also used for *Dientamoeba fragilis* and *Blastocystis* infections.

C. AROMATIC DIAMIDINE

6. Pentamidine isethionate

- **Chemical classification:** Aromatic diamidine.
- **Structure:** Scaffold = two **para-amidinophenyl** units (benzene rings each carrying –C(=NH)NH_2, a strongly basic amidine, at para position) joined by a flexible spacer: **–O–$(CH_2)_5$–O–** (pentamethylene chain with ether oxygens). The two positively charged amidine ends grip the negatively charged DNA minor groove; the spacer length matches the groove. Supplied as the **isethionate salt** (bis-2-hydroxyethanesulphonate) for water solubility for injection/inhalation.
- **Uses: Pneumocystis jirovecii pneumonia** — treatment and prophylaxis (second-line after co-trimoxazole); **early-stage African trypanosomiasis** (*T. brucei gambiense*, before CNS invasion); **visceral leishmaniasis** (alternative/second-line).

D. HYDROXYNAPHTHOQUINONE

7. Atovaquone

- **Chemical classification:** Hydroxynaphthoquinone.
- **Structure:** Scaffold = **3-hydroxy-1,4-naphthoquinone** (two fused rings; one ring carries two C=O groups at 1,4 and an –OH at 3 — the redox-active "head" that mimics ubiquinone in the electron-transport chain). Key substituent: at C2, a bulky lipophilic tail — **trans-4-(4-chlorophenyl)cyclohexyl** (a cyclohexane ring carrying a para-chlorophenyl group). The tail anchors the drug into the mitochondrial membrane next to Complex III.
- **Uses: Pneumocystis pneumonia** (mild-to-moderate, in patients who cannot take co-trimoxazole); **toxoplasmosis**; **babesiosis** (with azithromycin); **malaria** — combined with proguanil (as the fixed combination) for prophylaxis and treatment.

E. ORNITHINE ANALOGUE

8. Eflornithine (DFMO)

- **Chemical classification:** α-Difluoromethyl amino acid — ornithine analogue.
- **Structure:** Scaffold = the amino acid **ornithine** backbone: HOOC–C–CH_2–CH_2–CH_2–NH_2 with an α-amino group. The trick: the α-carbon also carries a **–CHF_2 (difluoromethyl) group**. The molecule looks exactly like ornithine to the enzyme, but the –CHF_2 group reacts irreversibly once bound — a "suicide" trap.
- **Uses: African trypanosomiasis — late (CNS) stage** caused by *T. brucei gambiense* (with nifurtimox, the NECT regimen — the current standard); topical cream for **hirsutism** (unwanted facial hair in women — polyamines also drive hair growth).

F. AMINOGLYCOSIDE

9. Paromomycin

- **Chemical classification:** Aminoglycoside antibiotic with antiprotozoal action.
- **Structure:** Scaffold = **2-deoxystreptamine** (a six-membered aminocyclitol ring with $–NH_2$ and –OH groups). Attached to it are **three amino-sugar rings** (amino and hydroxy groups everywhere). The crowd of $–NH_2$ groups (protonated at gut pH) and –OH groups makes the molecule **extremely water-soluble and virtually unabsorbed** from the intestine — perfect for luminal action.
- **Uses: Intestinal amoebiasis** (luminal amoebicide, oral); **giardiasis**; **cryptosporidiosis**; **visceral leishmaniasis (kala-azar)** — by intramuscular injection, a key drug in India's Bihar kala-azar elimination programme.

G. NITROTHIAZOLE

10. Nitazoxanide

- **Chemical classification:** Nitrothiazole (thiazolide).
- **Structure:** Scaffold = a **salicylamide** (benzene with ortho $–OCOCH_3$ acetoxy and –CONH– groups) linked through the amide nitrogen to a **thiazole ring** (five-membered, S and N) carrying **$–NO_2$ at C5**. Two pharmacophores in one molecule: the **nitrothiazole warhead** (anaerobic activation, like nitroimidazoles) and the salicylate half (PFOR inhibition).
- **Uses: Cryptosporidiosis** (especially in immunocompromised patients) and **giardiasis** (first-line in some guidelines); broad activity also covers helminths; investigated for viral infections (influenza).

12. SAR of Nitroimidazoles (Rule Table)

Technical concept. Structure–Activity Relationship (SAR) records which parts of the nitroimidazole molecule are essential and which can be varied. The rules below were worked out by making hundreds of analogues and testing them against *Trichomonas*, *Giardia*, and anaerobic bacteria.

Simple explanation. Think of the molecule as a weapon with three parts — warhead, booster, and handle. SAR tells you: never remove the warhead, keep the booster, and you may redesign the handle to change solubility and duration.

Rule	Structural feature	Effect on activity	Example
1	**$–NO_2$ at C5 of the imidazole ring**	**Essential — the warhead.** Removing it or moving it destroys antiprotozoal activity, because there is nothing for ferredoxin to reduce.	All active nitroimidazoles carry 5-NO_2; des-nitro analogues are inactive.
2	**$–CH_3$ at C2**	**Strongly preferred.** A methyl at C2 gives the best balance of redox potential and activity; larger groups at C2 reduce activity.	Metronidazole, tinidazole, ornidazole all keep 2-methyl.
3	**N1 must be substituted (no free N–H)**	**Essential.** A hydrogen at N1 allows tautomerism and poor activity; an N1 side chain locks the structure and tunes properties.	All three drugs have N1 alkyl side chains.

Rule	Structural feature	Effect on activity	Example
4	**Nature of the N1 side chain**	**Tunes solubility, half-life, and tissue reach.** Hydroxyethyl (–CH_2CH_2OH) gives good water solubility (metronidazole — oral and IV). Bulky electron-withdrawing groups (sulphone in tinidazole) slow metabolism longer half-life.	Tinidazole (sulphone side chain): t½ ~12–14 h, single-dose therapy possible.
5	**Redox potential of the nitro group**	Activity tracks the ease of nitro reduction: the side chain's elec tron-withdrawing/donating character shifts the reduction potential; an optimal window gives selective activation in parasites without host toxicity.	Ornidazole's chloro-hydroxypropyl chain fine-tunes this window.
6	**Lipophilicity balance**	Enough lipid solubility to enter the parasite, enough water solubility to dissolve in body fluids. Too lipophilic trapped in fat; too hydrophilic cannot cross parasite membranes.	Metronidazole's hydroxyethyl gives the balanced profile — crosses the blood–brain barrier and placenta.

Key takeaway. Nitroimidazole SAR in one line: **5-NO_2 is the warhead, 2-CH_3 is the booster, N1 is the handle you redesign** — the handle decides solubility, half-life, and formulation.

13. Synthesis of Metronidazole* (Starred — Full Steps)

Technical concept. Metronidazole is built in two operations: (1) **electrophilic nitration** of 2-methylimidazole installs the –NO_2 warhead on the ring; (2) **N-alkylation** with ethylene oxide (oxirane) attaches the 2-hydroxyethyl side chain to N1.

Step 1 — Nitration of 2-methylimidazole to 2-methyl-4(5)-nitroimidazole.

- **Starting material:** 2-Methylimidazole — the imidazole ring with a methyl group at C2.
- **Reagents:** Concentrated nitric acid (conc. HNO_3) + concentrated sulphuric acid (conc. H_2SO_4) — **mixed acid** (the sulphuric acid generates the nitronium ion, NO_2^+, the active nitrating species).
- **Conditions:** Heating (the reaction mixture is warmed; temperature controlled because nitration is exothermic).
- **Reaction:** Electrophilic aromatic substitution — NO_2^+ attacks the electron-rich imidazole ring. (Nitration occurs at the 4/5 position; the 4-nitro and 5-nitro forms are tautomers of the same compound, so a single product is obtained.)
- **Intermediate/product of Step 1: 2-Methyl-4(5)-nitroimidazole** — the nitro warhead is now on the ring.

Step 2 — N-Hydroxyethylation to Metronidazole.

- **Starting material:** 2-Methyl-4(5)-nitroimidazole (from Step 1).
- **Reagents: Ethylene oxide (oxirane)** — a three-membered cyclic ether; base (e.g., dilute alkali) to deprotonate the imidazole N–H and make N1 nucleophilic.

- **Conditions:** Mild heating in a suitable solvent; the strained epoxide ring opens on attack by the imidazole nitrogen.
- **Reaction:** The N1 nitrogen of the imidazole attacks ethylene oxide, opening the three-membered ring and attaching a $–CH_2CH_2OH$ group to N1. (Alkylation occurs selectively at N1, adjacent to the 2-methyl group, giving the 5-nitro isomer as the product.)
- **Final product: Metronidazole — 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole** [2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol].

Simple explanation. Start with 2-methylimidazole, a simple ring with a methyl tag. Boil it with the classic nitrating mixture (nitric + sulphuric acids) and a nitro group ($–NO_2$) gets hammered onto the ring — that is your warhead. Then add ethylene oxide, a tiny triangular molecule that springs open when the ring's nitrogen grabs it, leaving a two-carbon chain ending in –OH attached to the nitrogen. That chain makes the drug dissolve in water. Two steps: **nitrate, then hydroxyethylate — and you have metronidazole.**

Key takeaway. Metronidazole = 2-methylimidazole (mixed-acid nitration) nitroimidazole (ethylene oxide, base) N1-hydroxyethylation final drug. Warhead first, solubility handle second.

14. Pharmacy Relevance

Technical concept. A pharmacist's chemistry knowledge of antiprotozoals directly guides dispensing, counselling, and rational use.

Simple explanation — what you will actually do at the counter:

- **Metronidazole + alcohol = danger.** Metronidazole blocks aldehyde dehydrogenase, so alcohol piles up as acetaldehyde — flushing, vomiting, pounding headache (disulfiram-like reaction). **Counsel every patient: no alcohol during treatment and for 48–72 hours after.** This is the single most important counselling point for India's most self-medicated antiprotozoal.
- **Metallic taste and dark urine** are harmless, expected effects of metronidazole — warn patients so they do not panic and stop the drug.
- **Treat the partner** in trichomoniasis — both partners take the single dose, or reinfection is certain.
- **Luminal follow-up:** after metronidazole for amoebic dysentery or liver abscess, dispense the luminal amoebicide (diloxanide) course — explain "the first drug killed the invaders in the tissues; this one cleans the gut so the disease does not come back."
- **Pentamidine and atovaquone** need special handling: pentamidine injection can drop blood pressure and blood sugar suddenly — it is a hospital drug, never a take-home tablet; atovaquone must be taken **with fatty food** (its bulky tail makes it fat-soluble — food doubles absorption).
- **Fixed-dose combinations** (e.g., ofloxacin + ornidazole) are hugely popular in India for diarrhoea — counsel that they are for **mixed bacterial + protozoal** infection, not for every loose motion, and that indiscriminate use breeds resistance.

Key takeaway. Your chemistry tells you *why* (nitro group alcohol interaction; fat-soluble tail take with food; non-absorbed gut-only action); your counselling turns that *why* into patient safety.

15. India Context

- **Amoebiasis and giardiasis** are among the commonest causes of diarrhoea and dysentery in India, spread through contaminated water — metronidazole, tinidazole, and ornidazole are therefore among the highest-volume anti-infectives dispensed in Indian retail pharmacies, and also among the most **self-medicated** (a major antimicrobial-stewardship concern).
- **Kala-azar (visceral leishmaniasis)** is endemic in **Bihar, Jharkhand, West Bengal, and eastern Uttar Pradesh**; India runs a kala-azar elimination programme in which **paromomycin injection** (often with miltefosine) is a frontline therapy — a pharmacist in these states must know its handling and counselling.
- **Pneumocystis pneumonia** is the classic opportunistic infection in Indian HIV/AIDS patients; **pentamidine** (nebulised for prophylaxis, injectable for treatment) and **atovaquone** are hospital formulary drugs for patients who cannot tolerate co-trimoxazole.
- **Sleeping sickness (trypanosomiasis)** does not occur in India, but **eflornithine and pentamidine** are exam-relevant as the textbook examples of ornithine-analogue and diamidine chemistry, and eflornithine cream is marketed in India for hirsutism.
- All ten drugs appear in the **Indian Pharmacopoeia** with official assay and purity standards — the pharmacist is the guardian of that quality at dispensing.

16. Key Points

1. Antiprotozoals kill single-celled parasites by attacking parasite-only chemistry (anaerobic activation, parasite DNA, mitochondria, polyamines, ribosomes).
2. The **nitroimidazole trio (M-T-O: Metronidazole, Tinidazole, Ornidazole)** shares the 5-nitroimidazole scaffold; $–NO_2$ at C5 is the warhead, $–CH_3$ at C2 the booster, N1 side chain the handle.
3. Nitroimidazoles are **sleeper agents**: ferredoxin in anaerobes reduces $–NO_2$ to DNA-shredding radicals; human cells cannot activate them.
4. **Luminal amoebicides** (Diloxanide, Iodoquinol, oral Paromomycin) stay in the gut; **tissue amoebicides** (nitroimidazoles) reach blood, wall, and liver. Invasive disease needs tissue drug first, then a luminal drug to clear cysts.
5. **Pentamidine** = twin amidines wedging into parasite DNA minor groove (PCP, early sleeping sickness).
6. **Atovaquone** = hydroxynaphthoquinone blocking mitochondrial Complex III (PCP, malaria with proguanil).
7. **Eflornithine** = fake ornithine that irreversibly jams ornithine decarboxylase no polyamines no trypanosome division.
8. **Paromomycin** = aminoglycoside; luminal amoebicide orally, kala-azar drug by injection.
9. **Nitazoxanide** = nitrothiazole blocking the anaerobe-only PFOR energy enzyme (+ nitro warhead); drug of choice for cryptosporidiosis.
10. Metronidazole synthesis: 2-methylimidazole (mixed-acid nitration) 2-methyl-4(5)-nitroimidazole (ethylene oxide, base) metronidazole.

17. Common Confusions

Confusion	Clarification
Metronidazole vs Tinidazole vs Ornidazole	All three are nitroimidazoles with the **same scaffold and same uses**; they differ only in the **N1 side chain** (hydroxyethyl / ethylsulphonylethyl / chloro-hydroxypropyl), which changes half-life and solubility — not the spectrum.
Diloxanide vs Metronidazole for amoebiasis	Diloxanide kills amoebae **only in the gut lumen** (cyst passers, follow-up); metronidazole reaches **tissues and liver** (invasive disease). They are partners, not substitutes.
Iodoquinol vs Diloxanide	Both are luminal amoebicides but different scaffolds: iodoquinol = halogenated **8-hydroxyquinoline**; diloxanide = **dichloroacetamide** (given as furoate prodrug).
Pentamidine vs "pent-" antibiotics	Pentamidine is a **diamidine antiprotozoal**, not a penicillin — the "pent-" refers to the five-carbon spacer, not the drug family.
Atovaquone is only antimalarial	Atovaquone is also a first-line alternative for **Pneumocystis pneumonia** and is used for **toxoplasmosis and babesiosis** — it is a hydroxynaphthoquinone, not a quinoline antimalarial.
Eflornithine is an antibiotic	It is an **amino-acid analogue** (fake ornithine), an enzyme suicide inhibitor — chemically unrelated to antibiotics.
Paromomycin is only for gut	Oral paromomycin is a luminal amoebicide, but **injectable** paromomycin is a systemic **kala-azar** drug — route decides reach.

18. Common Mistakes

1. **Leaving editorial markings or checklist notes in a final answer** — exams and clean notes must present only finished content, never working notes or status labels.
2. Saying metronidazole "kills by stopping protein synthesis" — wrong class; nitroimidazoles kill by **nitro reduction DNA damage**.
3. Prescribing/dispensing a luminal amoebicide alone for **amoebic liver abscess** — it never reaches the liver; a tissue nitroimidazole is mandatory.
4. Forgetting the **alcohol warning** with metronidazole/tinidazole/ornidazole (disulfiram-like reaction).
5. Confusing **isethionate** (a salt for solubility) with the active drug — pentamidine isethionate's action comes from pentamidine; the salt only helps it dissolve.
6. Stating atovaquone's target as "DNA" — it targets **mitochondrial Complex III**, not DNA.
7. Mixing up **ferredoxin activation** (nitroimidazoles) with **PFOR inhibition** (nitazoxanide) — related anaerobe chemistry, different molecular targets.

19. Mnemonics

- **Nitroimidazole trio: "M-T-O"** — **M**etronidazole, **T**inidazole, **O**rnidazole. Memory hook: "**M**y **T**ummy's **O**kay" — they fix tummy parasites (amoeba, Giardia).
- **Nitroimidazole scaffold: "5-2-1"** — **5**-nitro warhead, **2**-methyl booster, **1**-side-chain handle. "The **5-2-1** rule: warhead–booster–handle."
- **Luminal amoebicides: "DIP"** — **D**iloxanide, **I**odoquinol, **P**aromomycin (oral). "Take a **DIP** in the gut — they never leave the intestine."

- **Tissue then luminal: "Kill the soldiers, then burn the camp"** — nitroimidazole kills tissue invaders first; luminal drug then clears gut cysts so there is no relapse.
- **Pentamidine: "PENTA"** — **P**neumocystis, **E**arly trypanosomiasis, **N**egative-charge DNA grip, **T**win amidines, **A**romatic. (Five-carbon spacer = "penta.")
- **Atovaquone: "A-TOVA-quone blocks Complex THREE"** — "**Q**uinone jams the **Q**-cycle (Complex III)."
- **Eflornithine: "Fake ORNithine FLies in, ORNithine decarboxylase dies"** — suicide inhibitor of polyamine synthesis.
- **Metronidazole synthesis: "Nitrate, then Hydroxyethylate"** — "**N**itro first, **H**andle second."

20. Exam Summary

Antiprotozoals (10 drugs, 7 chemical classes). **Nitroimidazoles** — Metronidazole*, Tinidazole, Ornidazole: 5-nitroimidazole scaffold (C5–NO_2 warhead, C2–CH_3, N1 side chain); activated by ferredoxin in anaerobes nitro radicals DNA strand breaks; uses: amoebiasis (gut + liver), giardiasis, trichomoniasis, anaerobic infections, bacterial vaginosis. SAR: 5-NO_2 essential; 2-CH_3 optimal; N1 substituted (tunes t½/solubility); redox window critical. **Luminal amoebicides** — Diloxanide furoate (dichloroacetamide prodrug), Iodoquinol (5,7-diiodo-8-hydroxyquinoline): stay in gut, kill cysts/trophozoites; follow-up after tissue drug. **Pentamidine isethionate** (aromatic diamidine): minor-groove DNA binder; PCP, early sleeping sickness. **Atovaquone** (hydroxynaphthoquinone): Complex III blocker; PCP, malaria (+proguanil). **Eflornithine** (α-difluoromethylornithine): suicide inhibitor of ornithine decarboxylase; late-stage sleeping sickness. **Paromomycin** (aminoglycoside): 30S binder; luminal amoebicide orally, kala-azar by injection. **Nitazoxanide** (nitrothiazole): PFOR inhibitor; cryptosporidiosis, giardiasis. Synthesis (starred): Metronidazole = 2-methylimidazole (HNO_3/H_2SO_4, heat) 2-methyl-4(5)-nitroimidazole (ethylene oxide, base) metronidazole.

21. One-Minute Revision

M-T-O = nitroimidazole trio (5-NO_2 warhead, 2-CH_3, N1 handle). **Sleeper agents**: ferredoxin wakes –NO_2 into DNA-shredding radicals — only in anaerobes. **DIP** (Diloxanide, Iodoquinol, Paromomycin-oral) = gut-only; tissue drug first, luminal drug after. **Pentamidine** = twin amidines wedge DNA (PCP, sleeping sickness). **Atovaquone** = quinone jams Complex III (PCP, malaria). **Eflornithine** = fake ornithine, suicide-jams polyamine enzyme (late sleeping sickness). **Nitazoxanide** = jams PFOR furnace (Crypto, Giardia). **Metronidazole synthesis**: nitrate 2-methylimidazole, then hydroxyethylate with ethylene oxide. **Counsel**: no alcohol with nitroimidazoles!

22. Exam Questions

Short answer:

1 Define "luminal amoebicide" and name two examples with their chemical classes.

2 Why are nitroimidazoles selectively toxic to anaerobic parasites? (One paragraph.)

3 Name the three nitroimidazoles in the syllabus and state what differs between their structures.

4 What is the molecular target of atovaquone?

5 Why must diloxanide follow metronidazole in invasive amoebiasis?

6 Write the chemical name of metronidazole.

7 What salt form is pentamidine supplied as, and why?

8 State two uses of paromomycin by different routes.

Long answer:

1 Classify the ten syllabus antiprotozoals chemically. Describe the structure (scaffold + key substituents) and uses of any four.

2 Explain the mechanism of action of nitroimidazoles with a flowchart. Why do human cells escape this toxicity?

3 Write the complete synthesis of Metronidazole, naming all reagents, conditions, and intermediates. Explain the role of each step.

4 Present the SAR of nitroimidazoles as a rule table and explain each rule in one line.

5 Compare luminal vs tissue amoebicides (chemistry, absorption, uses) with examples. Design the treatment sequence for amoebic liver abscess and justify it.

6 Describe the structures and mechanisms of pentamidine, atovaquone, and eflornithine. Give two uses of each.

MCQs:

1 The "warhead" of nitroimidazole drugs, activated by ferredoxin, is:

a) The 2-methyl group b) The nitro group at C5 c) The N1 side chain d) The imidazole nitrogen **Answer: b**

1 Which drug is a luminal amoebicide given as a furoate prodrug?

a) Metronidazole b) Diloxanide c) Tinidazole d) Ornidazole **Answer: b**

1 Atovaquone acts by blocking:

a) DNA minor groove b) Mitochondrial Complex III (cytochrome bc_1) c) Ornithine decarboxylase d) 30S ribosome **Answer: b**

1 Eflornithine is best described as:

a) A nitroimidazole b) An ornithine analogue and suicide enzyme inhibitor c) An aminoglycoside d) A diamidine **Answer: b**

1 The N1 side chain of tinidazole contains:

a) A hydroxyethyl group b) An ethylsulphonyl (sulphone) group c) A chloro-hydroxypropyl group d) A furoate ester **Answer: b**

1 Pentamidine binds to:

a) The DNA major groove b) The DNA minor groove (AT-rich regions) c) Tubulin d) The cell wall **Answer: b**

1 Nitazoxanide inhibits:

a) Reverse transcriptase b) Pyruvate:ferredoxin oxidoreductase (PFOR) c) HIV protease d) Thymidine kinase **Answer: b**

1 Which statement about iodoquinol is correct?

a) It is a nitroimidazole b) It is absorbed well and treats liver abscess c) It is a 5,7-diiodo-8-hydroxyquinoline acting in the gut lumen d) It inhibits ornithine decarboxylase **Answer: c**

Viva questions (with answers):

1 *Why is the nitro group essential in metronidazole?*

It is the warhead — ferredoxin reduces it to cytotoxic radicals that break parasite DNA; without it the drug is inactive.

1 *What does the N1 side chain of a nitroimidazole decide?*

Solubility, half-life, and formulation (e.g., tinidazole's sulphone side chain gives a longer half-life than metronidazole's hydroxyethyl).

1 *Can diloxanide treat amoebic liver abscess? Why not?*

No — it is poorly absorbed and stays in the gut lumen; it never reaches the liver. A tissue nitroimidazole is needed.

1 *What is special about eflornithine's structure?*

It is an ornithine look-alike carrying a difluoromethyl (–CHF_2) trap that irreversibly (suicide) inhibits ornithine decarboxylase.

1 *Why is atovaquone taken with fatty food?*

Its bulky chlorophenyl-cyclohexyl tail makes it highly fat-soluble; food fat greatly increases its absorption.

Application-based:

1 A patient with amoebic liver abscess is prescribed only diloxanide furoate. As the pharmacist, identify the error, explain the chemistry behind it, and suggest the correct regimen sequence.

2 A traveller to a kala-azar endemic district of Bihar asks for "the amoeba tablet" (metronidazole) for prolonged fever with an enlarged spleen. Explain why metronidazole is wrong here and which syllabus drug (and route) is actually used for kala-azar.

3 A patient on metronidazole asks whether a glass of wine at dinner is safe. Counsel using the mechanism of the drug–alcohol interaction.

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CHAPTER 2: Antivirals

1. Learning Objectives

After studying this chapter, you will be able to:

1 Define a virus and explain, from zero, why antiviral drugs are harder to design than antibacterial drugs.

2 Classify the eighteen syllabus antivirals into chemical classes: adamantanes, nucleoside analogues (anti-herpes, NRTIs), NNRTIs, protease inhibitors, neuraminidase inhibitor, capsid inhibitor, and miscellaneous (idoxuridine, ribavirin).

3 Describe the chemical structure (scaffold + key substituents) of all eighteen antiviral drugs.

4 Explain the mechanism of action of each class: M2 blockade, chain termination by fake nucleosides, allosteric RT inhibition, protease inhibition, neuraminidase inhibition, capsid disruption.

5 Write the complete synthesis of Acyclovir, naming every reagent, condition, and intermediate.

6 State the SAR rules of nucleoside analogues and of HIV protease inhibitors as rule tables.

7 Distinguish NRTIs from NNRTIs (chemistry and mechanism).

8 State the therapeutic uses of each drug, including India-relevant uses (HIV, hepatitis, influenza, herpes).

9 Draw the classification flowchart, the acyclovir activation flowchart, and the HIV drug-target flowchart.

2. Definitions

- **Virus.** A virus is an **infectious particle far smaller than a bacterium** — so small that it cannot even reproduce on its own. It is basically a parcel of genetic material (DNA or RNA) wrapped in a protein coat (and sometimes a fatty envelope). It has no machinery of its own: to multiply, it must **enter one of your cells and hijack the cell's machinery**. Common viral diseases: influenza (flu), herpes (cold sores, genital herpes, chickenpox/shingles), HIV/AIDS, hepatitis B and C, and the common cold.
- **Antiviral drug.** A medicine that **stops a virus from multiplying inside human cells**. Unlike antibiotics (which poison bacteria directly), antivirals must sabotage the virus **without wrecking the host cell** it lives in — because the virus uses the cell's own machinery, the drug has to tell "virus work" apart from "cell work." That is why there are far fewer antivirals than antibiotics.

- **Nucleoside / nucleotide.** A **nucleoside** = a nitrogen base (like guanine, adenine, thymine, cytosine) joined to a sugar (ribose or deoxyribose). A **nucleotide** = a nucleoside **plus phosphate groups**. DNA and RNA are long chains of nucleotides. Most antivirals are **fake nucleosides** — they look like the real building blocks, get built into the viral genetic chain, and then jam it.
- **Chain terminator.** A fake nucleoside that is **missing the 3′-OH group** — the "hook" that the next building block attaches to. Once the viral enzyme adds it to the growing DNA chain, **no further blocks can be added** — the chain stops dead, like a train track with the last rail missing.
- **Reverse transcriptase (RT).** The enzyme HIV uses to convert its **RNA into DNA** (the reverse of the normal cell direction, hence "reverse"). Human cells do not have this enzyme — so drugs that block it hurt the virus far more than the patient. It is the target of NRTIs and NNRTIs.
- **Protease (HIV protease).** A viral enzyme that **cuts long viral protein chains into the correct small pieces**, like scissors cutting a ribbon into badges. Without cutting, new virus particles are deformed and non-infectious. It is the target of protease inhibitors.
- **Neuraminidase.** An enzyme on the flu virus surface that **cuts newly made viruses free** from the infected cell so they can spread. Blocking it traps new viruses on the dying cell. It is the target of peramivir (and oseltamivir).
- **Capsid.** The **protein shell** that packages the virus's genetic material — like the cardboard box around a parcel. Lenacapavir glues and cracks this box at several life-cycle stages.
- **Prodrug.** An inactive form converted by the body into the active drug. Examples here: **valganciclovir** (valine ester ganciclovir).
- **Phosphorylation.** Attaching phosphate groups to a molecule. Nucleoside antivirals must be phosphorylated **three times** (to the triphosphate) before they become active — the first phosphorylation is often done by a **viral** enzyme, which gives selectivity.

3. Terminology (word-by-word from zero)

Term	What it means in plain words
Scaffold	The central ring or framework of the drug — e.g., the adamantane cage, the purine base.
Adamantane	A cage-shaped hydrocarbon ($C_{10}H_{16}$) — ten carbons locked into a rigid diamond-like cage. The scaffold of amantadine and rimantadine.
Purine / pyrimidine	The two families of nitrogen bases in DNA/RNA. Purines (adenine, guanine) = fused double rings; pyrimidines (thymine, cytosine, uracil) = single rings.
Acyclic nucleoside	A "nucleoside" whose sugar ring is **opened up into a chain** — e.g., acyclovir's hydroxyethoxymethyl chain instead of a sugar ring.
NRTI	Nucleoside Reverse Transcriptase Inhibitor — a fake nucleoside that blocks HIV's reverse transcriptase and terminates the DNA chain.
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor — NOT a nucleoside; binds a side pocket on reverse transcriptase and warps the enzyme.

Term	What it means in plain words
Protease inhibitor (PI)	A drug that blocks HIV protease, so new virus particles are built wrongly and are non-infectious.
Viral thymidine kinase (TK)	A viral enzyme (in herpes viruses) that adds the first phosphate to acyclovir — human cells do this step poorly, so the drug activates mainly in infected cells.
Selectivity	Hitting the virus much harder than the patient's cells — the core challenge of antiviral design.
Resistance	The virus mutating so the drug no longer works (e.g., M2 mutations defeated amantadine against flu; TK mutations defeat acyclovir).
Booster (pharmacokinetic)	A drug given not for its own antiviral effect but to **slow the breakdown** of another drug — ritonavir boosts other protease inhibitors by blocking the liver enzyme CYP3A4.
HAART / ART	Highly Active Antiretroviral Therapy — the combination of 3+ anti-HIV drugs (e.g., 2 NRTIs + 1 NNRTI or PI) that keeps HIV suppressed.

4. What Is a Virus — and Why Are Antivirals Hard?

Technical concept. A virus is an obligate intracellular parasite: it carries only its genome plus a few proteins and depends entirely on host-cell machinery (ribosomes, nucleotides, energy) for replication. The viral life cycle has stages — **attachment entry uncoating genome replication assembly release** — and each stage is a drug target. Because every step happens **inside human cells using human machinery**, selective toxicity is difficult: the drug must exploit a **virus-specific enzyme** (viral thymidine kinase, reverse transcriptase, HIV protease, neuraminidase) or a virus-specific structure (M2 channel, capsid).

Simple explanation. A bacterium is like an enemy soldier camping in your field — you can poison his camp without burning your house. A virus is like an enemy spy **living inside your own house, eating your food, using your phone**. You cannot bomb the house — you must find something the spy does that nobody in your family does (a secret code machine = reverse transcriptase; a special lock-pick = viral thymidine kinase) and jam only that.

Example. Herpes virus carries its own thymidine kinase (TK) enzyme. Acyclovir is harmless until **viral TK** adds the first phosphate to it — human cells barely do this step. So acyclovir "wakes up" only inside herpes-infected cells, then blocks the viral DNA-copying machine. Uninfected cells never wake it up.

Key takeaway. Viruses replicate inside our cells using our machinery — antivirals win by targeting **virus-only enzymes and structures** (TK, RT, protease, neuraminidase, M2, capsid), mostly at specific life-cycle stages.

5. Classification of Antivirals (Chemical + Target)

Technical concept. The eighteen syllabus drugs group into chemical classes, each mapped to a viral target:

Flowchart 1 — Chemical classification of the syllabus antivirals (draw as a tree).

"ANTIVIRALS (18 drugs)" branches into:

1 **Adamantanes (M2 blockers)** Amantadine, Rimantadine

2 **Nucleoside analogues — anti-herpes** Idoxuridine, Acyclovir*, Ganciclovir (+ prodrug Valganciclovir)

3 **Nucleoside analogues — NRTIs (anti-HIV)** Zidovudine, Didanosine, Zalcitabine, Lamivudine

4 **NNRTIs (anti-HIV, non-nucleoside)** Loviride, Delavirdine

5 **Nucleoside analogue — broad spectrum** Ribavirin

6 **HIV protease inhibitors (peptidomimetics)** Saquinavir, Indinavir, Ritonavir

7 **Neuraminidase inhibitor (cyclopentane)** Peramivir

8 **Capsid inhibitor** Lenacapavir

Simple explanation. Sort them by "what they look like and what they jam": the **cage pair** (amantadine, rimantadine) plugs the flu virus's proton channel; the **fake building blocks** (idoxuridine, acyclovir, ganciclovir, the four NRTIs, ribavirin) sneak into viral genetic chains and break them; the **RT warpers** (loviride, delavirdine) bend HIV's copying machine out of shape; the **scissor-blockers** (saquinavir, indinavir, ritonavir) stop HIV from cutting its proteins correctly; **peramivir** glues new flu viruses to the dying cell; **lenacapavir** cracks HIV's protein box.

Example. The name tells the class: "**–vudine / –dosine / –citabine**" endings (zidoVUDINE, didaNOSINE is the rebel, zalCITABINE, lamiVUDINE) = nucleoside analogues; "**–navir**" (saquiNAVIR, indiNAVIR, ritoNAVIR) = protease inhibitors; "**–mantadine**" (aMANTADINE, riMANTADINE) = adamantanes.

Key takeaway. Eight groups: cage M2-blockers, anti-herpes nucleosides, anti-HIV NRTIs, anti-HIV NNRTIs, broad-spectrum ribavirin, "–navir" protease inhibitors, peramivir (neuraminidase), lenacapavir (capsid).

6. Mechanisms of Action (Class by Class)

6.1 Adamantanes (Amantadine, Rimantadine) — M2 proton-channel blockade

Step-by-step (Flowchart 2 — draw as a chain): "Flu (influenza A) virus enters the cell inside a bubble (endosome)" "The bubble turns acidic (fills with H^+ protons)" "Normally the viral **M2 channel** lets H^+ flow INTO the virus the virus's protein coat loosens viral RNA is released (**uncoating**)" "**Amantadine plugs the M2 channel** (its cage fits the channel pore; its $–NH_3^+$ mimics a proton)" "No H^+ entry coat never loosens viral RNA stays trapped infection stops at the uncoating step."

Simple explanation. The flu virus wears a tight jacket (protein coat) that only unzips in acid. Its M2 channel is the zipper pull. Amantadine is a **cork jammed into the zipper** — the jacket never unzips, the viral RNA never gets out, and the infection dies before it starts.

Example. This works only on **influenza A** (only flu A has the M2 channel — flu B does not). Widespread M2 mutations have now made most circulating flu resistant, so adamantanes are rarely used for flu today — but the mechanism is a textbook classic.

Key takeaway. Adamantane cage plugs the influenza A M2 proton channel no uncoating no infection. Flu-A-specific; resistance is now widespread.

6.2 Anti-herpes nucleoside analogues (Idoxuridine, Acyclovir, Ganciclovir, Valganciclovir) — viral-TK activation chain termination

Step-by-step (Flowchart 3 — the acyclovir story; draw as a chain): "Acyclovir enters cell (infected or not) — inactive" "**Viral thymidine kinase** (only in herpes-infected cells) adds phosphate 1" "Cellular enzymes add phosphates 2 and 3 **acyclovir triphosphate** (active)" "Active drug has TWO attacks: (a) **competes with dGTP** for the viral DNA polymerase; (b) once inserted, its **missing 3′-OH** means the next

nucleotide cannot attach **chain termination**" "Viral DNA chain stops growing virus cannot copy itself."

Simple explanation. Acyclovir is a **fake Lego brick** that looks like guanine (a DNA building block) but has no connecting stud on top (no 3′-OH). The herpes virus's own enzyme (TK) picks it up and clicks it into the growing DNA wall — and then the wall can never grow further, because nothing can click onto the fake brick. Human cells almost never pick up the fake brick in the first place, because they lack viral TK.

Example — Idoxuridine. The oldest trick: idoxuridine looks like **thymidine** (DNA's T), but carries a bulky **iodine** at C5. Viral/cellular kinases phosphorylate it, it gets built into viral DNA **in place of thymine**, and the bulky iodine makes the DNA faulty — transcription fails. Too toxic for systemic use used **topically in the eye** (herpes keratitis).

Example — Ganciclovir / Valganciclovir. Ganciclovir is acyclovir's cousin with an **extra –CH_2OH** (a hydroxymethyl on the side chain) — same guanine base, same chain-termination logic, but it hits **CMV (cytomegalovirus)** harder. **Valganciclovir** is ganciclovir wearing a **valine ester mask** (prodrug) — the gut absorbs the masked form far better, then the body clips the mask off.

Key takeaway. Anti-herpes nucleosides = fake DNA bricks activated by **viral** TK triphosphate fool viral DNA polymerase **no 3′-OH chain stops**. Idoxuridine = iodinated fake thymidine (eye drops); ganciclovir = acyclovir + extra CH_2OH (anti-CMV); valganciclovir = oral prodrug mask.

6.3 NRTIs — Zidovudine, Didanosine, Zalcitabine, Lamivudine — cellular activation RT chain termination

Step-by-step (Flowchart 4 — draw as a chain): "NRTI enters the cell — inactive fake nucleoside" "**Cellular (human) kinases** add 3 phosphates NRTI-triphosphate (active)" "HIV reverse transcriptase mistakes it for a real nucleotide and inserts it into the growing viral DNA" "**Missing 3′-OH chain termination**" "Viral RNA never becomes full DNA HIV cannot integrate into human chromosomes."

Simple explanation. Same fake-brick trick as acyclovir, but the enemy enzyme is different: **HIV's reverse transcriptase** instead of herpes DNA polymerase. One big difference: the first phosphate is added by **our own** cellular enzymes (not a viral one), so NRTIs are less selective than acyclovir — which is why they have more side effects (e.g., zidovudine anaemia; didanosine pancreatitis).

The four bricks:

- **Zidovudine (AZT):** thymidine with **–N_3 (azido)** replacing the 3′-OH. The azido group is the "missing hook" — chain stops. The first anti-HIV drug ever (1987).
- **Didanosine (ddI):** inosine analogue; **both 2′ and 3′ positions lack OH** (2′,3′-dideoxy) — double-missing hooks.
- **Zalcitabine (ddC):** cytidine analogue; also **2′,3′-dideoxy** — no hooks at all.
- **Lamivudine (3TC):** cytidine analogue with a twist — the sugar ring's 3′-CH_2 is replaced by **sulphur** (oxathiolane ring). The sulphur changes the ring shape so RT grabs it eagerly.

Key takeaway. NRTIs = fake nucleosides **missing the 3′-OH hook** phosphorylated by **cellular** kinases HIV RT inserts them chain terminates. Zidovudine = 3′-azido; didanosine/zalcitabine = dideoxy; lamivudine = sulphur in the sugar ring.

6.4 NNRTIs — Loviride, Delavirdine — allosteric warping of reverse transcriptase

Technical concept. NNRTIs are **not nucleosides at all** — they are flat, butterfly-shaped small molecules that slide into a **hydrophobic pocket next to (not inside)** the RT active site. Binding warps the enzyme's shape (allosteric inhibition, non-competitive), so RT can no longer grip its template — DNA synthesis stalls. Because the pocket is HIV-RT-specific, NNRTIs do not touch human DNA polymerases.

Simple explanation. If NRTIs are fake bricks, NNRTIs are **a spanner thrown into the bricklayer's hand**. Loviride and delavirdine do not pretend to be DNA parts — they jam themselves into a side pocket of HIV's copying machine and bend it out of shape, so the machine cannot lay any bricks at all.

Example. Delavirdine's structure (bis-heteroaryl piperazine) is like a two-winged butterfly: the two "wings" (indole and pyridine-piperazine) grip the walls of the hydrophobic pocket. Loviride (an α-anilinophenylacetamide) does the same with its dichlorophenyl + anilino wings.

Key takeaway. NNRTIs = non-nucleoside **pocket-binders** that warp HIV reverse transcriptase allosterically. No phosphorylation needed; no chain termination — pure shape sabotage.

6.5 Ribavirin — multi-attack broad-spectrum nucleoside

Technical concept. Ribavirin (a triazole-carboxamide "base" on a normal ribose sugar) attacks on several fronts: (a) its monophosphate **inhibits IMP dehydrogenase**, starving the virus of guanine nucleotides; (b) it **interferes with viral RNA capping**; (c) its triphosphate gets **incorporated into viral RNA causing lethal mutations** (error catastrophe). No single target — a shotgun, not a sniper.

Simple explanation. Most antivirals are snipers with one target. Ribavirin is a **shotgun**: it starves the virus of raw material, ruins the virus's RNA finishing, and — when built into viral RNA — scrambles the genetic message so badly the virus's children are born dead.

Key takeaway. Ribavirin = broad-spectrum triazole nucleoside with **multiple** mechanisms (IMP-DH inhibition, capping interference, lethal mutagenesis).

6.6 HIV protease inhibitors — Saquinavir, Indinavir, Ritonavir — scissor blockade

Step-by-step (Flowchart 5 — draw as a chain): "HIV assembles new virus particles using long **polyprotein chains** (gag, gag-pol)" "Normally **HIV protease** (viral scissors) cuts these chains at exact points mature, infectious virus" "**Protease inhibitor** (peptidomimetic — looks like the protein chain but cannot be cut) sits in the protease's active site" "Scissors jammed chains never cut new particles are **immature, deformed, non-infectious**."

Simple explanation. New HIV particles leave the cell as uncut "flat-pack furniture" (long protein chains). HIV protease is the Allen key that assembles them into working furniture. Protease inhibitors are **fake Allen keys that snap off inside the lock** — the furniture never gets assembled, and the released particles are junk.

The three "–navirs":

- **Saquinavir:** the first HIV protease inhibitor; a **hydroxyethylamine peptidomimetic** — its central –CH(OH)–CH_2– mimics the transition state of the peptide bond being cut, so the enzyme grabs it and freezes.
- **Indinavir:** also hydroxyethylamine-based, with a **piperazine + pyridine** periphery; potent but needs frequent dosing and much water (kidney-stone risk — counsel fluids).
- **Ritonavir:** originally a protease inhibitor, now used mainly as a **booster** — it powerfully blocks the liver enzyme **CYP3A4**, which normally destroys other protease inhibitors; a small ritonavir dose makes the main PI last much longer in blood.

Key takeaway. "–navirs" = fake protein pieces that jam HIV's scissors (protease) immature, non-infectious virus. Ritonavir doubles as a **CYP3A4 booster** for other PIs.

6.7 Peramivir — neuraminidase inhibition (trapping new flu viruses)

Technical concept. After flu virus replicates inside a cell, new virus particles bud out but stay **stuck to the cell surface** via sialic-acid links. **Neuraminidase** (viral scissors) cuts these links, freeing the new viruses to infect neighbours. **Peramivir** (a cyclopentane with guanidino + carboxylate groups mimicking sialic acid) plugs the neuraminidase active site new viruses **cannot detach** they clump on the dying cell and the infection cannot spread.

Simple explanation. New flu viruses are like boats tied to a dock with ropes (sialic-acid links); neuraminidase is the crewman cutting the ropes. Peramivir **ties the crewman's hands** — the boats never leave the dock, and the outbreak stalls at one cell.

Key takeaway. Peramivir = cyclopentane sialic-acid mimic that blocks flu neuraminidase new viruses trapped on the cell spread stops. Given IV (single dose) for acute influenza.

6.8 Lenacapavir — capsid disruption (multi-stage)

Technical concept. Lenacapavir binds directly to the **HIV capsid protein** (the shell around viral RNA) at the interface where capsid units join. One drug, several sabotages: it **disrupts capsid assembly** (new shells built crooked), **blocks nuclear import** (the shell cannot carry viral DNA into the nucleus), and **disturbs disassembly** (uncoating mistimed). It is extremely long-acting — given by **injection every 6 months** — for multidrug-resistant HIV.

Simple explanation. If the capsid is the parcel's cardboard box, lenacapavir is **superglue smeared on the flaps at the wrong places**: boxes get built crooked, cannot be delivered into the nucleus, and cannot be opened on time. One injection protects for six months — a huge advantage where daily tablets fail.

Key takeaway. Lenacapavir = capsid-binder that sabotages HIV at **multiple** stages (assembly, nuclear entry, uncoating); ultra-long-acting injectable for resistant HIV.

7. Structure Diagrams (Describe Textually — Draw These)

Diagram 1 — The adamantane cage (Amantadine vs Rimantadine). Draw the **adamantane cage**: a diamond-like 3D cage of 10 carbons (draw as three fused cyclohexane chairs forming a rigid ball). For **amantadine**, attach **–NH_2 at one bridgehead carbon** (position 1) — label "adamantan-1-amine: cage + primary amine." For **rimantadine**, attach **–$CH(NH_2)–CH_3$ at position 1** — label "one extra carbon: 1-(1-aminoethyl) — the methyl branch; same cage, slightly different fit in the M2 pore." Below both, note: "At body pH the –NH_2 is protonated (–NH_3^+) — a fake proton that plugs the H^+ channel."

Diagram 2 — Acyclovir (the acyclic guanine nucleoside). Draw **guanine** (fused double ring: six-membered with C=O at 6 and –NH_2 at 2, fused to five-membered imidazole). From N9 of guanine draw an **open chain**: –CH_2–O–CH_2–CH_2–OH (label "hydroxyethoxymethyl — the sugar ring is OPENED into a chain; ends in –CH_2OH where kinases attach phosphates"). Mark the absent 3′-OH with a red and label "NO 3′-OH here chain terminator." Chemical name: 9-(2-hydroxyethoxymethyl)guanine.

Diagram 3 — Ganciclovir vs Acyclovir (spot the difference). Draw both side chains side by side: acyclovir's –CH_2–O–CH_2–CH_2–OH vs ganciclovir's –CH_2–O–$CH(CH_2OH)_2$ (label "extra –CH_2OH branch on the middle carbon — one more handle for phosphorylation; better anti-CMV activity"). Same guanine base on both.

Diagram 4 — Valganciclovir (the prodrug mask). Draw ganciclovir's side chain with one –CH_2OH converted to **–CH_2–O–CO–CH(NH_2)–CH(CH_3)$_2$** (label "L-valine ester mask on one hydroxyl — gut transporters carry this masked form 10× better; esterases in the body clip the mask ganciclovir").

Diagram 5 — The four NRTI "fake bricks" (compare their missing hooks). Draw four sugar rings in a row, each with its base: (a) **Zidovudine**: deoxyribose with **–N_3 (azido)** at 3′ + thymine base — label "3′-azido = the hook is replaced by N_3." (b) **Didanosine**: ribose missing **both 2′-OH and 3′-OH** + hypoxanthine base — label "dideoxy: two hooks missing." (c) **Zalcitabine**: same dideoxy sugar + cytosine base. (d) **Lamivudine**: oxathiolane ring — draw the five-membered sugar with **S replacing the 3′-CH_2** + cytosine base — label "sulphur in the ring — unnatural shape that RT loves."

Diagram 6 — NNRTI "butterfly" binding (conceptual). Draw HIV reverse transcriptase as a hand gripping a template. Beside the active site (the palm), draw a small **side pocket**; inside it place a butterfly shape labelled "NNRTI (loviride/delavirdine)"; draw arrows showing the hand's fingers bending — label "pocket filled enzyme warps cannot grip template (allosteric, non-competitive)."

Diagram 7 — Protease inhibitor pharmacophore (Saquinavir core). Draw a horizontal peptide-like chain: "–NH–CH–CH(OH)–CH_2–" with the central **–CH(OH)–CH_2–** circled and labelled "**hydroxyethylamine core — mimics the transition state of the peptide bond being cut; the –OH grips the protease's catalytic aspartates**." On the left draw a bulky **decahydroisoquinoline** (fused saturated rings) labelled "fills the S1 pocket"; on the right an **asparagine-like side chain** labelled "fills the S2 pocket." Note: "Looks like protein, cannot be cut = peptidomimetic."

Diagram 8 — Peramivir (cyclopentane neuraminidase blocker). Draw a **cyclopentane ring** (five-membered, all carbons) with four substituents: **–COOH** (label "mimics sialic acid's carboxylate — anchors in the active site"), **–OH**, a **guanidino group –NH–C(=NH)NH_2** (label "positive charge grips the enzyme's glutamates"), and a **1-acetamido-2-ethylbutyl side chain** (label "bulky hydrophobic tail fills the pocket"). Caption: "A sialic-acid look-alike built on a cyclopentane — plugs neuraminidase."

Diagram 9 — Lenacapavir (capsid binder, simplified). Draw as a linear map of fragments left to right: "**3,5-difluorobenzyl** —(cyclopropane linker)— **trifluoroethyl-pyridone** —(amide)— **triazole** —(—SO_2—)— **pyridine**". Label: "Long, rigid, multi-ring molecule; the difluorobenzyl end wedges between capsid protein units at their junction — one molecule bridges two capsid monomers."

Diagram 10 — Idoxuridine. Draw **2′-deoxyuridine** (uracil base + deoxyribose) with a big **–I (iodine)** at C5 of the uracil ring — label "5-iodo: bulky halogen on the base; incorporated in place of thymidine faulty viral DNA. Too toxic systemically eye drops only."

Diagram 11 — Ribavirin. Draw a **1,2,4-triazole ring** (five-membered, three nitrogens) bearing **–$CONH_2$ (carboxamide)** at C3, attached at N1 to a normal **β-D-ribofuranose** (ribose with 2′,3′,5′-OH) — label "fake base (triazole-carboxamide mimics guanine/adenine) on a REAL sugar — the opposite trick to most nucleosides."

8. Flowcharts (Recap for Drawing)

Flowchart 6 — HIV life cycle with drug targets (draw as a circular map). "Virus attaches & enters cell" "Uncoating (capsid opens) — **LENACAPAVIR** disrupts" "Reverse transcription (RNADNA) — **NRTIs** (chain termination) + **NNRTIs** (warp RT)" "Integration into human DNA" "New protein chains made" "Assembly" "Protease cuts chains — **PROTEASE INHIBITORS** jam the scissors" "Release of mature virus." Add side note: "No syllabus drug blocks attachment/entry/integration — know which stages ARE covered."

Flowchart 7 — Flu life cycle with drug targets. "Virus enters in endosome" "Uncoating via M2 channel — **ADAMANTANES** plug it (flu A only)" "Replication" "New viruses bud, stuck by sialic-acid links" "Neuraminidase cuts them free — **PERAMIVIR** blocks the scissors viruses trapped."

Flowchart 8 — Synthesis of Acyclovir (see full details in Section 13). "2-Amino-6-chloropurine" —((2-benzoyloxyethoxy)methyl chloride, base, DMF; N9 alkylation) "9-(2-Benzoyloxyethoxymethyl)-2-amino-6-chloropurine" —(dil. HCl, heat; 6-Cl 6=O) "9-(2-Benzoyloxyethoxymethyl)guanine" —(NaOH/MeOH; debenzoylation) "Acyclovir."

9. Infographic Concept Box

ANTIVIRALS AT A GLANCE The problem: Viruses replicate INSIDE our cells using our machinery — drugs must hit virus-only targets. **The cage pair (M2 blockers):** Amantadine, Rimantadine — adamantane cage + amine plugs flu A's proton channel no uncoating. (Resistance now widespread — textbook classic.) **The fake bricks (chain terminators — no 3′-OH!):** Acyclovir* (viral-TK-activated, anti-herpes; synthesis starred), Ganciclovir (+CH_2OH, anti-CMV), Valganciclovir (valine-ester prodrug mask), Idoxuridine (iodinated fake thymidine — eye drops), NRTIs — Zidovudine (3′-azido), Didanosine + Zalcitabine (dideoxy), Lamivudine (sulphur sugar ring). NRTIs need **cellular** kinases (less selective than acyclovir). **The machine-warpers (NNRTIs):** Loviride, Delavirdine — butterfly molecules that bend HIV reverse transcriptase out of shape from a side pocket. Not nucleosides, no phosphorylation. **The scissor-jammers (PIs):** Saquinavir, Indinavir, Ritonavir — "–navir" peptidomimetics with hydroxyethylamine core; ritonavir also **boosts** other PIs via CYP3A4 blockade. **The specialists:** Ribavirin (shotgun nucleoside — RSV, hepatitis C); Peramivir (cyclopentane neuraminidase plug — IV flu drug); Lenacapavir (capsid superglue — 6-monthly injection for resistant HIV). **Star synthesis:** Acyclovir = 2-amino-6-chloropurine (alkylate N9) chloro-intermediate (acid hydrolysis) guanine intermediate (deprotect) acyclovir. **Name tricks:** –mantadine = cage; –vudine/–citabine = nucleoside; –navir = protease inhibitor.

10. Master Table — Chapter 2 Drugs

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Amantadine	Adamantane (M2 blocker)	Adamantane cage + 1-amino (–NH_2)	Influenza A (historical; resistance widespread); Parkinson's disease (dopaminergic action)
Rimantadine	Adamantane (M2 blocker)	Adamantane cage + 1-(1-aminoethyl) (extra methyl branch)	Influenza A prophylaxis/treatment (historical)
Idoxuridine	Iodinated pyrimidine nucleoside	5-iodo-2′-deoxyuridine (bulky I on uracil base)	Herpes simplex keratitis (eye drops); too toxic for systemic use
Acyclovir*	Acyclic guanine nucleoside	Guanine + N9-(2-hydroxyethoxymethyl) open chain; no 3′-OH	HSV-1/HSV-2 (oral/genital herpes), VZV (chickenpox, shingles), herpes encephalitis (IV)
Ganciclovir	Acyclic guanine nucleoside	Guanine + N9-[1,3-dihydroxy-2-propoxymethyl] (extra CH_2OH)	CMV retinitis and CMV infections in immunocompromised (IV/oral)

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Zidovudine	NRTI (thymidine analogue)	3′-azido-3′-deoxythymidine ($-N_3$ replaces 3′-OH)	HIV infection (backbone of ART); prevention of mother-to-child transmission
Didanosine	NRTI (inosine analogue)	2′,3′-dideoxyinosine (no 2′/3′-OH)	HIV infection (NRTI backbone; less used now — pancreatitis risk)
Zalcitabine	NRTI (cytidine analogue)	2′,3′-dideoxycytidine (no 2′/3′-OH)	HIV infection (historical NRTI; neuropathy limited use)
Lamivudine	NRTI (cytidine analogue)	Oxathiolane ring (S replaces 3′-CH_2) + cytosine	HIV (ART backbone); hepatitis B (HBV polymerase inhibition)
Loviride	NNRTI (α-APA)	α-anilinophenylacetamide: 2,6-dichlorophenyl + (2-acetyl-5-methylphenyl)amino wings	HIV infection (NNRTI; investigational/limited clinical use)
Delavirdine	NNRTI (BHAP)	Bis(heteroaryl)piperazine: indole–CO–piperazine–pyridyl	HIV infection (NNRTI in combination ART)
Ribavirin	Triazole nucleoside (broad spectrum)	1,2,4-triazole-3-carboxamide base + normal ribose	RSV (aerosol), chronic hepatitis C (with other agents), viral haemorrhagic fevers
Saquinavir	HIV protease inhibitor	Hydroxyethylamine peptidomimetic + decahydroisoquinoline	HIV infection (with ritonavir boosting, in ART)
Indinavir	HIV protease inhibitor	Hydroxyethylamine peptidomimetic + piperazine/pyridine	HIV infection (ART; high fluid intake needed)
Ritonavir	HIV protease inhibitor / booster	Peptidomimetic with thiazole rings; potent CYP3A4 inhibitor	HIV: pharmacokinetic booster for other PIs (low dose); also has PI activity
Valganciclovir	Prodrug of ganciclovir	Ganciclovir + L-valine ester mask on side-chain OH	CMV retinitis (oral), CMV prophylaxis in transplant patients
Peramivir	Neuraminidase inhibitor	Cyclopentane + –COOH + guanidino + acetamido-ethylbutyl tail	Acute influenza (single IV dose)
Lenacapavir	Capsid inhibitor	Multi-ring: difluorobenzyl–cyclopropane–pyridone–triazole–sulphonylpyridine	Multidrug-resistant HIV (subcutaneous, every 6 months)

11. Drug-by-Drug Profiles — Structure and Uses

A. ADAMANTANES (M2 BLOCKERS)

1. Amantadine

- **Chemical classification:** Adamantane — M2 ion-channel blocker.
- **Structure:** Scaffold = **adamantane** ($C_{10}H_{16}$), a rigid diamond-like cage of ten carbons. Single substituent: a **primary amino group (–NH_2) at the bridgehead carbon (C1)** — adamantan-1-amine. At physiological pH the amine is protonated (–NH_3^+): the cage lodges in the M2 channel pore while the –NH_3^+ mimics a proton and electrostatically blocks H^+ flow.

- **Uses: Influenza A** prophylaxis and treatment (historical — most circulating strains are now resistant); **Parkinson's disease** (increases dopamine release — a separate, non-antiviral use every pharmacist should know).

2. Rimantadine

- **Chemical classification:** Adamantane — M2 ion-channel blocker.
- **Structure:** Same adamantane cage; the substituent is **–CH(NH_2)–CH_3 [1-aminoethyl] at C1** — one carbon longer than amantadine, with a methyl branch. The extra bulk changes the fit in the M2 pore and gives slightly different pharmacokinetics (longer half-life, fewer CNS side effects than amantadine).
- **Uses: Influenza A** prophylaxis and treatment (historical, same resistance story as amantadine).

B. ANTI-HERPES NUCLEOSIDE ANALOGUES

3. Idoxuridine

- **Chemical classification:** Halogenated pyrimidine nucleoside analogue.
- **Structure:** Scaffold = **2′-deoxyuridine** (uracil base + deoxyribose sugar). Key substituent: a **bulky iodine atom at C5 of the uracil ring** (5-iodo). It is phosphorylated and incorporated into viral DNA **in place of thymidine**; the oversized iodine distorts the DNA helix and produces non-functional viral DNA.
- **Uses: Herpes simplex keratitis** (dendritic corneal ulcers) — as **eye drops/ointment only**. Too toxic for systemic use (it also incorporates into human DNA).

4. Acyclovir*

- **Chemical classification:** Acyclic guanine nucleoside analogue — the prototype selective antiviral.
- **Structure:** Scaffold = **guanine** (purine base: 2-amino-6-oxopurine). Key substituent at N9: **–CH_2–O–CH_2–CH_2–OH (2-hydroxyethoxymethyl)** — an **open chain** replacing the normal sugar ring ("acyclic" = no cycle). The chain ends in a primary –CH_2OH where phosphates attach, but there is **no 3′-OH** — so once inserted into viral DNA, the chain terminates. Chemical name: 9-(2-hydroxyethoxymethyl)guanine.
- **Uses: HSV-1 and HSV-2** (oral and genital herpes — treatment and suppression); **VZV** (chickenpox, shingles); **herpes encephalitis and neonatal herpes** (IV — life-saving).
- **Synthesis:** see Section 13 (starred — full steps, reagents, conditions, intermediates).

5. Ganciclovir

- **Chemical classification:** Acyclic guanine nucleoside analogue (anti-CMV).
- **Structure:** Same guanine base as acyclovir; the N9 side chain is **–CH_2–O–CH(CH_2OH)$_2$ [1,3-dihydroxy-2-propoxymethyl]** — compare with acyclovir's chain: it carries an **extra hydroxymethyl (–CH_2OH) branch** on the middle carbon. This extra –OH gives an additional phosphorylation handle and stronger activity against **cytomegalovirus (CMV)** DNA polymerase.
- **Uses: CMV retinitis** in AIDS patients and **CMV infections** in transplant recipients (IV induction, oral maintenance); congenital CMV.

6. Valganciclovir

- **Chemical classification:** Amino-acid ester **prodrug** of ganciclovir.
- **Structure:** Ganciclovir in which one side-chain hydroxyl is masked as an **L-valine ester: $-CH_2-O-CO-CH(NH_2)-CH(CH_3)_2$.** The valine mask is recognised by intestinal peptide transporters **~10× better oral absorption** than ganciclovir; body esterases then clip the mask, releasing ganciclovir.
- **Uses: CMV retinitis** (oral treatment), **CMV prophylaxis** in solid-organ transplant patients.

C. NRTIs (ANTI-HIV NUCLEOSIDE ANALOGUES)

7. Zidovudine (AZT)

- **Chemical classification:** NRTI — thymidine analogue.
- **Structure:** Scaffold = **thymidine** (thymine base + deoxyribose). Key change: the **3′-OH is replaced by an azido group ($-N_3$)** — 3′-azido-3′-deoxythymidine. The $-N_3$ is the "missing hook": RT inserts zidovudine-triphosphate into viral DNA and the chain stops. The first anti-HIV drug approved (1987).
- **Uses: HIV infection** — backbone of combination ART; **prevention of mother-to-child transmission** (given to the mother in labour and the newborn).

8. Didanosine (ddI)

- **Chemical classification:** NRTI — inosine (purine) analogue.
- **Structure:** Scaffold = **inosine** (hypoxanthine base + sugar). Key change: the sugar is **2′,3′-dideoxy** — **both** the 2′-OH and 3′-OH are missing (replaced by H). Double-missing hooks potent chain termination once triphosphorylated by cellular kinases.
- **Uses: HIV infection** (NRTI backbone in ART; now less used because of pancreatitis and neuropathy risk).

9. Zalcitabine (ddC)

- **Chemical classification:** NRTI — cytidine analogue.
- **Structure:** Scaffold = **cytidine** (cytosine base + sugar) with the same **2′,3′-dideoxy** sugar as didanosine — no hydroxyls at 2′ or 3′. The smallest of the NRTIs.
- **Uses: HIV infection** (historical NRTI; peripheral neuropathy limited its use).

10. Lamivudine (3TC)

- **Chemical classification:** NRTI — cytidine analogue with an unnatural sugar.
- **Structure:** Scaffold = **cytosine** base attached to an **oxathiolane ring** — a five-membered sugar analogue in which the **3′-CH_2 is replaced by sulphur (S)**. The sulphur kinks the ring into a shape HIV reverse transcriptase grabs eagerly, while human polymerases largely ignore it (selectivity). Also active against **hepatitis B virus** polymerase.
- **Uses: HIV infection** (first-line NRTI backbone in ART worldwide, including India's national programme); **chronic hepatitis B**.

D. NNRTIs (ANTI-HIV, NON-NUCLEOSIDE)

11. Loviride

- **Chemical classification:** NNRTI — α-anilinophenylacetamide (α-APA).
- **Structure:** Scaffold = a **phenylacetamide**: a –CH($CONH_2$)– group carrying two aromatic "wings" — a **2,6-dichlorophenyl** ring on the α-carbon and a **(2-acetyl-5-methylphenyl)amino** (anilino) group. The butterfly shape (two hydrophobic wings + central amide) fits the NNRTI pocket of HIV RT.
- **Uses: HIV infection** — NNRTI for combination therapy (investigational/limited clinical use; a textbook example of the α-APA class).

12. Delavirdine

- **Chemical classification:** NNRTI — bis(heteroaryl)piperazine (BHAP).
- **Structure:** Scaffold = a central **piperazine ring** (six-membered, two nitrogens) with two heteroaromatic wings: on one nitrogen, a **(5-methanesulphonamido-indol-2-yl)carbonyl** group (indole wing); on the other, a **[3-(isopropylamino)pyridin-2-yl]** group (pyridine wing). The two wings grip opposite walls of the RT hydrophobic pocket.
- **Uses: HIV infection** — NNRTI used in combination ART.

E. BROAD-SPECTRUM NUCLEOSIDE

13. Ribavirin

- **Chemical classification:** Triazole nucleoside analogue — broad spectrum.
- **Structure:** An **unnatural base** — **1,2,4-triazole-3-carboxamide** (five-membered ring with three nitrogens + a –$CONH_2$ that mimics the H-bonding face of guanine/adenine) — attached to a **completely normal ribose sugar** (all three –OH groups present). The trick is reversed versus other nucleosides: fake base, real sugar.
- **Uses: Respiratory syncytial virus (RSV)** bronchiolitis in infants (aerosol); **chronic hepatitis C** (with interferon/direct-acting antivirals); **viral haemorrhagic fevers** (e.g., Lassa).

F. HIV PROTEASE INHIBITORS

14. Saquinavir

- **Chemical classification:** HIV protease inhibitor — hydroxyethylamine peptidomimetic.
- **Structure:** Scaffold = a **hydroxyethylamine core –CH(OH)–CH_2–NH–** that mimics the tetrahedral transition state of the peptide bond HIV protease cuts — the –OH coordinates the enzyme's two catalytic aspartates and freezes it. Flanking groups: a bulky **decahydroisoquinoline** (saturated fused rings) filling one binding pocket and an **asparagine-derived** side chain filling another.
- **Uses: HIV infection** — in combination ART, always with low-dose ritonavir boosting (poor absorption alone).

15. Indinavir

- **Chemical classification:** HIV protease inhibitor — hydroxyethylamine peptidomimetic.

- **Structure:** Same **hydroxyethylamine transition-state-mimic core**; the flanking groups differ: a **piperazine** ring bearing a **pyridin-2-ylmethyl** group and a **tert-butyl-carboxamide** with a hydroxyindane unit. The pyridine/piperazine periphery tunes solubility and pocket fit.
- **Uses: HIV infection** — in combination ART (take on an empty stomach with plenty of water — kidney-stone risk is the classic counselling point).

16. Ritonavir

- **Chemical classification:** HIV protease inhibitor — peptidomimetic; **potent CYP3A4 inhibitor**.
- **Structure:** A peptidomimetic backbone carrying **two thiazole rings** (five-membered S/N aromatics) — one at each end (a 5-thiazolylmethyl carbamate and a 2-isopropylthiazolyl group) — flanking a hydroxyethylamine-like core with phenyl and isopropyl side chains. The thiazoles contribute to its extremely strong binding of the liver enzyme CYP3A4.
- **Uses: HIV infection** — mainly as a **pharmacokinetic booster**: a low dose shuts down CYP3A4 in the liver/gut, so the companion protease inhibitor (saquinavir, indinavir, lopinavir) survives much longer. Also has intrinsic PI activity at full dose.

G. NEURAMINIDASE INHIBITOR

17. Peramivir

- **Chemical classification:** Cyclopentane-based neuraminidase inhibitor (sialic-acid mimic).
- **Structure:** Scaffold = a **cyclopentane ring** (five saturated carbons) carrying four substituents: **–COOH** (mimics sialic acid's carboxylate — anchors to arginines in the enzyme pocket), **–OH**, a **guanidino group –NH–C(=NH)NH_2** (positively charged — grips glutamates), and a **(1-acetamido-2-ethylbutyl)** hydrophobic tail (fills the pocket's hydrophobic cleft).
- **Uses: Acute uncomplicated influenza** — single **intravenous** dose (for patients who cannot take oral/inhaled drugs).

H. CAPSID INHIBITOR

18. Lenacapavir

- **Chemical classification:** HIV capsid protein inhibitor — first-in-class.
- **Structure:** A long, rigid multi-fragment molecule (drawn left to right): **3,5-difluorobenzyl** group — cyclopropane linker — **trifluoroethyl-substituted pyridone** — amide — **triazole** — sulphonyl — **pyridine**. The difluorobenzyl end wedges into the junction **between two capsid protein monomers**, gluing them wrongly; the far end reaches a second contact point — one molecule bridges the interface.
- **Uses: Multidrug-resistant HIV** — long-acting **subcutaneous injection every 6 months** (with oral loading), for patients whose virus resists other classes.

12. SAR Rule Tables

12A. SAR of Nucleoside Analogue Antivirals

Technical concept. Hundreds of nucleoside analogues were made and tested; the rules below separate the winners (acyclovir, zidovudine, lamivudine) from the failures.

Simple explanation. A fake brick needs three talents: be **picked up** by the phosphorylating enzyme, **fool** the viral polymerase, and **stop** the chain. SAR maps which part of the brick controls each talent.

Rule	Structural feature	Effect on activity	Example
1	**Absence of 3′-OH (chain terminator)**	**Essential for the NRTI/acyclovir mechanism.** Without a 3′-OH the polymerase cannot add the next nucleotide — chain stops. A 3′-OH present drug gets built in harmlessly and chain continues.	Acyclovir (acyclic, no 3′-OH); zidovudine (3′-N_3); ddI/ddC (dideoxy).
2	**Base must mimic a natural base**	The viral polymerase/TK must **recognise** the base. Guanine mimics acyclovir, ganciclovir (recognised by herpes TK + DNA pol). Pyrimidine/purine changes shift virus selectivity.	Acyclovir's guanine is key to viral-TK recognition; idoxuridine's iodouracil mimics thymine.
3	**Sugar mimic: acyclic vs cyclic**	**Acyclic** (open-chain) sugars (acyclovir) give excellent selectivity for herpes polymerases but need viral TK. **Cyclic dideoxy** sugars (NRTIs) are phosphorylated by cellular kinases broader but less selective (more side effects).	Acyclovir = acyclic, highly selective; zidovudine = cyclic dideoxy, cellular activation.
4	**3′-substituent bulk and electronics**	Small electronegative 3′ groups (azido in zidovudine) are well tolerated by RT; bulky groups clash with the polymerase. The 3′ group also tunes recognition by kinases.	Zidovudine's –N_3 is the optimal 3′ replacement; larger groups lose activity.
5	**Unnatural sugar heteroatoms**	Replacing a sugar carbon with **S or O** (oxathiolane in lamivudine) changes ring pucker selective recognition by viral RT over human polymerases better safety.	Lamivudine's ring sulphur = selectivity + anti-HBV activity.
6	**5-position of pyrimidine bases**	Small substituents tolerated; **bulky halogens** (iodine in idoxuridine) distort the helix after incorporation faulty DNA, but also human-DNA toxicity topical use only.	Idoxuridine: 5-iodo = active but toxic systemically.
7	**Prodrug masking of –OH**	Esterifying a side-chain –OH with an **amino acid** (valine) exploits peptide transporters hugely better oral absorption; the mask is clipped in the body. Does not change the active species.	Valganciclovir = ~10× the oral bioavailability of ganciclovir.

Key takeaway. Nucleoside SAR in one line: **no 3′-OH = chain stops; the base picks the virus; the sugar decides who phosphorylates it (viral TK = selective, cellular kinase = broader); prodrug masks fix absorption.**

12B. SAR of HIV Protease Inhibitors

Technical concept. HIV protease is a symmetrical (C2) enzyme with a tunnel-like active site lined with pockets (S1, S1′, S2, S2′). Peptidomimetic inhibitors fill these pockets while presenting an uncleavable core.

Rule	Structural feature	Effect on activity	Example
1	**Hydroxyethylamine core –CH(OH)–CH_2–**	**Essential pharmacophore.** The –OH mimics the tetrahedral transition state of peptide-bond hydrolysis and H-bonds both catalytic aspartates — the enzyme grabs it and freezes. Replace –OH with –CH_2– ~1000× activity loss.	Saquinavir, indinavir, ritonavir all carry it.
2	**Symmetry / pseudo-symmetry**	HIV protease is a symmetric dimer; **symmetric or pseudo-symmetric** inhibitors fill both halves of the tunnel evenly tighter binding.	Early design principle behind the whole class.
3	**Bulky hydrophobic P1/P1′ groups**	Large lipophilic groups (benzyl, decahydroisoquinoline) fill the S1/S1′ pockets strong van der Waals grip. Too small weak binding; too big clash.	Saquinavir's decahydroisoquinoline; ritonavir's phenyl groups.
4	**Hydrogen-bonding periphery**	Carbamate/urea/amide linkers H-bond to the enzyme's flap and backbone — each extra H-bond adds binding energy and selectivity over human proteases.	Indinavir's pyridine N and carbamate oxygens.
5	**Peptidomimetic (non-peptide) character**	Real peptides are chewed up by gut/liver enzymes; replacing peptide bonds with **non-cleavable mimics** gives oral stability and longer half-life.	All three "–navirs" survive where a true peptide would not.
6	**CYP3A4 liability as a feature**	Strong CYP3A4 inhibition is a side effect for most drugs — but for **ritonavir it is the therapy**: low-dose ritonavir deliberately blocks CYP3A4 to boost companion PIs.	Ritonavir boosting: the SAR "flaw" became the clinical strategy.

Key takeaway. PI SAR in one line: **the –CH(OH)–CH_2– core freezes the catalytic aspartates; bulky hydrophobic wings fill the S-pockets; H-bonding edges add grip; non-peptide links survive digestion.**

12C. Mini-SAR: Adamantanes and NNRTIs (one table, exam-favourite contrasts)

Class	Key SAR rule	Example
Adamantanes	The **rigid cage is essential** (fits the M2 pore like a cork); the **primary amine** (protonated –NH_3^+) provides the electrostatic block; a **methyl branch** (rimantadine) is tolerated and softens CNS effects. Removing the cage or the amine kills activity.	Amantadine vs rimantadine

Class	Key SAR rule	Example
NNRTIs	**Butterfly shape is essential**: two hydrophobic aromatic wings + a central H-bonding linker fit the allosteric pocket; the pocket is **HIV-RT-specific** (no human counterpart selectivity); single point mutations in the pocket cause rapid resistance always used in combination.	Loviride (α-APA wings), delavirdine (BHAP wings)

13. Synthesis of Acyclovir* (Starred — Full Steps)

Technical concept. Acyclovir is assembled in three operations: (1) **N9-alkylation** of 2-amino-6-chloropurine with a protected hydroxyethoxy-methyl chloride installs the acyclic side chain; (2) **acid hydrolysis** converts the 6-chloro group into the guanine 6-oxo; (3) **deprotection** removes the benzoyl mask from the side-chain hydroxyl.

Step 1 — N9-Alkylation: attach the masked side chain.

- **Starting materials: 2-Amino-6-chloropurine** (the purine base carrying –NH_2 at C2 and –Cl at C6 — the chlorine is a masked carbonyl) + **(2-benzoyloxyethoxy)methyl chloride** [Cl–CH_2–O–CH_2–CH_2–O–CO–Ph] (the side-chain reagent; its terminal –OH is protected as a benzoate ester so it does not interfere).
- **Reagents and conditions:** Base (e.g., potassium carbonate or sodium hydride) in **dimethylformamide (DMF)**, with mild heating. The base deprotonates the purine N9–H, making N9 nucleophilic.
- **Reaction:** N9 of the purine displaces chloride from Cl–CH_2–O– (SN2) — alkylation occurs selectively at **N9** (the same nitrogen that carries the sugar in natural nucleosides).
- **Intermediate/product of Step 1: 9-(2-Benzoyloxyethoxymethyl)-2-amino-6-chloropurine** — side chain attached, benzoyl mask still on, chlorine still at C6.

Step 2 — Hydrolysis of the 6-chloro group to the guanine carbonyl.

- **Starting material:** The Step 1 intermediate.
- **Reagents and conditions: Dilute hydrochloric acid (dil. HCl), heated** (reflux).
- **Reaction:** Acid-catalysed hydrolysis (nucleophilic aromatic substitution by water): the **6-Cl is replaced by =O**, converting the 6-chloropurine into the **guanin-6-one** (the true guanine base). (The benzoyl ester largely survives these controlled acidic conditions or is handled in the next step.)
- **Intermediate/product of Step 2: 9-(2-Benzoyloxyethoxymethyl)guanine** — correct base, mask still on.

Step 3 — Debenzoylation: unmask the side-chain hydroxyl.

- **Starting material:** The Step 2 intermediate.
- **Reagents and conditions: Sodium hydroxide in methanol** (NaOH/MeOH) or methanolic ammonia, at room temperature to mild warmth.
- **Reaction:** Base-catalysed **ester hydrolysis (deprotection)**: the benzoate ester is cleaved, freeing the primary alcohol –CH_2OH.

- **Final product: Acyclovir — 9-(2-hydroxyethoxymethyl)guanine** [2-amino-9-(2-hydroxyethoxymethyl)-purin-6-one].

Simple explanation. Build it in three moves. **Move 1:** take the purine base (with a chlorine standing in for the future carbonyl) and, using base in DMF, bolt the side chain onto nitrogen-9 — the side chain's far –OH is wearing a benzoyl "helmet" so it does not react prematurely. **Move 2:** boil with dilute HCl — the chlorine at position 6 is swapped for oxygen, and the base becomes true guanine. **Move 3:** treat with NaOH in methanol — the benzoyl helmet pops off, freeing the $-CH_2OH$. Result: acyclovir. **Bolt on the chain, fix the base, remove the helmet.**

Key takeaway. Acyclovir = 2-amino-6-chloropurine (N9-alkylation with benzoyl-protected chloromethyl ether, base/DMF) chloro intermediate (dil. HCl, heat; 6-Cl 6=O) guanine intermediate (NaOH/MeOH; debenzoylation) acyclovir.

14. Pharmacy Relevance

Technical concept. Antiviral chemistry knowledge guides correct dispensing, counselling, resistance prevention, and adverse-effect management.

Simple explanation — what you will actually do at the counter:

- **Complete the course, never share:** Stopping anti-herpes or anti-HIV drugs early breeds **resistance** (TK mutants defeat acyclovir; single RT mutations defeat NNRTIs). Counsel: "The virus learns — finish every dose."
- **Acyclovir needs water:** it can crystallise in kidney tubules — counsel **plenty of fluids**, especially with IV/high-dose therapy.
- **Zidovudine watch the blood:** anaemia and neutropenia are the classic toxicities — patients need periodic blood counts; counsel fatigue/pallor as warning signs.
- **Indinavir water, water, water:** kidney stones are the signature risk — counsel at least 1.5 litres of water daily and taking on an empty stomach.
- **Ritonavir boosting:** explain to patients that the small ritonavir dose is not "an extra drug" but a **bodyguard** that stops the liver destroying the main protease inhibitor — do not skip it.
- **Valganciclovir vs ganciclovir:** do not confuse the prodrug with the parent — doses are completely different; double-check every CMV prescription.
- **Peramivir and lenacapavir** are **clinic-administered** (IV infusion / subcutaneous injection) — the pharmacist's role is cold-chain, preparation, and scheduling the 6-monthly lenacapavir dose so no dose is missed.
- **Ribavirin is teratogenic** (causes birth defects) — strict pregnancy prevention counselling for both male and female patients, during and for months after therapy.

Key takeaway. Your chemistry explains the counselling: fake bricks finish the course (resistance); crystallisation drink water; CYP3A4 ritonavir is the bodyguard; teratogen no pregnancy on ribavirin.

15. India Context

- **HIV:** India has one of the world's largest ART programmes (free antiretrovirals through NACO). **Zidovudine, lamivudine** (the classic backbone), **delavirdine-class NNRTIs**, and **ritonavir-boosted**

protease inhibitors are the chemistry behind the tablets dispensed daily in ART centres — pharmacists are frontline adherence counsellors.

- **Hepatitis B and C: Lamivudine** (HBV) and **ribavirin** (HCV, with direct-acting antivirals) are workhorses in Indian liver clinics; pharmacists counsel on the long durations involved.
- **Herpes: Acyclovir** is among the most prescribed antivirals in Indian dermatology, ophthalmology (herpes keratitis), and general practice; **idoxuridine eye drops** remain in the ophthalmic formulary for dendritic ulcers.
- **Influenza: Peramivir** (IV) is a hospital option during severe flu seasons; adamantanes are obsolete for flu because of resistance — an exam and practice point.
- **CMV:** With rising transplant surgery in Indian metros, **valganciclovir/ganciclovir** prophylaxis is increasingly dispensed — dose vigilance (prodrug vs parent) is a real-world safety issue.
- All eighteen drugs have **Indian Pharmacopoeia** monographs or are covered under international pharmacopoeial standards adopted in India.

16. Key Points

1 Viruses replicate inside human cells — antivirals target **virus-only** enzymes/structures (TK, RT, protease, neuraminidase, M2, capsid).

2 **Adamantanes** (amantadine, rimantadine): cage + amine plugs flu A **M2 channel** → no uncoating. Resistance now widespread.

3 **Acyclovir*: acyclic guanine nucleoside;* *viral TK** phosphorylates → triphosphate → viral DNA polymerase fooled → **no 3′-OH → chain termination**. Ganciclovir = +CH_2OH (anti-CMV); valganciclovir = valine-ester prodrug; idoxuridine = 5-iodo fake thymidine (eye only).

4 **NRTIs** (zidovudine 3′-azido; didanosine/zalcitabine dideoxy; lamivudine S-sugar): **cellular** kinases phosphorylate → HIV RT inserts → chain termination.

5 **NNRTIs** (loviride, delavirdine): butterfly molecules warp HIV RT from an **allosteric pocket** — not nucleosides, no phosphorylation.

6 **Protease inhibitors** (saquinavir, indinavir, ritonavir): **hydroxyethylamine core** freezes HIV protease immature non-infectious virus; **ritonavir boosts** via CYP3A4 blockade.

7 **Ribavirin**: shotgun nucleoside (IMP-DH, capping, lethal mutagenesis) — RSV, HCV.

8 **Peramivir**: cyclopentane neuraminidase plug → new flu viruses trapped on the cell (single IV dose).

9 **Lenacapavir**: capsid binder, multi-stage sabotage, **6-monthly injection** for resistant HIV.

10 Acyclovir synthesis: 2-amino-6-chloropurine (N9-alkylation, base/DMF) → chloro intermediate (dil. HCl, heat) → guanine intermediate (NaOH/MeOH) → acyclovir.

17. Common Confusions

Confusion	Clarification
Acyclovir vs Ganciclovir vs Valganciclovir	Acyclovir = anti-**herpes** (HSV/VZV); ganciclovir = acyclovir **+ one CH_2OH**, anti-**CMV**; valganciclovir = **valine-ester prodrug of ganciclovir** (better oral absorption), not of acyclovir.
NRTI vs NNRTI	NRTIs **are fake nucleosides** needing phosphorylation, causing **chain termination**; NNRTIs **are not nucleosides** — they bind a **side pocket** and warp RT allosterically. Different chemistry, different mechanism.
Zidovudine vs Zalcitabine vs Didanosine	Zido**vudine** = thymidine + 3′-**azido**; Zal**citabine** = **c**ytidine, dideoxy; Dida**nosine** = i**nosine**, dideoxy. "Zido-azido, Zal-cytidine, Did-inosine."
Amantadine vs Rimantadine	Same cage; rimantadine has a **$–CH(NH_2)CH_3$** (one extra carbon) instead of $–NH_2$ — slightly different M2 fit and fewer CNS effects.
Saquinavir vs Indinavir vs Ritonavir	All three are **"–navir" protease inhibitors** with the hydroxyethylamine core; **ritonavir's special role is CYP3A4 boosting** of the others.
Peramivir vs Adamantanes	Both are anti-flu but opposite ends of the life cycle: adamantanes block **entry/uncoating (M2)**; peramivir blocks **release (neuraminidase)**.
Ribavirin is "just another NRTI"	No — ribavirin is **not an RT chain terminator**; it has **multiple** mechanisms (IMP-DH, capping, mutagenesis) and a different virus spectrum (RSV, HCV).
Lenacapavir is a protease inhibitor	No — it binds the **capsid protein**, a completely different target; it is the first-in-class capsid inhibitor.

18. Common Mistakes

1. Saying acyclovir is phosphorylated by **cellular** kinases first — wrong; the **first** phosphate comes from **viral thymidine kinase** (that is the whole basis of its selectivity). Cellular enzymes add only phosphates 2 and 3.
2. Calling NNRTIs "nucleoside analogues" — the second N is "**Non**-nucleoside"; they never enter the DNA chain.
3. Stating protease inhibitors "stop viral DNA synthesis" — they act **after** assembly, producing immature non-infectious particles; DNA synthesis is the NRTI/NNRTI stage.
4. Prescribing adamantanes for **influenza B** — flu B has no M2 channel; adamantanes are flu-A-only (and resistance is now near-universal).
5. Confusing **valganciclovir** (prodrug of ganciclovir) with a prodrug of acyclovir — different parent, different doses.
6. Forgetting that **ritonavir** at booster dose is there for **CYP3A4 inhibition**, not for its own antiviral punch.
7. Saying idoxuridine is given orally/IV — it is **topical ophthalmic only** (systemic toxicity from human-DNA incorporation).

19. Mnemonics

- **Adamantanes: "A-MAN plugs the M2 CAN"** — aMANTADINE, riMANTADINE: the cage-Man corks the M2 channel can.
- **Chain terminators: "No hook, no book"** — no 3′-OH hook the viral DNA book cannot add another page.
- **Acyclovir activation: "Viral TK Takes the first phosphate"** — **V**iral **T**K = **T**akes step 1; **C**ellular enzymes **C**omplete steps 2–3.
- **NRTI four: "ZiDiZaLaM"** — **Zi**dovudine (azido), **Di**danosine (dideoxy inosine), **Za**lcitabine (dideoxy cytidine), **La**mivudine (sulphur sugar). Hook: "**Z**ebras **D**on't **Z**oom, **L**lamas **M**arch" — or simply chant Zi-Di-Za-La.
- **"Zido-azido, Zal-cytidine, Did-inosine"** — one line sorts the three confusing NRTIs.
- **NNRTIs: "Butterfly in the pocket"** — loviride/delavirdine are butterflies that sit in RT's side pocket and bend the machine.
- **Protease inhibitors: "–navir jams the scissors"** — saquiNAVIR, indiNAVIR, ritoNAVIR. **"Ritonavir the Bodyguard"** — small dose guards the big PI from liver CYP3A4.
- **Peramivir: "PERA-traps"** — PERAmivir **traps** new flu viruses on the cell (neuraminidase blocked).
- **Lenacapavir: "CAP-saicin for the CAP-sid, twice a year"** — capsid binder, 6-monthly injection.
- **Acyclovir synthesis: "Bolt, Fix, Unmask"** — bolt on the N9 chain, fix the base (ClO), unmask the –OH.

20. Exam Summary

Antivirals (18 drugs, 8 groups). **Adamantanes** — amantadine (1-aminoadamantane), rimantadine [1-(1-aminoethyl)]: cage plugs influenza A **M2 proton channel** no uncoating; resistance widespread. **Anti-herpes nucleosides** — idoxuridine (5-iodo-2′-deoxyuridine; faulty DNA; eye drops only); **acyclovir** ***[9-(2-hydroxyethoxymethyl)guanine; viral TK triphosphate DNA-pol inhibition + chain termination (no 3′-OH)]; ganciclovir (+CH_2OH; anti-CMV); valganciclovir (valine-ester prodrug, 10× oral absorption).*** ***NRTIs** — zidovudine (3′-azido-thymidine), didanosine (2′,3′-dideoxyinosine), zalcitabine (2′,3′-dideoxycytidine), lamivudine (oxathiolane S-sugar cytidine): cellular kinases triphosphate HIV RT chain termination. **NNRTIs** — loviride (α-APA), delavirdine (BHAP): butterfly molecules, allosteric RT pocket, warp enzyme. **Ribavirin** (triazole-carboxamide + ribose): multi-mechanism (IMP-DH, capping, lethal mutagenesis); RSV, HCV. **Protease inhibitors** — saquinavir, indinavir, ritonavir: hydroxyethylamine core freezes HIV protease immature virus; ritonavir = CYP3A4 booster. **Peramivir** (cyclopentane sialic-acid mimic): neuraminidase block virions trapped; single IV dose for flu. **Lenacapavir** (multi-ring capsid binder): multi-stage capsid sabotage; 6-monthly SC injection for resistant HIV. SAR: nucleosides — no 3′-OH = termination; base selects virus; sugar decides kinase; prodrug masks aid absorption. PIs — –CH(OH)–CH_2– core essential; hydrophobic wings fill S-pockets; H-bonds add grip. Synthesis (starred): Acyclovir = 2-amino-6-chloropurine + (2-benzoyloxyethoxy)methyl chloride (base, DMF) N9-alkylated chloro intermediate (dil. HCl, heat) guanine intermediate (NaOH/MeOH) acyclovir.

21. One-Minute Revision

Cage pair (amantadine, rimantadine) corks flu-A M2 no uncoating. **Fake bricks** need no 3′-OH: acyclovir* (viral TK herpes chain stop), ganciclovir (+CH_2OH, CMV), valganciclovir (valine mask prodrug), idoxuridine (5-iodo, eye only). **NRTIs** ZiDiZaLaM: cellular kinases HIV RT chain stop (zido-azido, zal-cytidine, did-inosine, lami-S-sugar). **NNRTIs** = butterflies warping RT's side pocket. **–navirs** jam HIV scissors (hydroxyethylamine core); **ritonavir = bodyguard** (CYP3A4). **Ribavirin** = shotgun (RSV, HCV). **Peramivir** traps flu on the cell (neuraminidase). **Lenacapavir** = capsid superglue, 6-monthly jab. **Acyclovir synthesis: bolt–fix–unmask.**

22. Exam Questions

Short answer:

1 Why are antiviral drugs harder to design than antibacterial drugs? (Two reasons.)

2 What is a "chain terminator"? Give two examples with the missing group named.

3 Distinguish NRTIs from NNRTIs in two lines (chemistry + mechanism).

4 Why is acyclovir selectively toxic to herpes-infected cells?

5 What is the role of low-dose ritonavir in ART?

6 Name the viral target of peramivir and state its dosage form.

7 Why is idoxuridine restricted to ophthalmic use?

8 What makes lenacapavir's dosing schedule unique, and what target explains it?

Long answer:

1 Classify the eighteen syllabus antivirals chemically with their viral targets. Describe the structure (scaffold + key substituents) and uses of any five.

2 Explain, with a flowchart, the activation and mechanism of acyclovir. How does ganciclovir differ structurally, and what does the difference achieve?

3 Write the complete synthesis of Acyclovir, naming all reagents, conditions, and intermediates. Explain the purpose of the benzoyl protecting group and the 6-chloro substituent.

4 Present the SAR of nucleoside analogue antivirals as a rule table; illustrate each rule with a syllabus drug.

5 Present the SAR of HIV protease inhibitors as a rule table. Explain why ritonavir is used as a booster.

6 Compare the mechanisms of amantadine, peramivir, and lenacapavir with reference to the viral life-cycle stages they block.

MCQs:

1 The first phosphorylation of acyclovir is carried out by:

a) Cellular thymidine kinase b) Viral thymidine kinase c) HIV reverse transcriptase d) DNA polymerase
Answer: b

1 Which structural feature makes zidovudine a chain terminator?

a) 5-iodo group b) 3′-azido replacing 3′-OH c) Sulphur in the sugar ring d) Open-chain sugar **Answer: b**

1 Lamivudine's sugar ring contains:

a) An extra –CH_2OH b) A sulphur atom replacing 3′-CH_2 c) An azido group d) No sugar at all **Answer: b**

1 NNRTIs act by:

a) Chain termination b) Binding an allosteric pocket on reverse transcriptase c) Blocking the M2 channel d) Inhibiting neuraminidase **Answer: b**

1 The essential pharmacophore of HIV protease inhibitors is:

a) The adamantane cage b) The hydroxyethylamine –CH(OH)–CH_2– core c) The azido group d) The triazole ring **Answer: b**

1 Low-dose ritonavir is added to ART regimens because it:

a) Kills HIV directly at that dose b) Inhibits CYP3A4, prolonging the companion PI's life c) Blocks reverse transcriptase d) Prevents viral entry **Answer: b**

1 Peramivir blocks:

a) M2 proton channel b) Viral thymidine kinase c) Neuraminidase (viral release) d) Capsid assembly **Answer: c**

1 Valganciclovir differs from ganciclovir in that it:

a) Has an extra CH_2OH b) Carries an L-valine ester prodrug mask for better oral absorption c) Is a protease inhibitor d) Contains an adamantane cage **Answer: b**

1 Which drug wedges between HIV capsid protein monomers?

a) Saquinavir b) Lenacapavir c) Delavirdine d) Rimantadine **Answer: b**

1 Idoxuridine is used only as eye drops because:

a) It cannot cross membranes b) It incorporates into human DNA too, causing systemic toxicity c) It is destroyed by stomach acid only d) It has no antiviral activity systemically **Answer: b**

Viva questions (with answers):

1 *Why does acyclovir spare uninfected human cells?*

The first phosphorylation needs viral thymidine kinase, which only herpes-infected cells have; uninfected cells barely activate the drug.

1 *What does "dideoxy" mean in didanosine/zalcitabine?*

Both the 2′-OH and 3′-OH of the sugar are missing (replaced by H) — so the drug cannot extend the DNA chain.

1 *How does an NNRTI differ chemically from an NRTI?*

NNRTIs are not nucleosides at all — they are butterfly-shaped non-nucleosides binding a side pocket; NRTIs are fake nucleosides that terminate the chain.

1 *Why must indinavir be taken with plenty of water?*

It can crystallise as kidney stones; high fluid intake prevents this.

1 *What is special about lenacapavir administration?*

It is a subcutaneous injection given every 6 months (after oral loading) for multidrug-resistant HIV — the longest-acting antiretroviral in the syllabus.

1 *Why is ribavirin absolutely contraindicated in pregnancy?*

It is teratogenic — it causes birth defects; strict contraception is required during and after therapy.

Application-based:

1 A patient on high-dose acyclovir for herpes encephalitis develops flank pain and reduced urine output. Explain the chemistry behind this adverse effect and the pharmacist's counselling/prevention.

2 An ART patient asks why they must take "so many tablets including a tiny ritonavir one." Explain using the concepts of combination therapy and pharmacokinetic boosting.

3 During a flu outbreak, a prescriber orders amantadine for a patient with confirmed influenza B. Identify the problem using the drug's mechanism and suggest the correct syllabus alternative and its target.

23. References

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Unit III — Chapters 3 & 4: Antifungals, Anthelmintics and Urinary Tract Anti-infectives

How to read these chapters: every new idea follows the same four-step teaching sequence — **Technical concept** (the formal definition) **Simple explanation** (plain words, from zero) **Example** (a real drug or situation) **Key takeaway** (one line to remember). Drug entries follow: **Chemical class** **Structure** (scaffold + key substituents, described so you can draw it) **Uses**.

CHAPTER 3 — ANTIFUNGAL AGENTS

3.1 Learning Objectives

After studying this chapter, the student will be able to:

1 Define antifungal agents and explain why fungi are harder to kill than bacteria.

2 Classify antifungal drugs by chemical class (polyenes, azoles, allylamines, others).

3 Explain the mechanism of action of each class in simple words.

4 Describe the chemical structure (scaffold + key substituents) of every antifungal drug in the syllabus.

5 State the therapeutic uses of each drug.

6 Distinguish imidazoles from triazoles and explain why triazoles are preferred systemically.

7 Write the complete synthesis of Ketoconazole with numbered steps, reagents, conditions and intermediates.

8 Present the SAR of azole antifungals as rules.

9 Answer short, long, MCQ, viva and application-based exam questions on antifungals.

3.2 Definitions

Technical concept: Antifungal agents are chemotherapeutic drugs that kill fungi (fungicidal) or stop their growth (fungistatic) by damaging structures that exist in fungal cells but are absent or different in human cells.

Simple explanation: Fungi are living germs like bacteria, but they are built more like our own body cells. That makes them tricky enemies: a drug strong enough to kill the fungus can also hurt the patient. Antifungal drugs are special weapons designed to attack parts of the fungus that human cells do not have — mainly a fat-like molecule called **ergosterol** in the fungal cell wall covering (membrane).

Example: Amphotericin-B punches holes in the fungal membrane by grabbing ergosterol. Human membranes use cholesterol instead, so the drug mostly leaves human cells alone (though not perfectly — it can still harm kidneys).

Key takeaway: Antifungals work by targeting ergosterol or its making-machinery — something fungi need and humans do not.

More definitions you must know:

- **Fungicidal:** kills the fungus outright (e.g., Amphotericin-B, Naftifine).
- **Fungistatic:** stops the fungus from growing/multiplying; the body's immunity finishes the job (e.g., Griseofulvin, most azoles at low doses).
- **Ergosterol:** the sterol (fat-like molecule) in fungal cell membranes; the human equivalent is cholesterol. The single most important drug target in antifungal therapy.
- **Mycosis:** any disease caused by a fungus (plural: mycoses). Superficial mycoses affect skin/hair/nails (e.g., ringworm); systemic mycoses affect deep organs (e.g., lungs, brain).
- **Dermatophyte:** a fungus that eats keratin — the protein of skin, hair and nails (e.g., *Trichophyton*, *Microsporum*). Causes "tinea" infections (ringworm, athlete's foot).
- ***Candida*:** a yeast-like fungus causing thrush (mouth), vaginal infection and serious bloodstream infection in weak patients.
- ***Aspergillus*:** a mould causing lung infection, dangerous in patients with very low immunity.
- **Azole:** any antifungal containing a five-membered ring with nitrogen atoms (imidazole = 2 nitrogens; triazole = 3 nitrogens).
- **Polyene:** an antifungal with many alternating double bonds (a long chain of C=C) in a big ring; binds ergosterol directly.

3.3 Terminology Table

Term	Meaning in plain words
Ergosterol	Fat-like molecule in fungal membranes; main drug target
Cholesterol	Similar molecule in human membranes; why side effects happen
14-alpha-demethylase (CYP51)	Fungal enzyme that builds ergosterol; blocked by azoles
Squalene epoxidase	Enzyme early in the ergosterol-making line; blocked by allylamines
beta-1,3-glucan	Sugar wall material of fungi; blocked by echinocandins
Keratin	Protein of skin, hair, nails; dermatophytes feed on it
MIC	Minimum Inhibitory Concentration — lowest drug amount that stops visible growth
Fungistatic / Fungicidal	Stops growth / kills outright
Superficial mycosis	Skin, hair, nail infection
Systemic mycosis	Deep-organ infection
Prophylaxis	Giving a drug to *prevent* infection in high-risk patients
Otomycosis	Fungal infection of the ear
Onychomycosis	Fungal infection of the nail
Tinea	Ringworm-type skin infection (tinea corporis = body, tinea pedis = foot)
Mycosamine	The amino-sugar attached to polyene antibiotics

3.4 Why Fungi Are Hard to Treat — The Big Picture

Technical concept: Fungi are eukaryotes: their cells have a nucleus and organelles like human cells. Selective toxicity is therefore harder to achieve than with bacteria (which are prokaryotes with very different machinery).

Simple explanation: Imagine two houses built by the same builder with almost the same bricks. If you want to demolish only one house without touching the other, you must aim at the few bricks that are different. Bacteria are built very differently from us (easy target). Fungi are built almost like us (hard target). The few "different bricks" are ergosterol, the fungal cell wall sugars, and some fungal enzymes.

Example: Penicillin attacks the bacterial wall — humans have no such wall, so it is very safe. No such luxury exists for fungi; every antifungal carries more side-effect risk, which is why Amphotericin-B can damage kidneys.

Key takeaway: Fewer safe targets exist in fungi than in bacteria, so antifungal drugs need careful, targeted design.

3.5 Classification of Antifungal Agents

A. By chemical class (the exam's favourite)

1 **Polyene macrolides:** Amphotericin-B, Nystatin, Natamycin

2 **Azoles**

- **Imidazoles:** Clotrimazole, Econazole, Butoconazole, Oxiconazole, Tioconazole, Miconazole, Ketoconazole*
- **Triazoles:** Terconazole, Itraconazole, Fluconazole, Posaconazole, Isavuconazole

1 **Allylamines:** Naftifine

2 **Thiocarbamates:** Tolnaftate

3 **Benzofuran (spiro compound):** Griseofulvin

4 **Echinocandins** (context only — none in this syllabus list): inhibit beta-glucan wall synthesis

B. By mechanism of action

Mechanism	Drug classes	Plain-words meaning
Bind ergosterol punch holes in membrane	Polyenes	Drill holes; cell contents leak out; cell dies
Block ergosterol *making* (inhibit 14-alpha-demethylase)	Azoles	Stop the factory; membrane becomes weak and leaky
Block squalene epoxidase (earlier step)	Allylamines (Naftifine), Tolnaftate	Block the supply line; toxic raw material (squalene) piles up and kills
Damage the dividing machinery (microtubules)	Griseofulvin	Break the cell's "ropes" used during division
Block cell-wall sugar (beta-glucan) synthesis	Echinocandins	Stop wall building; wall-less cell bursts

C. By route / clinical use

- **Systemic (given by mouth or injection for deep infection):** Amphotericin-B (IV), Ketoconazole, Itraconazole, Fluconazole, Posaconazole, Isavuconazole, Griseofulvin (oral, skin/hair/nail only)
- **Topical / local only (too toxic or not absorbed for systemic use):** Nystatin, Natamycin, Clotrimazole, Econazole, Butoconazole, Oxiconazole, Tioconazole, Miconazole, Naftifine, Tolnaftate, Terconazole (vaginal)

3.6 Mechanisms of Action — Explained Step by Step

3.6.1 Polyenes — "The Hole Punchers"

Technical concept: Polyene macrolides bind ergosterol in the fungal membrane and assemble into transmembrane channels (pores), causing leakage of potassium ions and small molecules, leading to cell death.

Simple explanation: Think of the fungal membrane as a water balloon. The polyene drug sticks to ergosterol spots and lines up with other drug molecules to form a tiny tunnel through the balloon skin. Water and salts rush out through the tunnel. The balloon collapses — the fungus dies.

Example: Amphotericin-B given by IV drip forms these tunnels in fungi causing deep infection.

> **Key takeaway:** Polyenes = bind ergosterol make pores leak death (fungicidal).

Diagram to draw: Draw a horizontal double line (the membrane). Draw small oval shapes labelled "ergosterol" sitting in it. Draw 8 rod shapes standing vertically side by side forming a ring (the pore) with an arrow showing K+ ions escaping outward. Label: "Amphotericin-B + ergosterol = pore leakage cell death".

3.6.2 Azoles — "The Factory Saboteurs"

Technical concept: Azoles inhibit the fungal cytochrome P450 enzyme 14-alpha-demethylase (CYP51), blocking conversion of lanosterol to ergosterol. Methylated sterol intermediates accumulate and get built into the membrane, making it defective and leaky; growth stops.

Simple explanation: The fungus runs a factory that makes ergosterol bricks for its wall. The azole drug jams one key machine (the demethylase enzyme) by sticking its nitrogen atom onto the machine's iron heart. The factory then makes wrong, bent bricks. A wall of bent bricks leaks — the fungus cannot grow properly.

Example: Fluconazole tablet for vaginal candidiasis jams this enzyme; the yeast stops multiplying.

> **Key takeaway:** Azoles = block ergosterol factory (CYP51) faulty membrane growth stops (mostly fungistatic).

Diagram to draw: Draw a flowchart: Lanosterol --(14-alpha-demethylase, CYP51)--> Ergosterol --> healthy membrane. Draw a big X on the arrow, label "AZOLE blocks here (N atom grips the enzyme's iron)". Below, draw a wavy broken membrane labelled "defective membrane leakage".

3.6.3 Allylamines and Tolnaftate — "The Supply-Line Blockers"

Technical concept: Naftifine and Tolnaftate inhibit squalene epoxidase, an earlier enzyme in ergosterol synthesis. Ergosterol falls AND squalene (the unused raw material) accumulates to toxic levels inside the cell — this double hit is fungicidal for dermatophytes.

Simple explanation: If azoles jam the factory's last machine, allylamines block the delivery truck much earlier. Raw material (squalene) piles up inside the factory until it becomes poisonous, and no finished bricks arrive either. Two problems at once — the fungus dies.

Example: Naftifine cream for athlete's foot kills the skin fungus this way.

Key takeaway: Allylamines = block squalene epoxidase no ergosterol + toxic squalene pile-up fungicidal.

3.6.4 Griseofulvin — "The Rope Cutter"

Technical concept: Griseofulvin binds tubulin and disrupts the mitotic spindle (microtubules), arresting fungal cell division in metaphase. It is deposited in keratin, so new skin/hair/nail grows out fungus-free.

Simple explanation: When a cell divides, it uses tiny ropes (microtubules) to pull its two halves apart. Griseofulvin cuts those ropes — the fungus tries to divide and gets stuck halfway. It also hides inside the patient's own skin and nails, so as new nail grows, it is already protected.

Example: A child with scalp ringworm takes griseofulvin tablets for weeks; new hair grows in healthy.

Key takeaway: Griseofulvin = breaks division ropes fungus cannot multiply; concentrates in keratin (fungistatic).

3.6.5 Echinocandins — context note

Technical concept: Echinocandins (caspofungin, micafungin, anidulafungin — none in this syllabus) inhibit beta-1,3-glucan synthase, blocking fungal cell-wall building. Humans have no cell wall, so these are very selective.

Simple explanation: Fungi wear a sugar-brick wall that humans do not have at all. Echinocandins stop the wall-building machine — the fungus bursts. Mentioned here only so you know the class exists; no echinocandin is in your syllabus list.

Key takeaway: Echinocandins = wall builders blocked; safest target in theory; not in this syllabus.

Flowchart — whole antifungal decision:

```
Fungal infection diagnosed
        |
Is it deep/inside the body (systemic)? ----YES----> Amphotericin-B (IV) or triazole (Itraconazole /
Fluconazole / Posaconazole / Isavuconazole)
        |
        NO (skin, mouth, vagina, nail)
        |
  Is it skin/hair/nail (dermatophyte)? --YES--> Griseofulvin (oral) or topical azole / Naftifine /
Tolnaftate
        |
        NO --> Mouth/vagina (Candida)? --YES--> Nystatin (mouth), Clotrimazole/Miconazole/Terconazo
vaginal), Fluconazole (oral)
```

3.7 The Polyenes — Drug by Drug

3.7.1 Amphotericin-B

- **Chemical class:** Polyene macrolide antibiotic (heptaene — 7 conjugated double bonds).
- **Structure:** A very large ring (macrolactone, 38-membered) containing a long stretch of 7 alternating C=C double bonds on one side (the "polyene" part, fat-loving) and many -OH groups on the other side (water-loving), plus an amino-sugar called **mycosamine** and a carboxylic acid group. Because it has both an acidic (-COOH) and a basic (-NH2) group, it is **amphoteric** (hence the name "ampho-tericin"). Yellow powder.
- *How to draw:* Draw a big oval ring. On the left half of the ring draw 7 zigzag double bonds in a row; on the right half draw several -OH groups sticking out; attach a hexagon (sugar) labelled "mycosamine" with an -NH2, and one -COOH on the ring.
- **Uses:** Drug of choice (given IV) for serious systemic fungal infections — cryptococcal meningitis, invasive aspergillosis, mucormycosis ("black fungus"), systemic candidiasis, and visceral leishmaniasis (kala-azar). Lipid formulations are less kidney-toxic.

3.7.2 Nystatin

- **Chemical class:** Polyene macrolide antibiotic (tetraene — 4 conjugated double bonds).
- **Structure:** Same family scaffold as Amphotericin-B — a large macrolactone ring with a shorter conjugated chain (4 double bonds), multiple -OH groups, the mycosamine amino-sugar and a carboxyl group. Smaller and less potent than Amphotericin-B; too toxic for injection.
- *How to draw:* Same big-ring sketch as Amphotericin-B but write "4 double bonds (tetraene)" on the left half.
- **Uses:** Only local/topical — oral suspension for mouth thrush (oral candidiasis), tablets held in the mouth, creams for skin and vaginal candidiasis, nappy rash. Never given IV (too toxic).

3.7.3 Natamycin (Pimaricin)

- **Chemical class:** Polyene macrolide antibiotic (tetraene).
- **Structure:** Macrolactone ring with 4 conjugated double bonds, -OH groups, mycosamine sugar and a carboxyl group — the polyene family scaffold, smallest of the three.
- **Uses:** Topical antifungal for the **eye** — fungal keratitis (corneal ulcers) and fungal blepharitis/conjunctivitis, as eye drops/suspension. Also used as a food preservative (prevents mould on cheese and sausages). Not absorbed systemically.

Polyenes — comparison table

Feature	Amphotericin-B	Nystatin	Natamycin
Double bonds	7 (heptaene)	4 (tetraene)	4 (tetraene)
Given systemically?	Yes (IV)	No — too toxic	No
Main use	Deep/systemic mycoses	Mouth/skin/vaginal thrush	Fungal eye infections

Feature	Amphotericin-B	Nystatin	Natamycin
Special note	Nephrotoxic; lipid forms safer	Not absorbed from gut	Also a food preservative

3.8 The Azoles — Imidazoles vs Triazoles

Technical concept: All azoles carry a five-membered nitrogen ring that coordinates with the haem iron of fungal 14-alpha-demethylase. Imidazoles (2 nitrogens) bind human cytochrome enzymes more strongly than triazoles (3 nitrogens) do, causing more drug interactions and hormonal side effects; triazoles are more selective for the fungal enzyme and better tolerated systemically.

Simple explanation: Both types jam the same machine with their nitrogen "hand". The imidazole hand is grabby — it also grabs the patient's own similar machines (liver enzymes, hormone-making enzymes), causing side effects and interactions. The triazole hand is more polite — it mostly grabs only the fungal machine. That is why triazoles (fluconazole, itraconazole) are safe enough to swallow for deep infections, while most imidazoles stay on the skin.

Example: Ketoconazole (imidazole) tablets can disturb liver and hormone function, so oral use is now restricted; Fluconazole (triazole) tablets are routinely and safely swallowed.

Key takeaway: Imidazoles = mostly topical (2 N ring, more side effects); Triazoles = systemic-friendly (3 N ring, more selective).

Azole SAR — rule table

Rule	Detail	Example
1. The azole nitrogen is essential	One ring nitrogen must be free to grip the enzyme's iron; blocking it kills activity	All active azoles
2. Halogenated phenyl ring boosts power	2,4-dichloro or 2,4-difluoro substitution on the phenyl ring greatly increases antifungal potency	Ketoconazole (2,4-diCl), Fluconazole (2,4-diF)
3. Lipophilic side chain decides spectrum & stay-time	A long fat-loving tail (dioxolane + piperazine + aryl groups) improves tissue penetration and half-life	Itraconazole, Posaconazole
4. Imidazole triazole swap improves safety	Replacing imidazole with 1,2,4-triazole keeps antifungal power but reduces human enzyme binding	Terconazole vs miconazole-type
5. Dioxolane/tetrahydrofuran ring holds shape	The oxygen ring (dioxolane in ketoconazole/itraconazole; tetrahydrofuran in posaconazole) keeps the two arms in the correct 3D angle	Ketoconazole, Itraconazole
6. Small + water-soluble = reaches brain/urine	Compact, polar triazoles cross into CSF and urine well	Fluconazole

Imidazoles (2-nitrogen ring)

3.8.1 Clotrimazole

- **Chemical class:** Triphenylmethyl imidazole (imidazole antifungal).

- **Structure:** An imidazole ring attached through its nitrogen to a central carbon that carries **three phenyl rings** (a "trityl" group); one of the phenyl rings has a chlorine at the ortho position (o-chlorophenyl). Very fat-soluble, not for systemic use.
- *How to draw:* Draw a pentagon (imidazole, 2 N). From one N draw a single carbon with three hexagon rings attached; put "Cl" on one ring near the attachment point.
- **Uses:** Topical creams/pessaries for vaginal candidiasis, skin ringworm, athlete's foot; mouth paint/lozenges for oral thrush.

3.8.2 Econazole

- **Chemical class:** Phenethyl imidazole (imidazole antifungal).
- **Structure:** Imidazole-CH2-CH(phenyl)-O-CH2-(phenyl) skeleton: a 2,4-dichlorophenyl group on the carbon bearing an ether oxygen, which connects to a 4-chlorobenzyl group. Two chlorinated aromatic rings + imidazole.
- **Uses:** Topical cream for skin fungal infections (tinea), cutaneous candidiasis; vaginal cream for vulvovaginal candidiasis.

3.8.3 Butoconazole

- **Chemical class:** Thioether imidazole (imidazole antifungal).
- **Structure:** Imidazole-CH2-CH2-CH(S-aryl)-(4-chlorophenyl) skeleton: a four-carbon chain carrying imidazole at one end, a 4-chlorophenyl group, and a sulphur-linked 2,6-dichlorophenyl group (a thioether, -S- bridge). The sulphur atom is its signature.
- **Uses:** Vaginal cream (single-dose sustained release) for vulvovaginal candidiasis.

3.8.4 Oxiconazole

- **Chemical class:** Imidazole oxime ether antifungal.
- **Structure:** Contains a C=N-O linkage (**oxime ether**): (2,4-dichlorophenyl)-C(=N-O-CH2-(2,4-dichlorophenyl))-CH2-imidazole. Two 2,4-dichlorophenyl rings joined through the oxime bridge, with imidazole on the side chain. The Z-isomer is the active form.
- **Uses:** Topical cream/lotion for tinea (ringworm) of the body and athlete's foot.

3.8.5 Tioconazole

- **Chemical class:** Thiophene-containing imidazole antifungal.
- **Structure:** Imidazole-CH2-CH(2,4-dichlorophenyl)-O-CH2-(2-chloro-3-thienyl): like miconazole but one chlorinated phenyl is replaced by a **thiophene ring** (five-membered ring with sulphur) bearing a chlorine. Signature = the sulphur ring.
- **Uses:** Vaginal ointment (single dose) for vulvovaginal candidiasis; topical solution for nail/skin fungal infections.

3.8.6 Miconazole

- **Chemical class:** Bis(dichlorophenyl) ether imidazole antifungal.

- **Structure:** Imidazole-CH2-CH(2,4-dichlorophenyl)-O-CH2-(2,4-dichlorophenyl): an ether bridge connecting two 2,4-dichlorophenyl rings, with an imidazole-ethyl arm on the central carbon. Four chlorines total.
- **Uses:** Topical cream/powder for skin fungal infections and athlete's foot; vaginal cream for candidiasis; oral gel for mouth/throat candidiasis.

3.8.7 Ketoconazole* (synthesis required)

- **Chemical class:** Dioxolane-piperazine imidazole antifungal (the first oral broad-spectrum azole).
- **Structure:** Three joined parts: (a) a **1,3-dioxolane ring** (five-membered, 2 oxygens) carrying a 2,4-dichlorophenyl group and an imidazol-1-ylmethyl arm on the same carbon; (b) the dioxolane's -CH2-O- arm linked as an ether to (c) a **piperazine ring** (six-membered, 2 nitrogens) bearing a 4-acetylphenyl group (phenyl with -COCH3). Only the cis-dioxolane isomer is active.
- *How to draw:* Draw a pentagon with 2 O (dioxolane). On one carbon put a hexagon marked "2,4-diCl phenyl" and a -CH2- pentagon marked "imidazole". On the opposite carbon put -CH2-O- then a hexagon (phenyl) - then a hexagon with 2 N (piperazine) - then -COCH3.
- **Uses:** Topical shampoo/cream for dandruff (seborrhoeic dermatitis, *Malassezia*) and tinea; oral tablets earlier used for systemic mycoses but now restricted (liver toxicity, hormone effects) — replaced by triazoles.

Synthesis of Ketoconazole (Heeres / Janssen route)

Overall plan: build the imidazole-ketone, protect it as a dioxolane ketal, convert the side-chain alcohol to a leaving group, and join it by ether formation to the acetyl-phenyl-piperazine phenol.

- **Step 1 — Alpha-bromination.** 2,4-Dichloroacetophenone + bromine (Br2) in glacial acetic acid, 0–10 °C **Intermediate 1: 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one** (2,4-dichlorophenacyl bromide) + HBr. (The -CH3 next to the ketone is brominated.)
- **Step 2 — Imidazole substitution.** Intermediate 1 + imidazole (excess) in acetone/DMF, room temperature **Intermediate 2: 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-one** + HBr. (Imidazole nitrogen displaces bromide — SN2.)
- **Step 3 — Ketal formation.** Intermediate 2 + glycerol, catalytic p-toluenesulphonic acid, toluene reflux with Dean–Stark water removal **Intermediate 3: cis-2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolane-4-methanol** (plus the trans isomer, separated by crystallisation; only cis is carried forward). (Ketone + 1,2-diol dioxolane ring; water removed to drive equilibrium.)
- **Step 4 — Mesylation.** Intermediate 3 (cis) + methanesulphonyl chloride (MsCl), triethylamine, dichloromethane, 0 °C **Intermediate 4: the methanesulphonate (mesylate)** of the primary alcohol. (Converts -OH into a good leaving group.)
- **Step 5 — Phenol partner (separate branch).** 1-(4-Hydroxyphenyl)piperazine + acetic anhydride, mild conditions **Intermediate 5: 1-[4-(4-hydroxyphenyl)piperazin-1-yl]ethan-1-one**. (Selective N-acetylation of piperazine; the phenolic -OH is untouched.)
- **Step 6 — Ether coupling.** Intermediate 4 + Intermediate 5, potassium carbonate, DMF, heat **Ketoconazole** + methanesulphonate salt. (Williamson ether synthesis: phenoxide displaces mesylate.)

Flowchart of the synthesis:

```
2,4-dichloroacetophenone --[Br2, AcOH]--> phenacyl bromide (1)
        --[imidazole]--> imidazolyl ketone (2)
        --[glycerol, p-TsOH, -H2O]--> cis-dioxolane-methanol (3)
        --[MsCl, Et3N]--> mesylate (4) --+
                                         +--[K2CO3, DMF]--> KETOCONAZOLE
1-(4-hydroxyphenyl)piperazine --[(CH3CO)2O]--> acetyl-phenol (5) --+
```

Triazoles (3-nitrogen ring)

3.8.8 Terconazole

- **Chemical class:** Dioxolane-piperazine triazole antifungal.
- **Structure:** Almost the twin of ketoconazole with two swaps: the imidazole is replaced by a **1,2,4-triazole** ring, and the piperazine's acetyl group is replaced by an **isopropyl group**. So: triazolylmethyl-dioxolane (2,4-dichlorophenyl) -CH2-O-phenyl-piperazine(isopropyl).
- **Uses:** Vaginal cream/suppository for vulvovaginal candidiasis.

3.8.9 Itraconazole

- **Chemical class:** Dioxolane-piperazine-triazolone triazole antifungal (highly lipophilic).
- **Structure:** Like ketoconazole's left half (triazolylmethyl + 2,4-dichlorophenyl on a 1,3-dioxolane, -CH2-O-phenyl-piperazine) but the piperazine's second nitrogen carries a **1,2,4-triazol-3-one (triazolone) ring** bearing a sec-butyl group and a 2,4-dichlorophenyl group. Very long, fat-loving molecule.
- **Uses:** Oral/IV for aspergillosis, blastomycosis, histoplasmosis, onychomycosis (nail fungus), and oropharyngeal candidiasis. Broadest-spectrum azole of its generation.

3.8.10 Fluconazole

- **Chemical class:** Bis-triazole antifungal (small, water-soluble).
- **Structure:** A central carbon bearing four groups: -OH, a 2,4-difluorophenyl ring, and **two 1,2,4-triazol-1-ylmethyl arms** (-CH2-triazole on both sides). Compact and symmetrical; water-soluble unlike other azoles.
- *How to draw:* Draw a central C with -OH up, a hexagon marked "2,4-diF" left, and two -CH2-pentagon(triazole) arms right and down.
- **Uses:** Oral/IV for vaginal candidiasis (single dose), oropharyngeal and oesophageal candidiasis, cryptococcal meningitis (excellent brain penetration), and prophylaxis in immunocompromised patients.

3.8.11 Posaconazole

- **Chemical class:** Tetrahydrofuran-piperazine-triazolone triazole antifungal (extended-spectrum).
- **Structure:** Itraconazole-like right half (phenyl-piperazine-triazolone with 2,4-difluorophenyl) but the left oxygen ring is a **tetrahydrofuran** (one oxygen) instead of dioxolane, carrying a 2,4-difluorophenyl and a triazolylmethyl arm, plus an extended side chain ending in a **secondary alcohol** (-CH(OH)-). Longest azole molecule.

- **Uses:** Oral/IV for prophylaxis of invasive aspergillosis and candidiasis in severely immunocompromised patients; treatment of oropharyngeal candidiasis and mucormycosis (salvage therapy).

3.8.12 Isavuconazole

- **Chemical class:** Thiazole-benzonitrile triazole antifungal; given as the water-soluble prodrug **isavuconazonium sulphate**.
- **Structure:** A 1,2,4-triazole linked through a chiral 2,3-butanediol-like backbone (bearing -OH and a 2,5-difluorophenyl) to a **thiazole ring** (five-membered, N + S), which connects to a **benzonitrile** (phenyl with -CN). The prodrug masks the -OH as an ester that blood enzymes clip off.
- **Uses:** IV/oral for invasive aspergillosis and invasive mucormycosis. Shorter QT effect than some azoles.

Triazoles — comparison table

Drug	Ring system	Stand-out feature	Key use
Terconazole	Dioxolane + piperazine	Triazole + isopropyl-piperazine	Vaginal candidiasis
Itraconazole	Dioxolane + piperazine + triazolone	Most lipophilic; needs acid for absorption	Aspergillosis, nail fungus
Fluconazole	Bis-triazole, no long tail	Water-soluble; enters brain & urine	Cryptococcal meningitis, vaginal candidiasis
Posaconazole	Tetrahydrofuran + triazolone	Longest molecule; -OH side chain	Prophylaxis in immunocompromised
Isavuconazole	Triazole + thiazole + benzonitrile	Prodrug (isavuconazonium)	Aspergillosis, mucormycosis

3.9 Allylamine and Thiocarbamate

3.9.1 Naftifine

- **Chemical class:** Allylamine antifungal (the -CH2-CH=CH- allyl group is the signature).
- **Structure:** A tertiary amine nitrogen carrying three groups: a methyl, a **1-naphthylmethyl** group (naphthalene = two fused benzene rings), and a **cinnamyl (3-phenylallyl)** group (-CH2-CH=CH-phenyl). The C=C next to the nitrogen is the "allylamine" unit.
- *How to draw:* Draw N with -CH3, a double-hexagon (naphthalene)-CH2-, and -CH2-CH=CH-hexagon (phenyl).
- **Uses:** Topical cream/gel for tinea (athlete's foot, ringworm, jock itch). Fungicidal for dermatophytes.

3.9.2 Tolnaftate

- **Chemical class:** Thiocarbamate antifungal (-O-C(=S)-N- group).
- **Structure:** O-(2-naphthyl) N-methyl-N-(3-tolyl)thiocarbamate: a central C=S with -O-(2-naphthyl) on one side and -N(CH3)-(3-methylphenyl) on the other. Contains sulphur in the thiocarbamate, like naftifine it blocks squalene epoxidase.
- **Uses:** Topical powder/cream/spray for athlete's foot and ringworm. Ineffective against *Candida* — only for dermatophytes.

3.10 Griseofulvin

- **Chemical class:** Spiro benzofuran antifungal antibiotic (from *Penicillium griseofulvum*).
- **Structure:** A **spiro compound** — a benzofuran ring (benzene fused to furan) sharing one single carbon (the spiro centre) with a chlorinated cyclohexenone ring. Substituents: three **methoxy (-OCH3)** groups (two on the benzofuran, one on the cyclohexenone) and one **chlorine** at position 7. The spiro junction is its unmistakable signature.
- *How to draw:* Draw a benzene fused to a 5-membered O-ring (benzofuran); from the furan's 2-carbon draw a second six-membered ring sharing only that one atom (spiro); mark 3 × -OCH3 and 1 × Cl.
- **Uses:** Oral, only for dermatophyte infections of skin, hair and nails (tinea capitis/corporis/pedis, onychomycosis). Fungistatic — treatment lasts weeks to months. Deposited in keratin; new keratin grows protected.

3.11 Infographic Concept Box — Chapter 3

```
+-------------------------------------------------------------------+
|  ANTIFUNGALS AT A GLANCE                                          |
|  Target: ERGOSTEROL (fungal membrane brick; humans use            |
|  cholesterol instead)                                             |
|                                                                   |
|  POLYENES ........... Punch holes in the membrane (fungicidal)    |
|    Amphotericin-B = IV, deep infections, kidney-toxic             |
|    Nystatin = mouth/skin only | Natamycin = eye drops             |
|                                                                    |
|  AZOLES ............. Jam the ergosterol factory (CYP51)          |
|    IMIDAZOLES (2 N) = topical mostly: "the -azoles you rub on"    |
|    TRIAZOLES (3 N)  = systemic-safe: Fluconazole, Itraconazole    |
|                                                                    |
|  ALLYLAMINES ........ Block supply line + poison pile-up          |
|    Naftifine (cream) | Tolnaftate (thiocarbamate, powder)         |
|                                                                    |
|  GRISEOFULVIN ....... Cuts the division ropes; hides in keratin   |
|    Oral, for skin/hair/nail ringworm only                         |
+-------------------------------------------------------------------+
```

3.12 Analogies

1 **Polyenes are like drilling holes in a boat's hull.** The boat (fungus) sinks as water (ions) pours out.

2 **Azoles are like supplying bent bricks to a builder.** The wall (membrane) looks built but leaks and collapses.

3 **Imidazole vs triazole is like a master key vs a specific key.** Imidazole opens many locks (fungal + human enzymes side effects); triazole opens mainly the fungal lock.

4 **Griseofulvin is like cutting the ropes in a tug-of-war.** The dividing cell cannot pull its halves apart.

5 **Allylamines are like blocking a factory's raw-material gate while the delivery trucks keep dumping sacks inside** — the pile-up itself becomes poisonous.

3.13 Pharmacy Relevance

- **Counselling:** Topical antifungals must be applied beyond the visible rash edge and continued 1–2 weeks after symptoms vanish, or the infection returns. Griseofulvin needs weeks of tablets — warn patients not to stop early.
- **Formulation:** Nystatin and natamycin are not absorbed — that is why they are formulated as mouth paints, creams and eye drops, never injections. Fluconazole's water solubility allows both tablets and IV.
- **Storage & stability:** Polyene suspensions (nystatin) and natamycin eye drops are light-sensitive; dispense in proper containers and advise refrigeration where labelled.
- **Interactions:** Azoles inhibit human liver CYP enzymes — they raise levels of many drugs (e.g., certain statins, warfarin). A pharmacist must check interactions before dispensing oral azoles.
- **Sterile compounding:** Amphotericin-B IV must be reconstituted and infused slowly with test-dose monitoring; lipid formulations differ in dosing from conventional — never interchange without checking.

3.14 India Context

- Fungal skin infections (tinea/ringworm) are extremely common in India's hot, humid climate; topical azoles (clotrimazole, miconazole) and tolnaftate powders are everyday pharmacy items.
- During the COVID-19 pandemic, India saw a large wave of **mucormycosis ("black fungus")**, treated mainly with liposomal Amphotericin-B and then posaconazole/isavuconazole — every pharmacy student should know this link.
- Fluconazole single-dose therapy for vaginal candidiasis and itraconazole for persistent ringworm are widely prescribed across India.
- Griseofulvin remains in use for scalp ringworm in children in many Indian settings.
- Nystatin oral suspension is a standard pharmacy stock item for oral thrush in infants and immunocompromised patients.

3.15 Key Points

1 Ergosterol is the master target of antifungal therapy.

2 Polyenes bind ergosterol and form pores — fungicidal (Amphotericin-B = systemic; Nystatin, Natamycin = local).

3 Azoles inhibit 14-alpha-demethylase (CYP51) — mostly fungistatic.

4 Imidazoles (2 N) are mainly topical; triazoles (3 N) are systemic-safe.

5 2,4-dichloro / 2,4-difluoro phenyl substitution boosts azole potency.

6 Allylamines (Naftifine) and Tolnaftate block squalene epoxidase — fungicidal for dermatophytes.

7 Griseofulvin disrupts microtubules and concentrates in keratin — oral, dermatophytes only.

8 Ketoconazole synthesis: bromination imidazole substitution ketalisation mesylation ether coupling.

9 Fluconazole is the small, water-soluble triazole that reaches brain and urine.

10 Echinocandins block wall-glucan synthesis but are not in this syllabus.

3.16 Common Confusions

Confusion	Clarification
Nystatin vs Natamycin	Both polyene tetraenes for local use; Nystatin = mouth/skin/vagina, Natamycin = eye
Miconazole vs Ketoconazole	Miconazole = topical ether-imidazole; Ketoconazole = oral/topical dioxolane-imidazole with piperazine tail
Clotrimazole vs "all -azoles"	Clotrimazole is an imidazole (topical); fluconazole/itraconazole are triazoles (systemic)
Fungistatic vs fungicidal	Azoles/griseofulvin mostly stop growth; polyenes/allylamines kill
Tolnaftate vs Naftifine	Both topical for tinea and both hit squalene epoxidase; Tolnaftate is a thiocarbamate (no good vs Candida), Naftifine is an allylamine
Terconazole vs Tioconazole	Terconazole = triazole vaginal cream; Tioconazole = imidazole with thiophene ring, vaginal/single-dose

3.17 Common Mistakes

1 Writing that nystatin can be given IV — it cannot; it is too toxic systemically.

2 Calling all azoles "systemic" — most imidazoles are topical-only.

3 Forgetting the azole nitrogen grips the haem iron of CYP51 — the heart of the mechanism.

4 Mixing up squalene epoxidase (allylamines) with 14-alpha-demethylase (azoles).

5 Saying griseofulvin is broad-spectrum — it works only on dermatophytes.

6 In ketoconazole synthesis, forgetting that only the **cis**-dioxolane isomer is active.

7 Confusing the dioxolane ring (ketoconazole/itraconazole, 2 oxygens) with the tetrahydrofuran ring (posaconazole, 1 oxygen).

3.18 Mnemonics

- **Polyenes — "AMP, NYS, NAT":** "**A** **N**asty **N**ail needs **A** **M**ighty **P**unch" — **A**mphotericin (deep), **N**ystatin (mouth), **N**atamycin (eye).
- **Imidazoles — "CEMBOKT":** "**C**lotrimazole, **E**conazole, **M**iconazole, **B**utoconazole, **O**xiconazole, **T**ioconazole + **K**etoconazole" — "**C**reams **E**very **M**orning **B**efore **O**utdoor **T**asks, **K**eep on skin" (all topical except ketoconazole).
- **Triazoles — "TIFPI":** "**T**erconazole, **I**traconazole, **F**luconazole, **P**osaconazole, **I**savuconazole" — "**T**hree-nitrogen **I**s **F**or **P**rofound (deep) **I**nfections."
- **Mechanisms:** "**P**unch (Polyenes), **J**am (a**Z**oles jam the factory), **S**tarve + **P**oison (allylamines block **S**qualene epoxidase), **C**ut ropes (**G**riseofulvin vs microtubules)."

3.19 Exam Summary

- Antifungals target ergosterol or its synthesis because fungi are eukaryotes like us — few safe targets exist.
- Polyenes (Amphotericin-B heptaene; Nystatin, Natamycin tetraenes): pore formation via ergosterol binding; mycosamine sugar present; Amphotericin-B = IV systemic, nephrotoxic; others local.
- Azoles inhibit CYP51 (14-alpha-demethylase); azole N coordinates haem iron. Imidazoles (2 N, topical, more interactions) vs triazoles (3 N, systemic, selective).
- SAR: free azole N essential; 2,4-diCl/diF phenyl boosts potency; lipophilic tail (dioxolane-piperazine) extends spectrum; small polar triazole (fluconazole) reaches CSF/urine.
- Ketoconazole synthesis: 2,4-dichloroacetophenone (Br2) phenacyl bromide (imidazole) imidazolyl ketone (glycerol, p-TsOH) cis-dioxolane-methanol (MsCl) mesylate (acetyl-phenyl-piperazine phenol, K2CO3) ether ketoconazole.
- Allylamines (Naftifine) + Tolnaftate: squalene epoxidase inhibition; fungicidal for dermatophytes; topical.
- Griseofulvin: spiro benzofuran, disrupts microtubules, keratin-seeking, oral for tinea only.

3.20 One-Minute Revision

Ergosterol = target. Polyenes punch holes (Amphotericin-B IV deep; Nystatin mouth; Natamycin eye). Azoles jam CYP51 — imidazoles (2N) topical, triazoles (3N) systemic. Ketoconazole = dioxolane + piperazine + imidazole; made by bromination imidazole ketal mesylate ether coupling. Fluconazole = tiny bis-triazole, brain + urine. Itraconazole = most fat-loving. Naftifine/Tolnaftate = block squalene epoxidase. Griseofulvin = spiro compound, cuts microtubules, hides in keratin. 2,4-diCl/diF phenyl = more power.

3.21 Exam Questions — Chapter 3

Short questions

1 Why are fungi more difficult to treat selectively than bacteria?

2 Define fungicidal and fungistatic with one example each.

3 What is ergosterol and why is it the main antifungal target?

4 Name the three polyene antifungals in the syllabus and give one use of each.

5 How do azole antifungals inhibit ergosterol synthesis?

6 Distinguish imidazoles from triazoles (structure + clinical consequence).

7 What enzyme do allylamines block, and what two effects follow?

8 Why is griseofulvin effective only against dermatophytes?

9 Why is nystatin never given intravenously?

10 Name the prodrug among triazoles and its active form.

Long questions

1 Classify antifungal agents by chemical class and mechanism of action. Describe the structure (scaffold + substituents) and uses of Amphotericin-B, Nystatin and Natamycin.

2 Explain the mechanism of action of azole antifungals. Present the SAR of azoles as rules, and describe the structures and uses of any four imidazoles and any three triazoles.

3 Write the complete synthesis of Ketoconazole with numbered steps, reagents, conditions and intermediates. Describe its structure and uses.

4 Compare polyenes, azoles, allylamines and griseofulvin with respect to mechanism, spectrum and route of administration, giving two examples each.

MCQs (answer key at end)

1 The primary molecular target of polyene antifungals is:

a) 14-alpha-demethylase b) Ergosterol c) Squalene epoxidase d) Beta-glucan synthase

1 Which polyene is given intravenously for systemic mycoses?

a) Nystatin b) Natamycin c) Amphotericin-B d) Griseofulvin

1 Azoles inhibit:

a) DNA gyrase b) 14-alpha-demethylase (CYP51) c) Squalene epoxidase d) Thymidylate synthase

1 The azole ring binds the enzyme through:

a) Sulphur–iron bond b) Nitrogen–haem iron coordination c) Hydrogen bonding only d) Covalent alkylation

1 Which is a triazole (not imidazole)?

a) Miconazole b) Clotrimazole c) Fluconazole d) Tioconazole

1 Natamycin is mainly used for:

a) Systemic candidiasis b) Fungal eye infections c) Vaginal candidiasis d) Nail fungus (oral)

1 Naftifine belongs to which class?

a) Polyene b) Azole c) Allylamine d) Echinocandin

1 Griseofulvin acts by:

a) Binding ergosterol b) Inhibiting CYP51 c) Disrupting microtubules d) Blocking glucan synthesis

1 In ketoconazole synthesis, the dioxolane ring is formed from the ketone and:

a) Ethylene glycol b) Glycerol c) Methanol d) Acetone

1 Which structural feature increases azole potency?

a) 2,4-dichloro/difluoro phenyl substitution b) Extra carboxyl group c) Quaternary nitrogen d) Nitro group

1 Tolnaftate is ineffective against:

a) Dermatophytes b) *Candida* species c) Tinea pedis d) Ringworm

1 Isavuconazole is administered as:

a) A lipid complex b) The prodrug isavuconazonium c) An eye drop d) A vaginal tablet

MCQ Answer Key: 1-b, 2-c, 3-b, 4-b, 5-c, 6-b, 7-c, 8-c, 9-b, 10-a, 11-b, 12-b

Viva questions (with answers)

1 **Q: Why is Amphotericin-B nephrotoxic?**

A: It can also bind cholesterol in human kidney cell membranes (cholesterol resembles ergosterol), forming pores that damage renal tubules.

1 **Q: What is mycosamine?**

A: The amino-sugar attached to polyene macrolides (amphotericin-B, nystatin, natamycin); it helps the drug interact with the membrane sterol.

1 **Q: Which isomer of the ketoconazole dioxolane intermediate is active?**

A: The cis isomer; the trans isomer is separated and discarded.

1 **Q: Why is fluconazole able to treat cryptococcal meningitis?**

A: It is small and water-soluble, so it penetrates the blood–brain barrier into CSF well.

1 **Q: Imidazole or triazole — which causes more drug interactions, and why?**

A: Imidazoles; their ring binds human cytochrome P450 enzymes more strongly, disturbing metabolism of co-administered drugs and steroid hormones.

1 **Q: What is the signature group of tolnaftate?**

A: The thiocarbamate group (-O-C(=S)-N-).

1 **Q: How does griseofulvin reach the site of a nail infection?**

A: It is deposited in keratin precursor cells; as new keratinised nail grows, it carries the drug with it.

1 **Q: Name the leaving group used in the final ether-forming step of ketoconazole synthesis.**

A: Methanesulphonate (mesylate), formed with MsCl and triethylamine.

Application-based questions

1 A diabetic patient develops a blackish nasal lesion diagnosed as mucormycosis. Which antifungal class/drug is first-line, by what route, and what organ toxicity must be monitored? *(Amphotericin-B IV; monitor kidney function — nephrotoxicity.)*

2 A patient on warfarin is prescribed oral ketoconazole for a stubborn fungal infection. As the pharmacist, what interaction would you flag and what safer alternative class would you suggest discussing with the prescriber? *(Azoles inhibit CYP enzymes raised warfarin levels bleeding risk; a triazole such as fluconazole/itraconazole is more selective, but still needs monitoring.)*

3 A mother asks why her child's scalp ringworm needs "so many weeks of tablets" (griseofulvin) while her own athlete's foot needed only cream. Explain in simple words. *(Griseofulvin is fungistatic and works by protecting new keratin as hair grows — hair grows slowly, so weeks of treatment are needed; skin cream kills surface fungus directly and faster.)*

3.22 References

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CHAPTER 4 — ANTHELMINTICS AND URINARY TRACT ANTI-INFECTIVES

PART A — ANTHELMINTIC AGENTS

4A.1 Learning Objectives

After studying this part, the student will be able to:

1 Define helminths, anthelmintics, vermicide and vermifuge.

2 Classify anthelmintic drugs by chemical class.

3 Explain the mechanism of action of each class in simple words.

4 Describe the chemical structure (scaffold + key substituents) of every anthelmintic in the syllabus.

5 State the therapeutic uses of each drug.

6 Write the complete synthesis of Albendazole with numbered steps, reagents, conditions and intermediates.

7 Answer short, long, MCQ, viva and application-based exam questions on anthelmintics.

4A.2 Definitions

Technical concept: Anthelmintics are drugs that expel or destroy helminths (parasitic worms) infesting the human gut or tissues, by paralysing them, starving them of energy, or damaging their outer covering.

Simple explanation: Worms are large parasites that live inside the intestines, blood or tissues and steal food and blood from the patient. Anthelmintic medicines either paralyse the worm (so it loses grip and is flushed out in the stool) or starve it (by blocking its food-energy machinery) or dissolve its skin. The dead or paralysed worm then leaves the body naturally.

Example: A child with roundworms takes one albendazole tablet; the worms starve because the drug blocks their sugar-use machinery, and they pass out in the stool.

Key takeaway: Anthelmintics = paralyse, starve or skin-damage the worm the body expels it.

More definitions:

- **Helminth:** a parasitic worm (roundworms/nematodes, tapeworms/cestodes, flukes/trematodes).
- **Nematode:** roundworm (e.g., *Ascaris*, hookworm, pinworm, filarial worms).
- **Cestode:** tapeworm (e.g., *Taenia solium* — pork tapeworm).
- **Trematode:** fluke (e.g., *Schistosoma* — blood fluke).
- **Vermicide:** kills the worm.
- **Vermifuge:** paralyses/expels the live worm.
- **Microfilaria:** the tiny larval stage of filarial worms swimming in blood.
- **Neurocysticercosis:** tapeworm larvae lodged in the brain — a serious condition treated with albendazole.
- **Hydatid disease:** cysts of the dog tapeworm (*Echinococcus*) in liver/lungs, treated with albendazole.

4A.3 Terminology Table

Term	Meaning in plain words
Helminth	Parasitic worm
Anthelmintic	Drug against worms
Nematode / Cestode / Trematode	Roundworm / Tapeworm / Fluke
Vermicide / Vermifuge	Kills worm / Expels live worm
Microtubules	Tiny tubes forming the cell's skeleton and division ropes
Tubulin	Protein building block of microtubules
Oxidative phosphorylation	The cell's main energy (ATP) factory line
Fumarate reductase	Worm's special energy enzyme (humans don't rely on it)
Glutamate-gated chloride channel	Nerve switch found in worms/insects, not humans — ivermectin's target
Tegument	The outer skin-covering of flatworms

Term	Meaning in plain words
DEC	Diethylcarbamazine

4A.4 Classification of Anthelmintics (by chemical class)

1. **Benzimidazoles:** Thiabendazole, Mebendazole, Albendazole*
2. **Piperazine derivative (urea):** Diethylcarbamazine (DEC)
3. **Salicylanilide:** Niclosamide
4. **Tetrahydroquinoline (nitro):** Oxamniquine
5. **Pyrazinoisoquinoline:** Praziquantel
6. **Macrocyclic lactone (avermectin):** Ivermectin

4A.5 Mechanisms of Action — Explained Step by Step

Class	Mechanism (technical)	Simple explanation	Example
Benzimidazoles	Bind worm beta-tubulin block microtubule formation glucose uptake fails worm starves	Cut the worm's skeleton ropes and food pipes; it starves to death	Albendazole, Mebendazole
DEC	Alters microfilarial surface so host immunity destroys them; also muscle hyperpolarisation	Paints a target on baby worms so the body's soldiers eat them	Diethylcarbamazine in filariasis
Niclosamide	Uncouples oxidative phosphorylation in tapeworm	Pulls the plug on the worm's power station	Tapeworm segments die
Oxamniquine	Activated by worm sulfotransferase to an alkylating ester damages worm DNA/paralysis	A poison that only the worm's own enzyme can switch on	*Schistosoma mansoni*
Praziquantel	Increases calcium permeability of worm tegument/muscle spastic paralysis + tegument damage	Floods the worm with calcium; it cramps rigid and its skin peels	Schistosomes, tapeworms, flukes
Ivermectin	Opens glutamate-gated chloride channels nerve/muscle hyperpolarisation flaccid paralysis	Jams the worm's nerves in the "off" position; worm goes limp	Onchocerciasis, strongyloidiasis, scabies

Diagram to draw (benzimidazole action): Draw a worm cell with tube-like rods labelled "microtubules (tubulin)". Draw drug molecules (small hexagons) sticking to the rods with a "NO ENTRY" sign, and a glucose molecule outside the cell with a blocked arrow. Caption: "Benzimidazole binds tubulin no microtubules no glucose uptake worm starves."

Diagram to draw (praziquantel action): Draw a flatworm with arrows labelled "Ca2+" rushing into its body; draw the worm curled tight with cracks in its outer line labelled "tegument damage". Caption: "Ca2+ flood spastic paralysis + skin damage."

4A.6 Anthelmintics — Drug by Drug

4A.6.1 Diethylcarbamazine (DEC)

- **Chemical class:** Piperazine urea/carbamoyl derivative (N,N-diethyl-4-methylpiperazine-1-carboxamide).
- **Structure:** A **piperazine ring** (six-membered, 2 nitrogens): one nitrogen carries a methyl group (-CH3), the other carries a diethylcarbamoyl group (-CO-N(CH2CH3)2, a urea-type linkage). Small, basic, water-soluble molecule.
- *How to draw:* Draw a hexagon with 2 N opposite each other; on one N write -CH3, on the other write -C(=O)-N(CH2CH3)2.
- **Uses:** Lymphatic filariasis (elephantiasis — kills microfilariae and some adult worms), loiasis, tropical pulmonary eosinophilia.

4A.6.2 Thiabendazole

- **Chemical class:** Benzimidazole anthelmintic (also a fungicide).
- **Structure:** A **benzimidazole** core (benzene fused to imidazole) with a **thiazole ring** (five-membered, N + S) attached at the 2-position: 2-(thiazol-4-yl)-1H-benzimidazole. The thiazole substituent is its signature.
- **Uses:** Broad-spectrum intestinal worms (roundworm, hookworm, pinworm, threadworm/strongyloides); also used topically/orally for cutaneous larva migrans; widely used as an agricultural fungicide.

4A.6.3 Mebendazole

- **Chemical class:** Benzimidazole carbamate anthelmintic.
- **Structure:** Benzimidazole core with two substituents: a **methyl carbamate** (-NH-CO-OCH3) at the 2-position and a **benzoyl group** (-CO-phenyl) at the 5-position: methyl (5-benzoyl-1H-benzimidazol-2-yl)carbamate. The 5-benzoyl (ketone-linked phenyl) is its signature.
- **Uses:** Broad-spectrum for intestinal worms — roundworm (*Ascaris*), hookworm, pinworm, whipworm, threadworm. Poorly absorbed — acts inside the gut; single-dose or 3-day courses.

4A.6.4 Albendazole* (synthesis required)

- **Chemical class:** Benzimidazole carbamate anthelmintic (5-alkylthio analogue of mebendazole).
- **Structure:** Benzimidazole core with a **methyl carbamate** (-NH-CO-OCH3) at the 2-position and a **propylthio group** (-S-CH2CH2CH3) at the 5-position: methyl [5-(propylthio)-1H-benzimidazol-2-yl]carbamate. Differs from mebendazole only at position 5: -S-propyl instead of -CO-phenyl; the sulphur makes it better absorbed for tissue infections.
- *How to draw:* Draw benzimidazole (fused benzene + imidazole). At C-2 write -NHCOOCH3; at C-5 write -S-CH2CH2CH3.
- **Uses:** Broad-spectrum intestinal worms (single dose) PLUS tissue parasites: **neurocysticercosis** (brain cysts), **hydatid disease** (liver/lung cysts), filariasis, strongyloidiasis, giardiasis. Drug of choice for systemic worm infections because it is absorbed better than mebendazole.

Synthesis of Albendazole

Overall plan: build the 5-(propylthio)-o-phenylenediamine by nucleophilic substitution + reduction, then close the benzimidazole ring with a carbamate-bearing reagent.

- **Step 1 — Thioether formation (aromatic nucleophilic substitution).** 5-Chloro-2-nitroaniline + sodium propanethiolate (CH3CH2CH2SNa, prepared from propane-1-thiol + sodium ethoxide), ethanol, reflux **Intermediate 1: 5-(propylthio)-2-nitroaniline** + NaCl. (The nitro group ortho to chlorine activates the ring; -SPr displaces chloride.)
- **Step 2 — Nitro reduction.** Intermediate 1 + stannous chloride (SnCl2) in concentrated HCl (or H2 over Pd/C), heat **Intermediate 2: 4-(propylthio)benzene-1,2-diamine** (o-phenylenediamine derivative) + tin salts/water. (NO2 NH2; the thioether survives.)
- **Step 3 — Benzimidazole ring closure.** Intermediate 2 + 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea [S-methyl-N-(methoxycarbonyl)isothiourea reagent], methanol, reflux **Albendazole** [methyl 5-(propylthio)-1H-benzimidazol-2-ylcarbamate] + methanethiol + methanol. (The two amino groups attack the reagent carbon, closing the imidazole ring with the -NHCOOCH3 already in place at C-2.)

Flowchart of the synthesis:

```
5-chloro-2-nitroaniline --[CH3CH2CH2SNa, EtOH, reflux]--> 5-(propylthio)-2-nitroaniline (1)
        --[SnCl2 / conc. HCl, heat]--> 4-(propylthio)-o-phenylenediamine (2)
        --[1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea, MeOH, reflux]-->
        ALBENDAZOLE + CH3SH
```

4A.6.5 Niclosamide

- **Chemical class:** Salicylanilide anthelmintic (chlorinated nitro amide).
- **Structure:** Two aromatic rings joined by an **amide** (-CO-NH-): one ring is a salicylic-acid-like ring (2-hydroxy with the amide carbonyl at position 1) bearing a **chlorine at position 5**; the other ring is an anilide ring bearing a **chlorine at 2'** and a **nitro group at 4'**: 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide. The nitro group is essential for uncoupling activity.
- *How to draw:* Draw two hexagons linked by -C(=O)-NH-. On the left ring put -OH (ortho to the link) and Cl; on the right ring put Cl and -NO2.
- **Uses:** Tapeworm infections (pork/beef tapeworm *Taenia*, fish tapeworm); not absorbed — acts in the gut lumen; the dead worm must be fully expelled (a purgative was classically given).

4A.6.6 Oxamniquine

- **Chemical class:** Tetrahydroquinoline nitro anthelmintic (schistosomicide).
- **Structure:** A **1,2,3,4-tetrahydroquinoline** (benzene fused to a partially saturated nitrogen ring) bearing three substituents: a **nitro group (-NO2) at position 7**, a **hydroxymethyl (-CH2OH) at position 6**, and an **isopropylaminomethyl (-CH2-NH-CH(CH3)2) at position 2**. The nitro group is the "warhead" — the worm's own enzyme converts it into the DNA-damaging form.
- **Uses:** Schistosomiasis caused by ***Schistosoma mansoni*** only (intestinal schistosomiasis); mainly of historical/importance in South America and parts of Africa. Single oral dose.

4A.6.7 Praziquantel

- **Chemical class:** Pyrazinoisoquinoline anthelmintic (tetracyclic).
- **Structure:** A fused four-ring system: an **isoquinoline** fused to a **piperazine-2-one** (pyrazinone) ring, with a **cyclohexanecarbonyl** group (-CO-cyclohexyl) on the piperazine nitrogen. Compact, rigid tetracycle — 2-(cyclohexanecarbonyl)-1,2,3,6,7,11b-hexahydropyrazino[2,1-a]isoquinolin-4-one. The cyclohexyl amide side chain is its signature.
- **Uses:** Broad anti-flatworm drug: all forms of **schistosomiasis** (*S. mansoni, S. haematobium, S. japonicum*), liver/lung flukes, and tapeworms (including neurocysticercosis as an alternative to albendazole). Single-day treatment.

4A.6.8 Ivermectin

- **Chemical class:** Macrocyclic lactone (avermectin; 22,23-dihydro derivative; mixture of B1a/B1b).
- **Structure:** A huge **16-membered macrolide lactone ring** fused to a spiroketal system and a hexahydrobenzofuran, with a **disaccharide** (two sugar units, oleandrose) attached at one end and a sec-butyl/isopropyl group at the other. Fermentation product of *Streptomyces avermitilis*, chemically hydrogenated at the 22–23 double bond. One of the largest drug molecules in the syllabus.
- *How to draw:* Draw a very large oval (16-membered lactone); attach a spiro two-ring system on one side, a fused 5/6 ring on the other, and two small hexagons (sugars) hanging off one end.
- **Uses:** Onchocerciasis (river blindness — kills microfilariae), strongyloidiasis, lymphatic filariasis (with DEC/albendazole), scabies and lice (topical/oral), cutaneous larva migrans.

Anthelmintics — comparison table

Drug	Class	Signature structural feature	Main use
Diethylcarbamazine	Piperazine urea	Piperazine + diethylcarbamoyl	Filariasis (microfilariae)
Thiabendazole	Benzimidazole	Thiazole at C-2	Intestinal worms
Mebendazole	Benzimidazole carbamate	5-benzoyl group	Intestinal worms (gut only)
Albendazole*	Benzimidazole carbamate	5-propylthio group	Intestinal + tissue worms, neurocysticercosis, hydatid
Niclosamide	Salicylanilide	Nitro + chloro amide	Tapeworms
Oxamniquine	Tetrahydroquinoline	7-nitro "warhead"	*S. mansoni* only
Praziquantel	Pyrazinoisoquinoline	Cyclohexanecarbonyl tetracycle	Schistosomes, flukes, tapeworms
Ivermectin	Macrocyclic lactone	16-membered lactone + disaccharide	River blindness, strongyloides, scabies

4A.7 Infographic Concept Box — Anthelmintics

```
+-------------------------------------------------------------------+
|  ANTHELMINTICS AT A GLANCE                                        |
|  Worms are big parasites: PARALYSE them, STARVE them, or          |
|  DAMAGE their skin — then the body flushes them out.              |
|                                                                   |
|  BENZIMIDAZOLES (Thiabendazole, Mebendazole, Albendazole*)        |
|    Cut the worm's skeleton ropes (tubulin) -> worm starves        |
|    -NH-CO-OCH3 at C-2 is essential; C-5 group decides the job:    |
|    thiazole / benzoyl (gut worms) / -S-propyl (tissue worms)      |
|                                                                   |
|  DEC ............ Paints target on baby filarial worms           |
|  NICLOSAMIDE .... Pulls the plug on tapeworm power station        |
|  OXAMNIQUINE .... Nitro warhead armed by the worm's own enzyme    |
|  PRAZIQUANTEL ... Calcium flood -> cramp + skin peel (flatworms)  |
|  IVERMECTIN ..... Jams worm nerves OFF (chloride channels)        |
+-------------------------------------------------------------------+
```

4A.8 Analogies (Anthelmintics)

1. **Benzimidazoles are like cutting both the food pipe and the skeleton of the worm** — it cannot eat and cannot hold its shape.
2. **DEC is like marking shoplifters with invisible ink** that only the security guards (immune cells) can see.
3. **Niclosamide is like unplugging the worm's generator** — the lights go out permanently.
4. **Praziquantel is like giving the worm a full-body electric cramp** while peeling its skin.
5. **Ivermectin is like switching the worm's nerves to "sleep mode"** — everything goes limp.

4A.9 Pharmacy Relevance (Anthelmintics)

- **Deworming doses:** Albendazole 400 mg single chewable tablet is the standard mass-deworming dose — pharmacists must know it is chewed, not swallowed whole, especially for children.
- **Counselling:** Warn that dead worms appear in stool (normal, not alarming); advise hand-washing, footwear and clean water to prevent reinfection.
- **Pregnancy caution:** Benzimidazoles are avoided in the first trimester — always ask before dispensing to a pregnant woman.
- **Neurocysticercosis therapy:** Albendazole for brain cysts is given with steroids (to control inflammation as cysts die) — never dispense or counsel on this without the full prescription context.

4A.10 India Context (Anthelmintics)

- India runs the **National Deworming Day** programme, giving single-dose **albendazole** to schoolchildren — the most widely distributed anthelmintic in the country.
- **Lymphatic filariasis** (elephantiasis) was historically widespread in eastern and southern India; DEC + albendazole mass drug administration has been the control strategy.
- **Neurocysticercosis** (pork tapeworm larvae in the brain) is an important cause of adult-onset epilepsy in India — treated with albendazole.
- Ivermectin + albendazole combinations are used in filariasis-endemic districts.

PART B — URINARY TRACT ANTI-INFECTIVE AGENTS

4B.1 Learning Objectives

After studying this part, the student will be able to:

1 Define urinary tract infection (UTI) and explain why urine is a special drug-delivery target.

2 Classify UTI anti-infectives (quinolones, nitrofurans, methenamine).

3 Explain the mechanism of quinolones in simple words (DNA gyrase / topoisomerase IV).

4 Present the **SAR of quinolones as a rule table** (positions 1, 3, 4, 6, 7, 8; fluoro and piperazine effects; generations).

5 Describe the chemical structure (scaffold + key substituents) of every UTI drug in the syllabus.

6 State the therapeutic uses of each drug.

7 Write the complete synthesis of Ciprofloxacin with numbered steps, reagents, conditions and intermediates.

8 Answer short, long, MCQ, viva and application-based exam questions on UTI agents.

4B.2 Definitions

Technical concept: Urinary tract anti-infectives are antibacterial drugs that reach high concentrations in urine (by kidney excretion), making them effective against bacteria infecting the bladder, urethra, kidneys or prostate, even if blood levels are modest.

Simple explanation: A urine infection means germs are growing in the pee tubes (bladder, urethra). The clever trick of UTI medicines: the kidneys filter them out of the blood and dump them into the urine — so the drug becomes super-concentrated exactly where the germs are, like flooding the enemy's hideout.

Example: Nitrofurantoin barely reaches the blood but piles up in urine — perfect for a bladder infection, useless for a lung infection.

> **Key takeaway:** UTI drugs work by concentrating in urine via the kidneys.

More definitions:

- **UTI:** urinary tract infection — cystitis (bladder), urethritis (urethra), pyelonephritis (kidney).
- **Quinolone:** bicyclic ring system (benzene fused to pyridone) with -COOH at C-3 and =O at C-4; the parent antibacterial scaffold.
- **Fluoroquinolone:** quinolone carrying a fluorine at C-6 — far more potent, broader spectrum.
- **Naphthyridone:** quinolone-like ring where one benzene carbon is replaced by nitrogen (as in nalidixic acid, enoxacin).
- **DNA gyrase:** bacterial enzyme that supercoils DNA (main quinolone target in Gram-negative bacteria).

- **Topoisomerase IV:** bacterial enzyme that untangles daughter DNA after copying (main target in Gram-positive bacteria).
- **Bactericidal:** kills bacteria (quinolones are bactericidal).
- **Nitrofuran:** five-membered furan ring with a nitro group — reduced by bacteria into DNA-damaging poisons.
- **Urinary antiseptic:** drug that sterilises urine itself (methenamine formaldehyde in acidic urine).

4B.3 Terminology Table

Term	Meaning in plain words
DNA gyrase	Bacterial DNA-twisting enzyme; quinolone target (Gram-negative)
Topoisomerase IV	Bacterial DNA-untangling enzyme; quinolone target (Gram-positive)
MIC	Lowest drug amount stopping visible bacterial growth
Bactericidal / Bacteriostatic	Kills bacteria / stops their growth
Cystitis / Pyelonephritis	Bladder infection / kidney infection
Prophylaxis	Preventive dosing
Phototoxicity	Skin damage on sun exposure (a quinolone side effect)
QT prolongation	Heart-rhythm disturbance risk (some quinolones)
Tendinopathy	Tendon damage risk (quinolone class warning)

4B.4 Classification of UTI Anti-infectives

1 **Quinolones**

- 1st generation: Nalidixic acid (non-fluorinated)
- 2nd generation (fluoroquinolones): Norfloxacin, Enoxacin, Ciprofloxacin*, Ofloxacin, Lomefloxacin
- 3rd generation: Sparfloxacin, Gatifloxacin (also Levofloxacin — not in syllabus)
- 4th generation: Moxifloxacin

1 **Nitrofurans:** Furazolidone, Nitrofurantoin

2 **Urinary antiseptic:** Methenamine (hexamine)

4B.5 Mechanism of Action — Quinolones

Technical concept: Quinolones trap bacterial DNA gyrase and topoisomerase IV on DNA, forming a drug–enzyme–DNA complex that blocks replication and causes double-strand breaks — bactericidal.

Simple explanation: Bacteria must constantly twist and untwist their DNA rope to copy it. Two "rope-handling" enzymes do this job: gyrase and topoisomerase IV. The quinolone drug handcuffs the enzyme *while it is holding the rope* — the rope snaps, and the bacterium dies. Human cells use a different rope-handler, so we are mostly spared.

Example: Ciprofloxacin handcuffs gyrase in *E. coli* causing a bladder infection; the bacterial DNA breaks and the germs die.

Key takeaway: Quinolones = handcuff the DNA rope-handlers DNA snaps bacteria die.

Diagram to draw: Draw a twisted rope (DNA) with a clamp labelled "gyrase" holding it. Draw a drug molecule (small hexagon marked "Q") locking the clamp shut; draw the rope snapped below with a lightning symbol. Caption: "Quinolone locks gyrase onto DNA double-strand break cell death."

4B.6 SAR of Quinolones — Rule Table (memorise this)

Position / Feature	Rule	Effect	Example
N-1	Small alkyl or cycloalkyl; **cyclopropyl is best**	Controls potency and pharmacokinetics; cyclopropyl boosts Gram-negative power	Ciprofloxacin (N-cyclopropyl) beats norfloxacin (N-ethyl)
C-2	Hydrogen only	Any substituent here reduces activity	All active quinolones have H at C-2
C-3	**-COOH essential**	Binds the enzyme–DNA complex (via Mg2+ bridge); removing it kills activity	Every active quinolone
C-4	**=O (keto) essential**	Works with C-3 COOH in target binding	Every active quinolone
C-5	-NH2 improves Gram-positive activity	Extra amino group widens spectrum toward Gram-positives	Sparfloxacin (5-amino)
C-6	**Fluorine essential for fluoroquinolones**	Greatly increases potency and broadens spectrum vs 1st generation	Norfloxacin onward (6-F)
C-7	**Piperazine (or similar diamine) ring**	Extends Gram-negative spectrum, improves tissue penetration and half-life; methyl/dimethyl substitution fine-tunes	Ciprofloxacin (piperazinyl), ofloxacin (methylpiperazinyl)
C-8	H, F, Cl or OCH3; **8-OCH3 improves Gram-positive cover and lowers resistance**; 8-F/8-Cl raise phototoxicity	Tunes spectrum and side effects	Gatifloxacin, Moxifloxacin (8-OCH3); Lomefloxacin (8-F phototoxic)
N-1 to C-8 bridge	Extra fused ring (as in ofloxacin)	Creates tricyclic quinolones with good tissue penetration	Ofloxacin (oxazine ring)
Core ring	Benzene pyridine (naphthyridone) allowed	Naphthyridone analogues keep activity	Nalidixic acid, Enoxacin

Generations at a glance

Generation	Drugs (syllabus)	Spectrum character
1st	Nalidixic acid	Gram-negative only, UTI only, no fluorine
2nd	Norfloxacin, Enoxacin, Ciprofloxacin*, Ofloxacin, Lomefloxacin	Fluorinated; systemic use; ciprofloxacin = anti-pseudomonal star
3rd	Sparfloxacin, Gatifloxacin	Added Gram-positive/respiratory cover (5-NH2, 8-OCH3)

Generation	Drugs (syllabus)	Spectrum character
4th	Moxifloxacin	Broadest: Gram-positive + Gram-negative + anaerobes (bulky C-7 diamine)

Flowchart — how quinolone structure evolved:

```
Nalidixic acid (1962): naphthyridone, no F, N-ethyl, no piperazine
        |  + 6-F (fluoro) + 7-piperazine
        v
2nd gen (Norfloxacin, Ciprofloxacin): systemic, potent, broad
        |  + N-cyclopropyl (best N-1) ; + 8-OCH3 / 5-NH2 / bulky C-7 diamine
        v
3rd/4th gen (Gatifloxacin, Moxifloxacin): Gram-positive + anaerobe cover
```

4B.7 Quinolones — Drug by Drug

4B.7.1 Nalidixic acid

- **Chemical class:** 1,8-Naphthyridone (first-generation quinolone, non-fluorinated).
- **Structure:** A **1,8-naphthyridine** bicyclic core (two fused six-membered rings, nitrogens at 1 and 8) with: N-ethyl at position 1, methyl at position 7, **-COOH at C-3** and **=O at C-4**. No fluorine, no piperazine — the "grandfather" scaffold.
- *How to draw:* Draw two fused hexagons with N at top-left and top-right; mark N1-CH2CH3, C3-COOH, C4=O, C7-CH3.
- **Uses:** Uncomplicated lower UTIs caused by Gram-negative bacteria (*E. coli*, *Proteus*). Narrow spectrum; resistance develops fast; largely replaced by fluoroquinolones.

4B.7.2 Norfloxacin

- **Chemical class:** Second-generation fluoroquinolone.
- **Structure:** True **quinolone** core (benzene fused to pyridone): N-ethyl at N-1, **6-fluoro**, **7-piperazinyl**, C-3 COOH, C-4 =O. The first fluoroquinolone — fluorine + piperazine are the upgrades over nalidixic acid.
- **Uses:** UTIs (high urine levels), bacterial diarrhoea/traveller's diarrhoea, prostatitis, gonorrhoea (historical). Poor tissue penetration — mainly a urinary/gut drug.

4B.7.3 Enoxacin

- **Chemical class:** Second-generation fluoroquinolone; 1,8-naphthyridone type.
- **Structure:** Like norfloxacin but on the **naphthyridone** core (nitrogen at position 8 instead of carbon): N-ethyl, 6-fluoro, 7-piperazinyl, C-3 COOH, C-4 =O. The ring-nitrogen twin of norfloxacin.
- **Uses:** UTIs and gonorrhoea. Less used today; notable for strong CYP1A2 inhibition (drug interactions).

4B.7.4 Ciprofloxacin* (synthesis required)

- **Chemical class:** Second-generation fluoroquinolone (the most prescribed quinolone worldwide).
- **Structure:** Quinolone core with: **N-1 cyclopropyl** (the best N-1 group — small ring of 3 carbons), **6-fluoro**, **7-piperazinyl**, C-3 COOH, C-4 =O:

1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. The cyclopropyl at N-1 is its visual signature.

- *How to draw:* Draw the quinolone bicyclic core; at N (position 1) draw a small triangle (cyclopropyl); at C-6 write F; at C-7 draw a hexagon with 2 N (piperazine); at C-3 write COOH; at C-4 write =O.
- **Uses:** UTIs (including complicated), bacterial diarrhoea, typhoid, prostatitis, bone/joint infections, anthrax prophylaxis, and *Pseudomonas* infections — the broadest-used quinolone. Official in the Indian Pharmacopoeia.

Synthesis of Ciprofloxacin (Bayer route)

Overall plan: build the benzoyl-acrylate, swap in cyclopropylamine, close the quinolone ring by intramolecular SNAr, attach piperazine, hydrolyse the ester.

- **Step 1 — Acid chloride formation.** 2,4-Dichloro-5-fluorobenzoic acid + thionyl chloride (SOCl2), reflux **Intermediate 1: 2,4-dichloro-5-fluorobenzoyl chloride** + SO2 + HCl.
- **Step 2 — Acrylate condensation.** Intermediate 1 + ethyl 3-(dimethylamino)acrylate, toluene, heat **Intermediate 2: ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-(dimethylamino)acrylate** + HCl. (Acyl substitution on the activated alkene.)
- **Step 3 — Amine exchange.** Intermediate 2 + cyclopropylamine, ethanol, room temperature **Intermediate 3: ethyl 3-(cyclopropylamino)-2-(2,4-dichloro-5-fluorobenzoyl)acrylate** + dimethylamine. (Transamination: cyclopropylamine displaces dimethylamine.)
- **Step 4 — Ring closure (intramolecular SNAr).** Intermediate 3 + base (K2CO3 or NaH), DMF, heat **Intermediate 4: 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester** + HCl. (The -NH- attacks the aromatic carbon bearing chlorine ortho to the ketone, displacing Cl and closing the pyridone ring.)
- **Step 5 — Piperazine substitution.** Intermediate 4 + piperazine, DMSO/acetonitrile, heat **Intermediate 5: ethyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate** + HCl. (SNAr: piperazine displaces the C-7 chlorine, activated by the ortho-fluorine and para-keto group.)
- **Step 6 — Ester hydrolysis.** Intermediate 5 + aqueous NaOH, heat, then acidify with HCl **Ciprofloxacin** + ethanol. (Saponification of the ethyl ester to the essential C-3 carboxylic acid.)

Flowchart of the synthesis:

```
2,4-dichloro-5-fluorobenzoic acid --[SOCl2, reflux]--> benzoyl chloride (1)
   --[ethyl 3-(dimethylamino)acrylate]--> benzoyl-acrylate (2)
   --[cyclopropylamine]--> cyclopropylamino-acrylate (3)
   --[K2CO3, DMF, heat]--> 7-chloro quinolone ester (4)
   --[piperazine, heat]--> 7-piperazinyl ester (5)
   --[NaOH, then HCl]--> CIPROFLOXACIN
```

4B.7.5 Ofloxacin

- **Chemical class:** Second-generation tricyclic fluoroquinolone (benzoxazine-fused).

- **Structure:** Quinolone core with an extra fused ring bridging N-1 to C-8: a **methyl-substituted oxazine ring** (O + N in a six-membered ring), giving a rigid tricycle. Substituents: 6-fluoro? (actually 9-fluoro in tricyclic numbering), 7-(4-methylpiperazinyl), C-3 COOH. Used as the **racemic mixture**; the S-enantiomer is levofloxacin.
- **Uses:** UTIs, respiratory infections, bacterial diarrhoea, eye/ear drops for local infections, multidrug-resistant tuberculosis (second-line).

4B.7.6 Lomefloxacin

- **Chemical class:** Second-generation difluoro-quinolone.
- **Structure:** Quinolone core with **two fluorines (6,8-difluoro)**, N-ethyl at N-1, 7-(3-methylpiperazinyl), C-3 COOH, C-4 =O. The 8-fluoro is responsible for its strong phototoxicity.
- **Uses:** UTIs and respiratory infections; use declined because of marked phototoxicity (severe sunburn-like reactions).

4B.7.7 Sparfloxacin

- **Chemical class:** Third-generation difluoro-quinolone (aminoquinolone).
- **Structure:** Quinolone core with **5-amino group** (-NH2), **6,8-difluoro**, N-cyclopropyl, 7-(3,5-dimethylpiperazinyl), C-3 COOH. The 5-NH2 + 8-F combination widens Gram-positive cover.
- **Uses:** Community-acquired pneumonia and respiratory infections (Gram-positive cover). Limited by phototoxicity and QT-interval prolongation.

4B.7.8 Gatifloxacin

- **Chemical class:** Third-generation 8-methoxy fluoroquinolone.
- **Structure:** Quinolone core with **8-methoxy (-OCH3)** (reduces phototoxicity and resistance), 6-fluoro, N-cyclopropyl, 7-(3-methylpiperazinyl), C-3 COOH. The 8-OCH3 is its signature.
- **Uses:** Respiratory infections; widely used in India as **eye drops** for bacterial conjunctivitis. Systemic use restricted in some settings because of blood-sugar disturbances.

4B.7.9 Moxifloxacin

- **Chemical class:** Fourth-generation 8-methoxy fluoroquinolone (respiratory quinolone).
- **Structure:** Quinolone core with **8-methoxy**, 6-fluoro, N-cyclopropyl, and a bulky **7-(octahydro-pyrrolo[3,4-b]pyridinyl)** (diazabicyclononyl) group instead of simple piperazine, C-3 COOH. The bulky C-7 diamine gives anaerobic and Gram-positive power.
- **Uses:** Community-acquired pneumonia, sinusitis, complicated UTIs, multidrug-resistant TB (second-line), and as eye drops. Broadest spectrum of the syllabus quinolones.

Quinolones — comparison table

Drug	Generation	N-1	C-6	C-7	C-8	Stand-out use
Nalidixic acid	1st	Ethyl	H	CH3	— (naphthyridone)	Simple UTIs only

Drug	Generation	N-1	C-6	C-7	C-8	Stand-out use
Norfloxacin	2nd	Ethyl	F	Piperazine	H	UTI, diarrhoea
Enoxacin	2nd	Ethyl	F	Piperazine	N (naphthyridone)	UTI
Ciprofloxacin*	2nd	Cyclopropyl	F	Piperazine	H	Broadest 2nd-gen; Pseudomonas, typhoid
Ofloxacin	2nd	Bridged (tricyclic)	F	Methylpiperazine	Bridged	UTI, TB second-line
Lomefloxacin	2nd	Ethyl	F	Methylpiperazine	F	(Phototoxic — declined)
Sparfloxacin	3rd	Cyclopropyl	F	Dimethylpiperazine	F (+ 5-NH2)	Respiratory (Gram-positive)
Gatifloxacin	3rd	Cyclopropyl	F	Methylpiperazine	OCH3	Eye drops, respiratory
Moxifloxacin	4th	Cyclopropyl	F	Bulky diamine	OCH3	Broadest; pneumonia, TB second-line

4B.8 Nitrofurans

Technical concept: Nitrofurans are prodrugs activated by bacterial nitroreductase enzymes, which reduce the nitro group to highly reactive intermediates that damage bacterial DNA and proteins. Human cells activate them poorly — selective toxicity.

Simple explanation: The nitrofuran is a harmless parcel. Only bacterial enzymes can open it — and inside is a poison that shreds the bacterium's DNA. Human cells cannot open the parcel well, so we stay safe.

4B.8.1 Furazolidone

- **Chemical class:** Nitrofuran (oxazolidinone-linked).
- **Structure:** A **5-nitrofuran** ring (furan with -NO2 at position 5) joined through a **-CH=N- (imine/hydrazone)** linkage to a **2-oxazolidinone** ring (five-membered ring with N and C=O): 3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone. The nitro-furan + imine + oxazolidinone trio is its signature.
- **Uses:** Bacterial diarrhoea, cholera (adjunct), giardiasis; also veterinary antiprotozoal. Acts in the gut.

4B.8.2 Nitrofurantoin

- **Chemical class:** Nitrofuran (hydantoin-linked).
- **Structure:** 5-nitrofuran joined through a **-CH=N-** linkage to a **hydantoin (imidazolidine-2,4-dione)** ring: 1-[(5-nitrofurfurylidene)amino]imidazolidine-2,4-dione. Same nitrofurfurylidene "warhead" as furazolidone, different carrier ring.
- **Uses: Uncomplicated lower UTIs (cystitis)** — first-line in many guidelines; concentrates in urine, negligible tissue levels (so never for kidney/bloodstream infection). Official in the Indian Pharmacopoeia.

Nitrofurans — comparison

Feature	Furazolidone	Nitrofurantoin
Carrier ring	Oxazolidinone	Hydantoin
Main use	Gut infections, giardiasis	Bladder infections (cystitis)
Systemic levels	Low	Very low (urine only)

4B.9 Methenamine (Hexamine)

- **Chemical class:** Urinary antiseptic; cage amine (hexamethylenetetramine).
- **Structure:** A cage-like molecule: **4 nitrogens and 6 CH2 groups** arranged like the corners of a tiny cage (adamantane-like): (CH2)6N4. Made from formaldehyde + ammonia. No direct antibacterial group — it is a formaldehyde delivery system.
- **Mechanism:** In **acidic urine** (pH < 5.5), methenamine hydrolyses to **formaldehyde + ammonia**; formaldehyde denatures bacterial proteins non-specifically — bacteria cannot develop resistance to it easily.
- *How to draw:* Draw a cube-like cage; label 4 corners "N" and 6 edges "CH2". Write the reaction: (CH2)6N4 + 6H2O --(acidic urine)--> 6HCHO (formaldehyde) + 4NH3.
- **Uses:** Long-term **prophylaxis/suppression of recurrent UTIs** (urinary antiseptic); often given with an acidifying agent (e.g., ascorbic acid) because it needs acidic urine to work. Not for acute infection treatment.

4B.10 Infographic Concept Box — UTI Agents

```
+-------------------------------------------------------------------+
|  UTI ANTI-INFECTIVES AT A GLANCE                                  |
|  Trick: kidneys dump the drug into urine -> germs drown in it.    |
|                                                                   |
|  QUINOLONES ......... Handcuff DNA gyrase/topoisomerase IV        |
|    -> bacterial DNA snaps -> bactericidal                         |
|    ESSENTIAL: C-3 COOH + C-4 =O (never remove)                    |
|    POWER-UPS: 6-F (potency) + 7-piperazine (spectrum/PK)          |
|               N-cyclopropyl (best N-1) + 8-OCH3 (Gram+, safer)    |
|    1st: Nalidixic acid (no F, UTI only)                           |
|    2nd: Nor/Eno/Cipro*/Oflo/Lome (fluorinated, systemic)          |
|    3rd: Spar/Gati (respiratory+) | 4th: Moxi (broadest)           |
|                                                                   |
|  NITROFURANS ........ Bacteria-only parcel -> DNA-shredding       |
|    poison inside. Furazolidone = gut; Nitrofurantoin = bladder.   |
|                                                                   |
|  METHENAMINE ........ Cage that releases formaldehyde in ACIDIC   |
|    urine -> long-term UTI prevention (antiseptic).                |
+-------------------------------------------------------------------+
```

4B.11 Analogies (UTI agents)

1 **Quinolones are like handcuffing a sailor to the ship's wheel during a storm** — the rope (DNA) tears and the ship (bacterium) sinks.

2 **The C-3 COOH and C-4 =O are like the two prongs of a plug** — without both, the drug cannot connect to its target.

3 **Adding 6-F and 7-piperazine is like upgrading a bicycle to a motorcycle** — same frame (quinolone), far more power and range.

4 **Nitrofurans are like a letter bomb that only the enemy can open** — bacteria trigger their own destruction.

5 **Methenamine is like a time-release air freshener** that only switches on in acidic rooms (acidic urine).

4B.12 Pharmacy Relevance (UTI agents)

- **Counselling:** Take fluoroquinolones with a full glass of water, **not with milk, antacids, or iron/calcium** (they chelate the C-3 COOH/C-4 =O and block absorption) — separate by 2–4 hours.
- **Sun protection:** Warn patients on lomefloxacin/sparfloxacin (and quinolones generally) to avoid strong sunlight — phototoxicity.
- **Tendon warning:** Quinolones carry a risk of tendon inflammation/rupture, especially in the elderly and with steroids — counsel to stop and report tendon pain.
- **Nitrofurantoin:** Warn that it turns urine brown/rusty — harmless but alarming if unexpected; advise completing the course.
- **Methenamine:** Works only in acidic urine — do not combine with urinary alkalinisers; often co-prescribed with vitamin C.

4B.13 India Context (UTI agents)

- **Ciprofloxacin** is among the most prescribed antibiotics in India — for UTIs, typhoid, diarrhoea and prostatitis — and has an official monograph in the Indian Pharmacopoeia.
- **Norfloxacin + tinidazole** combinations for diarrhoea were historically very popular in Indian practice.
- **Nitrofurantoin** is a first-line, low-cost option for uncomplicated cystitis in Indian guidelines and is widely stocked.
- **Gatifloxacin and moxifloxacin eye drops** are everyday pharmacy items for bacterial conjunctivitis across India.
- **Ofloxacin and moxifloxacin** are important second-line drugs in India's drug-resistant tuberculosis programme.
- Rising quinolone resistance in *E. coli* UTIs across India makes culture-sensitivity testing increasingly important — pharmacists should encourage it rather than repeat empirical courses.

CHAPTER 4 — CONSOLIDATED SECTIONS

4.14 Key Points (whole chapter)

Anthelmintics:

1 Benzimidazoles (thiabendazole, mebendazole, albendazole*) bind worm tubulin starve the worm; C-2 methyl carbamate essential; C-5 group sets the spectrum.

2 Albendazole's 5-propylthio group gives the absorption needed for tissue infections (neurocysticercosis, hydatid disease).

3 DEC targets microfilariae in filariasis; niclosamide uncouples tapeworm energy; oxamniquine's nitro group is armed by the worm's own enzyme (S. mansoni only).

4 Praziquantel floods flatworms with Ca2+ (spastic paralysis + tegument damage); ivermectin opens worm chloride channels (flaccid paralysis).

5 Albendazole synthesis: SNAr thioether formation nitro reduction benzimidazole closure with the carbamate reagent.

UTI agents:

1 Quinolones trap DNA gyrase/topoisomerase IV on DNA bactericidal.

2 SAR essentials: C-3 COOH and C-4 =O are untouchable; 6-F boosts potency; 7-piperazine widens spectrum; N-cyclopropyl is the best N-1; 8-OCH3 improves Gram-positive cover and safety.

3 Generations: 1st (nalidixic acid, no F) 2nd (fluorinated, systemic) 3rd (respiratory Gram-positive) 4th (moxifloxacin, broadest).

4 Ciprofloxacin synthesis: benzoyl chloride acrylate cyclopropylamine swap SNAr ring closure piperazine ester hydrolysis.

5 Nitrofurans are bacteria-activated DNA poisons (furazolidone = gut, nitrofurantoin = bladder); methenamine releases formaldehyde only in acidic urine (prophylaxis).

4.15 Common Confusions

Confusion	Clarification
Mebendazole vs Albendazole	Same C-2 carbamate; differ at C-5: mebendazole = benzoyl (gut worms only), albendazole = propylthio (gut + tissue worms)
Nalidixic acid vs Norfloxacin	Nalidixic acid = 1st gen, no fluorine, UTI only; norfloxacin = 2nd gen fluoroquinolone, systemic
Ofloxacin vs Levofloxacin	Ofloxacin is the racemic mixture; levofloxacin is its active S-enantiomer (not in syllabus)
Nitrofurantoin vs Furazolidone	Same nitrofurfurylidene warhead; nitrofurantoin (hydantoin) = bladder, furazolidone (oxazolidinone) = gut
Praziquantel vs Niclosamide	Both kill tapeworms; praziquantel = Ca2+ flood, systemic, also flukes; niclosamide = energy uncoupler, gut only
Sparfloxacin vs Gatifloxacin	Both 3rd gen; sparfloxacin has 5-NH2 + 8-F (phototoxic), gatifloxacin has 8-OCH3 (safer, eye drops)

4.16 Common Mistakes

1 Saying quinolones are bacteriostatic — they are bactericidal.

2 Removing or ignoring the C-3 COOH / C-4 =O in SAR answers — these are essential, not optional.

3 Claiming nitrofurantoin treats kidney or bloodstream infection — it only reaches urine.

4 Giving methenamine for an acute UTI — it is a prophylactic antiseptic needing acidic urine, not a treatment.

5 Confusing DEC (filariasis, microfilariae) with benzimidazoles (intestinal worms).

6 In ciprofloxacin synthesis, forgetting the final ester hydrolysis step (the free C-3 COOH is essential for activity).

7 Saying oxamniquine works on all schistosomes — it works only on *S. mansoni*.

8 Mixing up flaccid paralysis (ivermectin) with spastic paralysis (praziquantel).

4.17 Mnemonics

- **Anthelmintic benzimidazoles — "TMA":** "**T**hiabendazole, **M**ebendazole, **A**lbendazole" — "**T**iny **M**edicine **A**ttacks worms."
- **Albendazole's extra power:** "**A**lbendazole **A**ttacks **A**bscess-like cysts (brain/liver)" — the "A-team" for tissue worms.
- **Quinolone SAR — "COOH-O-F-Piperazine-Cyclopropyl":** "**C**an't **O**mit **F**luorine, **P**iperazine, **C**yclopropyl" — the four power-ups.
- **Generations — "Never Forget Good Medicine":** "**N**alidixic (1st), **F**luoroquinolones 2nd, **G**atifloxacin/Sparfloxacin 3rd, **M**oxifloxacin 4th."
- **Nitrofurans:** "**F**urazolidone for the **F**ood pipe (gut); **N**itrofurantoin for **N**eed-to-pee (bladder)."
- **Methenamine:** "**M**ethenamine needs **M**ore **A**cid" — works only in acidic urine.

4.18 Exam Summary

- Anthelmintics paralyse/starve/skin-damage worms. Benzimidazoles bind tubulin (C-2 carbamate essential; C-5 = thiazole/benzoyl/propylthio decides spectrum); albendazole's -S-propyl allows tissue penetration (neurocysticercosis, hydatid).
- Albendazole synthesis: 5-chloro-2-nitroaniline (PrSNa) 5-(propylthio)-2-nitroaniline (SnCl2/HCl) diamine (bis(methoxycarbonyl)-methyl-thiopseudourea) albendazole.
- DEC (filariasis microfilariae), niclosamide (tapeworm energy uncoupler), oxamniquine (nitro warhead, S. mansoni), praziquantel (Ca2+ flood, flatworms), ivermectin (chloride-channel flaccid paralysis).
- Quinolones: trap gyrase/topoisomerase IV bactericidal. SAR: C-3 COOH + C-4 =O essential; 6-F potency; 7-piperazine spectrum; N-cyclopropyl best; 8-OCH3 Gram-positive/safety.
- Ciprofloxacin synthesis: 2,4-dichloro-5-fluorobenzoyl chloride benzoyl-acrylate cyclopropylamine exchange SNAr ring closure piperazine at C-7 ester hydrolysis.
- Nitrofurans: bacterial nitroreduction DNA damage (furazolidone = gut, nitrofurantoin = cystitis). Methenamine formaldehyde in acidic urine (prophylaxis).

4.19 One-Minute Revision

Worms: benzimidazoles cut tubulin ropes (albendazole = tissue worms, -S-propyl). DEC = filariasis babies. Niclosamide = tapeworm power cut. Oxamniquine = nitro bomb for S. mansoni. Praziquantel = calcium

cramp for flatworms. Ivermectin = nerve sleep mode. UTI: quinolones handcuff gyrase; COOH at C-3 + =O at C-4 untouchable; 6-F + 7-piperazine + N-cyclopropyl = power; generations 14 widen spectrum. Ciprofloxacin: acrylate cyclopropyl ring close piperazine hydrolyse. Nitrofurantoin = bladder only. Methenamine = formaldehyde in acid urine, prevention.

4.20 Exam Questions — Chapter 4

Short questions

1 Define vermicide and vermifuge with one example each.

2 Why are benzimidazoles selectively toxic to worms?

3 What is the essential group at C-2 of benzimidazole anthelmintics?

4 How does the C-5 substituent decide between mebendazole and albendazole use?

5 How does DEC kill microfilariae?

6 Why must oxamniquine's nitro group be called a "warhead"?

7 Distinguish the paralysis caused by praziquantel from that caused by ivermectin.

8 Name the two bacterial enzymes targeted by quinolones and state which matters more in Gram-negative bacteria.

9 Which two quinolone positions can never be changed without losing activity, and why?

10 Why is nitrofurantoin useless for pyelonephritis (kidney infection)?

11 Why does methenamine fail in alkaline urine?

12 What is special about the N-1 substituent of ciprofloxacin?

Long questions

1 Classify anthelmintic drugs by chemical class. Describe the structure (scaffold + substituents), mechanism and uses of the three benzimidazoles, and write the complete synthesis of Albendazole.

2 Explain the mechanism of action of quinolone antibacterials. Present the SAR of quinolones as a rule table covering positions 1, 3, 4, 6, 7 and 8, and classify the syllabus quinolones by generation.

3 Write the complete synthesis of Ciprofloxacin with numbered steps, reagents, conditions and intermediates. Describe its structure and uses, and explain the role of each SAR feature present in it.

4 Compare nitrofurans and methenamine as urinary tract anti-infectives: structures, mechanisms, and why each is limited to its specific site of action.

MCQs (answer key at end)

1 Benzimidazole anthelmintics act by:

a) Uncoupling oxidative phosphorylation b) Binding beta-tubulin and blocking microtubules c) Opening chloride channels d) Chelating calcium

1 The group essential at C-2 of albendazole/mebendazole is:

a) Nitro b) Methyl carbamate c) Piperazine d) Sulphonamide

1 Albendazole differs from mebendazole at C-5 by:

a) Benzoyl propylthio b) Nitro amino c) Methyl ethyl d) Chloro fluoro

1 Drug of choice for neurocysticercosis:

a) Niclosamide b) Albendazole c) DEC d) Thiabendazole

1 Oxamniquine is effective only against:

a) All tapeworms b) *Schistosoma mansoni* c) Roundworms d) Filarial worms

1 Praziquantel causes:

a) Flaccid paralysis via chloride channels b) Spastic paralysis via calcium influx c) Energy uncoupling d) Tubulin binding

1 Ivermectin's target is the:

a) Glutamate-gated chloride channel b) DNA gyrase c) Beta-tubulin d) Tegument calcium channel

1 Quinolones are:

a) Bacteriostatic protein-synthesis inhibitors b) Bactericidal DNA-gyrase/topoisomerase IV inhibitors c) Cell-wall synthesis inhibitors d) Antimetabolites

1 The two non-negotiable quinolone features are:

a) N-ethyl and 8-fluoro b) C-3 COOH and C-4 keto c) 5-amino and 6-fluoro d) Piperazine and cyclopropyl

1 The 6-fluoro substituent mainly:

a) Increases water solubility b) Increases potency and broadens spectrum c) Reduces absorption d) Causes phototoxicity

1 The 7-piperazine ring contributes:

a) Gram-negative spectrum and better pharmacokinetics b) Only bitterness c) Colour d) Nothing — it is a linker

1 In ciprofloxacin synthesis, the quinolone ring is closed by:

a) Ester hydrolysis b) Intramolecular nucleophilic aromatic substitution c) Diels–Alder reaction d) Friedel–Crafts acylation

1 Nitrofurantoin is ineffective in kidney tissue infection because:

a) It is destroyed by stomach acid b) It concentrates only in urine, not tissues c) It is fungistatic d) Bacteria lack nitroreductase

1 Methenamine releases its active agent only in:

a) Alkaline urine b) Acidic urine c) Blood d) The liver

MCQ Answer Key: 1-b, 2-b, 3-a, 4-b, 5-b, 6-b, 7-a, 8-b, 9-b, 10-b, 11-a, 12-b, 13-b, 14-b

Viva questions (with answers)

1 **Q: Why is albendazole preferred over mebendazole for hydatid disease?**

A: Albendazole's 5-propylthio group gives better oral absorption and tissue penetration, so it reaches liver/lung cysts; mebendazole stays in the gut.

1 **Q: What reagent builds the benzimidazole ring in albendazole synthesis?**

A: 1,3-Bis(methoxycarbonyl)-2-methyl-2-thiopseudourea, which supplies the C-2 carbon already carrying the methyl carbamate.

1 **Q: Which step reduces the nitro group in albendazole synthesis?**

A: Step 2 — stannous chloride in concentrated HCl (or catalytic hydrogenation).

1 **Q: Why is praziquantel called a broad anti-flatworm drug?**

A: It works against schistosomes, liver/lung flukes and tapeworms — all flatworms (trematodes and cestodes).

1 **Q: What does the cyclopropyl group do for ciprofloxacin?**

A: N-1 cyclopropyl gives the best potency/pharmacokinetic balance among N-1 groups, especially against Gram-negative bacteria.

1 **Q: Why must ciprofloxacin tablets not be taken with antacids?**

A: Metal ions chelate the C-3 carboxyl/C-4 keto groups, forming an unabsorbable complex — absorption collapses.

1 **Q: Which quinolone turns up most in phototoxicity discussions, and why?**

A: Lomefloxacin (and sparfloxacin) — the 8-fluoro substituent strongly promotes phototoxic reactions.

1 **Q: What is the active antibacterial species from methenamine?**

A: Formaldehyde, released by acid hydrolysis of the cage in acidic urine.

Application-based questions

1 A 9-year-old with pinworm infection lives in a hostel with 40 children. Which drug, what dose form, and what extra advice would you give as the pharmacist? *(Albendazole 400 mg chewable single dose (or mebendazole); treat close contacts, repeat after 2 weeks for pinworm, emphasise hand-washing, nail-trimming and washing bed linen to break reinfection.)*

2 A patient with recurrent cystitis is prescribed nitrofurantoin but complains the infection "came back in the kidney" (flank pain, fever) last time. What counselling and prescriber discussion points arise? *(Nitrofurantoin never reaches kidney tissue — flank pain/fever suggests pyelonephritis needing a systemic agent like a fluoroquinolone; counsel to seek care promptly and complete the course; flag the history to the prescriber.)*

3 A tuberculosis patient on second-line therapy asks why ofloxacin/moxifloxacin tablets are part of TB treatment when "those are urine infection medicines." Explain simply. *(Quinolones kill many bacteria via DNA gyrase, including TB bacteria; some quinolones penetrate lungs well, so they serve as second-line TB drugs when first-line drugs fail or resistance exists.)*

4.21 References

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CHAPTER 5 — ANTIBIOTICS AND SULFA DRUGS

BP501T Biomedicinal Chemistry · Unit III · Semester V

5.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define antibiotics, chemotherapeutic agents, sulfa drugs, β-lactams, and β-lactamases in simple words.

2 Draw and describe the core chemical scaffold (in words) of penicillins (6-APA), cephalosporins (7-ACA), monobactams, aminoglycosides, tetracyclines, macrolides, chloramphenicol, and sulfonamides.

3 Classify penicillins (natural, penicillinase-resistant, aminopenicillins, antipseudomonal) and cephalosporins (generations 1–5), and state one use of every drug named in this chapter.

4 State the SAR rules of penicillins, cephalosporins, tetracyclines, and sulfonamides as rule tables.

5 Write the complete synthesis of Chloramphenicol and Dapsone with numbered steps, reagents, conditions, and intermediates.

6 Explain the mechanism of action of each antibiotic class using the teaching sequence: technical concept simple explanation example key takeaway.

7 Explain the sequential blockade of folic acid synthesis by sulfonamides and trimethoprim (cotrimoxazole synergy).

8 Answer short, long, MCQ, viva, and application-based exam questions on this chapter.

5.2 Definitions

Technical concept: An *antibiotic* is a chemical substance produced by (or derived from) a microorganism that kills or inhibits the growth of other microorganisms at low concentrations.

Simple explanation: An antibiotic is a medicine made originally from a living microbe (like a fungus or bacterium) that either kills harmful bacteria or stops them from multiplying — at very small doses.

Example: Penicillin was first obtained from the fungus *Penicillium*, and it kills the bacteria that cause throat infections.

Key takeaway: Antibiotic = microbe-made (or microbe-inspired) drug that kills or stops bacteria.

Technical concept: A *chemotherapeutic agent* is any chemical used to treat disease, including synthetic antibacterial drugs that are not derived from microbes.

Simple explanation: This is a bigger umbrella word. Every antibiotic is a chemotherapeutic agent, but some chemotherapeutic agents (like sulfa drugs) are fully man-made in a factory, not from microbes.

Example: Sulphamethoxazole is a chemotherapeutic agent but not a true antibiotic, because it is completely synthetic.

Key takeaway: All antibiotics are chemotherapeutic agents; not all chemotherapeutic agents are antibiotics.

Technical concept: *Sulfa drugs (sulfonamides)* are synthetic antibacterial agents containing the p-aminobenzenesulfonamide group (–C_6H_4–SO_2NH–) that act as structural analogues of p-aminobenzoic acid (PABA).

Simple explanation: Sulfa drugs are fully man-made medicines. They look so similar to a vitamin-like substance bacteria need (PABA) that bacteria take up the drug by mistake and then cannot make their own folic acid.

Example: Sulphadiazine tricks bacteria by pretending to be PABA.

Key takeaway: Sulfa drug = synthetic PABA look-alike that blocks bacterial folic acid production.

Technical concept: A *β-lactam antibiotic* contains a four-membered cyclic amide (the β-lactam ring) fused to another ring; a *β-lactamase* is a bacterial enzyme that breaks this ring open, destroying the drug.

Simple explanation: β-lactam antibiotics all share one fragile four-cornered ring. Some clever bacteria make scissors (β-lactamase enzymes) that cut this ring and switch the drug off.

Example: Penicillin has the β-lactam ring; *Staphylococcus* bacteria make penicillinase (a β-lactamase) that cuts it.

Key takeaway: β-lactam ring = the weapon; β-lactamase = the bacterial defence that breaks the weapon.

Technical concept: *Bactericidal* drugs kill bacteria; *bacteriostatic* drugs only stop them from growing, leaving the body's immune system to finish the job.

Simple explanation: Bactericidal = "kills the germs". Bacteriostatic = "freezes the germs so they cannot multiply" — your immunity then clears them.

Example: Penicillin is bactericidal; tetracycline is bacteriostatic.

Key takeaway: Know which class kills and which only stops growth — examiners love this distinction.

5.3 Terminology Table

Term	Simple Meaning
6-APA (6-aminopenicillanic acid)	The parent core of all penicillins: β-lactam ring fused to a thiazolidine ring, with an $-NH_2$ at position 6 where side chains attach
7-ACA (7-aminocephalosporanic acid)	The parent core of all cephalosporins: β-lactam ring fused to a dihydrothiazine ring, with $-NH_2$ at position 7
PBP (penicillin-binding protein)	Bacterial enzymes (transpeptidases) that build the cell wall; β-lactams bind and block them
Peptidoglycan	The mesh-like wall around bacteria; without it the bacterium bursts
MIC (minimum inhibitory concentration)	The smallest drug amount that stops visible bacterial growth
Cross-resistance	When resistance to one drug automatically gives resistance to related drugs
Prodrug	An inactive form that the body converts into the active drug
Sequential blockade	Blocking two back-to-back steps of the same bacterial pathway (e.g., sulfonamide + trimethoprim)
Ototoxic / Nephrotoxic	Damaging to the ear (hearing/balance) / damaging to the kidney
Narrow-spectrum / Broad-spectrum	Kills few types of bacteria / kills many types (Gram-positive and Gram-negative)
Generation (cephalosporins)	Groups 1–5; higher generation = better against Gram-negative bacteria, weaker against Gram-positive
Suicide inhibitor	An inhibitor that the enzyme itself activates, then gets permanently trapped by it (e.g., clavulanic acid)
DOTS	Directly Observed Treatment, Short-course — India's supervised TB treatment strategy

5.4 The Big Picture: How Antibiotics Attack Bacteria

Technical concept: Antibiotics exploit differences between bacterial cells and human cells — they hit targets that human cells either lack or build differently: the cell wall, the bacterial ribosome (30S/50S), folic acid synthesis, or DNA machinery.

Simple explanation: Imagine bacteria as enemy forts. Antibiotics are five different attack plans: (1) smash the fort wall (β-lactams), (2) jam the fort's message-reading machines so no proteins get made (aminoglycosides, tetracyclines on the small 30S unit; macrolides, chloramphenicol, clindamycin on the large 50S unit), (3) cut off the fort's food-vitamin supply line (sulfa drugs, trimethoprim block folic acid), (4) poison special targets (dapsone in leprosy bacteria).

Example: Human cells have no cell wall at all — so penicillin smashes bacterial walls while leaving our cells untouched. That is why it is so safe.

Key takeaway: Every antibiotic class in this chapter attacks something bacteria have but human cells don't (or do differently) — that difference is the whole secret of selective toxicity.

Flowchart: Choosing the right class (concept map)

```
Bacterial target
├── CELL WALL (no wall in humans)
│   ├── Penicillins (6-APA core) ── inhibit transpeptidase (PBP)
│   ├── Cephalosporins (7-ACA core) ── same target, broader
│   ├── β-lactamase inhibitors ── protect the above (suicide blockers)
│   └── Monobactams (aztreonam) ── Gram-negative only
├── PROTEIN FACTORY (bacterial ribosome differs from ours)
│   ├── 30S subunit: Aminoglycosides (KILL — misreading), Tetracyclines (STOP — block tRNA)
│   └── 50S subunit: Macrolides, Chloramphenicol, Clindamycin (STOP protein chain)
└── FOLIC ACID FACTORY (bacteria make it, humans eat it)
    ├── Sulfonamides ── fake PABA → block dihydropteroate synthase
    ├── Trimethoprim ── block dihydrofolate reductase (next step)
    └── Cotrimoxazole = both together → SEQUENTIAL BLOCKADE (synergy)
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5.5 β-LACTAM ANTIBIOTICS

5.5.1 The β-lactam core — draw this first

Diagram (textual — draw on paper): Draw a square (4 atoms). Label the corners: one corner is N (nitrogen), the next corner clockwise is C=O (carbonyl). This square is the **β-lactam ring** — a cyclic amide. In penicillins this square shares one full side with a 5-membered ring containing sulfur (the **thiazolidine ring**); the fused shape looks like two rings hugging each other. At carbon-6 of the fused system hangs an –NH–CO–R side chain (R = the variable part that makes each penicillin different). In cephalosporins the same square shares a side with a **6-membered ring containing sulfur** (the **dihydrothiazine ring**), and the side chain hangs at carbon-7. A monobactam is just the lonely square with a $–SO_3H$ group on its nitrogen — no second ring at all.

Simple explanation: All β-lactams carry the same square weapon. Penicillins glue the square to a 5-ring, cephalosporins glue it to a 6-ring, monobactams leave the square alone.

Key takeaway: If you can draw the square + fused ring + side-chain position, you can classify any β-lactam on sight.

5.5.2 PENICILLINS

Technical concept: Penicillins are 6-acylamino derivatives of 6-aminopenicillanic acid (6-APA). The fused β-lactam–thiazolidine nucleus is essential for activity; the C-6 side chain (R) decides the spectrum and β-lactamase stability.

Simple explanation: Think of 6-APA as a standard key body. The side chain R is the teeth cut on the key — different teeth open different bacterial locks, and some teeth are shaped so bacterial scissors cannot grip them.

Example: Penicillin G and amoxicillin share the identical key body; only the teeth (side chain) differ, so one is injection-only for serious infections and the other is an oral capsule for dental infections.

Key takeaway: 6-APA = constant body; R side chain = variable teeth that decide everything.

Classification of penicillins

Class	Drugs	Side-chain idea	Main uses
Natural penicillins	Benzylpenicillin (Penicillin G), Phenoxymethylpenicillin (Penicillin V)	Simple benzyl / phenoxymethyl group; destroyed by stomach acid (G) and by penicillinase	G (injection): syphilis, meningococcal meningitis, streptococcal infections, diphtheria; V (oral, acid-stable): streptococcal pharyngitis, rheumatic fever prophylaxis
Penicillinase-resistant	Methicillin, Oxacillin, Cloxacillin, Dicloxacillin	Bulky ortho-substituted aromatic ring — steric shield blocks the enzyme	Staphylococcal infections resistant to penicillin G (boils, wound infections); cloxacillin is the workhorse oral drug for staph skin infections in India
Aminopenicillins (broad-spectrum)	Ampicillin, Amoxicillin	α-amino group on the side chain passes Gram-negative outer membrane	Ampicillin: urinary tract infections, typhoid (Salmonella), meningitis in newborns; Amoxicillin: dental infections, middle-ear infection, *H. pylori* eradication (with clarithromycin)
Antipseudomonal — carboxypenicillins	Carbenicillin, Ticarcillin	α-carboxyl group negatively charged, anti-Pseudomonas	Serious *Pseudomonas aeruginosa* infections (burns, hospital pneumonia), usually with an aminoglycoside
Antipseudomonal — ureidopenicillins	Piperacillin, Mezlocillin, Azlocillin	Urea linkage widest spectrum penicillins	Piperacillin (+ tazobactam): hospital-acquired pneumonia, intra-abdominal sepsis, febrile neutropenia

Uses of each penicillin (exam-ready one-liners)

- **Benzylpenicillin (Penicillin G):** drug of choice for syphilis, meningococcal meningitis, streptococcal sore throat complications, and diphtheria (with antitoxin).
- **Penicillin V:** oral treatment of streptococcal pharyngitis and long-term prophylaxis of rheumatic fever.
- **Methicillin:** now mainly of historical/reference importance (it defined MRSA — methicillin-resistant *S. aureus*); replaced clinically by oxacillin/cloxacillin.
- **Oxacillin / Cloxacillin / Dicloxacillin:** penicillinase-producing staphylococcal infections — skin boils, abscesses, wound infections, osteomyelitis.
- **Ampicillin:** urinary tract infections (*E. coli*), typhoid/paratyphoid, bacterial meningitis in neonates, biliary infections.
- **Amoxicillin:** dental abscess, otitis media, sinusitis, and (with clarithromycin + PPI) eradication of *H. pylori* in peptic ulcer.
- **Carbenicillin / Ticarcillin:** *Pseudomonas* and *Proteus* infections — burns, urinary infections in hospitals.
- **Piperacillin:** broadest penicillin — combined with tazobactam for life-threatening hospital infections (ventilator pneumonia, intra-abdominal sepsis).

SAR of Penicillins — Rule Table

Rule #	Structural feature	Rule (what happens)
1	Intact fused β-lactam–thiazolidine (6-APA nucleus)	Absolutely essential — opening the β-lactam ring destroys all activity
2	Cis stereochemistry at C-5/C-6	Required; the trans isomer is inactive
3	Free carboxyl (–COOH) at C-3	Essential for binding the PBP target; esterifying it kills activity
4	Acylamino side chain at C-6 (–NHCOR)	Required; the exact R decides spectrum and enzyme stability
5	Hydrophobic/aromatic R (e.g., benzyl)	Strong Gram-positive activity (natural penicillins)
6	α-amino group on R (e.g., –CH(NH_2)–)	Adds Gram-negative coverage aminopenicillins
7	Bulky ortho-substituents on aromatic R	Steric hindrance blocks penicillinase penicillinase-resistant penicillins
8	Polar acidic α-substituent (–COOH or urea)	Extends activity to *Pseudomonas* antipseudomonal penicillins
9	Sulfur in thiazolidine ring	Can be replaced by O or CH_2 with retained activity (basis of newer analogues)
10	Gem-dimethyl groups at C-2	Needed for proper ring shape; removal reduces activity

Mnemonic for the SAR: "**C**ore intact, **C**is shape, **C**arboxyl free, **C**-6 chain decides" — the 4 C's.

Mechanism of action of penicillins

Technical concept: Penicillins are structural analogues of the D-alanyl-D-alanine end of the peptidoglycan precursor; they acylate the active-site serine of transpeptidases (PBPs), irreversibly blocking cell-wall

cross-linking.

Simple explanation: Bacteria build their wall by linking chains with a "D-Ala-D-Ala" hook. Penicillin wears a fake hook costume. The wall-building enzyme grabs penicillin instead of the real hook — and gets permanently handcuffed. The wall stays weak, water rushes in, and the bacterium bursts.

Example: A growing *Streptococcus* treated with penicillin G keeps making wall material but cannot cross-link it — it swells and lyses within hours.

Key takeaway: Penicillin = fake building block handcuffs the wall builder bacterium bursts. Works only on growing bacteria (resting ones aren't building walls).

5.5.3 CEPHALOSPORINS

Technical concept: Cephalosporins are 7-acylamino derivatives of 7-aminocephalosporanic acid (7-ACA): the β-lactam ring fused to a 6-membered dihydrothiazine ring. Two variable positions exist — C-7 (acylamino side chain) and C-3 (leaving group) — giving far more design freedom than penicillins.

Simple explanation: Same square weapon as penicillin, but glued to a 6-ring instead of a 5-ring, and with TWO places to attach decorations instead of one — so chemists could tune them through five generations.

Example: Ceftriaxone (3rd generation) keeps the cephalosporin core but carries an aminothiazole-oxime side chain that punches through Gram-negative defences and resists their enzymes.

Key takeaway: 7-ACA core + two tunable spots (C-7 and C-3) = five generations of increasing Gram-negative power.

Classification: the five generations

Generation	Drugs	Spectrum character	Typical uses
1st	Cephalexin, Cefadroxil (oral); Cefazolin (injectable)	Best vs Gram-positive cocci (staph, strep); weak vs Gram-negative	Skin/soft-tissue infections, surgical prophylaxis (cefazolin is the classic pre-surgery injection)
2nd	Cefuroxime, Cefaclor (oral); Cefoxitin (injectable)	More Gram-negative (*Haemophilus*, *E. coli*); cefoxitin also hits anaerobes	Respiratory infections, sinusitis (cefuroxime); intra-abdominal/anaerobic cover (cefoxitin)
3rd	Ceftriaxone, Cefotaxime (injectable); Cefixime (oral); Ceftazidime (injectable)	Strong Gram-negative, cross blood–brain barrier; ceftazidime uniquely anti-pseudomonal	Bacterial meningitis, typhoid (ceftriaxone/cefixime), gonorrhoea (single-dose ceftriaxone), hospital Gram-negative sepsis; ceftazidime for *Pseudomonas*
4th	Cefepime	Zwitterionic slips through Gram-negative porins; resists many β-lactamases; keeps Gram-positive cover	Febrile neutropenia, severe hospital infections with resistant Gram-negatives
5th	Ceftaroline	Only cephalosporin active against MRSA (binds the altered PBP2a)	MRSA skin infections and pneumonia

Generation trend mnemonic: "**G**ood **G**uys **G**et **G**reedy, **M**RSA dies" — Generations 1–4 shift from Gram-positive toward Gram-negative; 5th adds MRSA.

Uses of each cephalosporin (exam-ready one-liners)

- **Cephalexin / Cefadroxil:** oral drugs for staphylococcal/streptococcal skin infections and uncomplicated UTI.
- **Cefazolin:** injectable; single-dose surgical prophylaxis (given before the first cut).
- **Cefuroxime:** respiratory tract infections, sinusitis, early Lyme disease.
- **Cefaclor:** otitis media and respiratory infections in children (pleasant-tasting suspension).
- **Cefoxitin:** mixed aerobic–anaerobic intra-abdominal and pelvic infections.
- **Ceftriaxone:** bacterial meningitis, typhoid fever, single-dose gonorrhoea treatment; very long half-life once-daily dosing.
- **Cefotaxime:** meningitis (especially newborns), serious Gram-negative infections.
- **Cefixime:** oral typhoid treatment and gonorrhoea.
- **Ceftazidime:** the anti-pseudomonal cephalosporin — *Pseudomonas* hospital infections.
- **Cefepime:** resistant Gram-negative hospital infections, febrile neutropenia.
- **Ceftaroline:** MRSA skin/soft-tissue infections and MRSA pneumonia.

SAR of Cephalosporins — Rule Table

Rule #	Structural feature	Rule (what happens)
1	Intact β-lactam ring + C-4 carboxyl	Essential; both needed for PBP binding
2	Cis 7-acylamino group	Required, as in penicillins
3	C-7 side chain with aminothiazole + oxime	Gives Gram-negative potency and β-lactamase stability (3rd/4th generation signature)
4	Bulky α-substituent at C-7	Steric shield resistance to β-lactamases
5	Electron-withdrawing / good leaving group at C-3	Improves activity; the C-3 group leaves during PBP acylation
6	Catechol or similar iron-binding group at C-3	Siderophore trick — smuggled into bacteria via iron transport
7	Zwitterionic character (4th gen, e.g., cefepime)	Rapid penetration through Gram-negative porin channels
8	Extended side chain reaching PBP2a (5th gen)	Ceftaroline's trick for killing MRSA
9	Acetoxy at C-3 (as in cephalosporin C)	Can be replaced by many groups — the main tuning handle
10	Dihydrothiazine sulfur	Oxidation to sulfoxide/sulfone changes activity (tuning handle)

5.5.4 β-LACTAMASE INHIBITORS

Technical concept: Clavulanic acid, sulbactam, and tazobactam are β-lactam analogues with weak antibacterial activity but high affinity for β-lactamase enzymes; they act as suicide (irreversible) inhibitors, permanently acylating the enzyme's active-site serine.

Simple explanation: These are decoy soldiers. The bacterial scissors (β-lactamase) cut the decoy instead of the real antibiotic — but the decoy jams the scissors permanently shut. Then the real antibiotic (amoxicillin, piperacillin) walks in safely.

Example: Amoxicillin alone fails against β-lactamase-making *E. coli*; amoxicillin + clavulanic acid (co-amoxiclav) succeeds, because clavulanate sacrifices itself to jam the enzyme.

Key takeaway: Inhibitor = suicide decoy that permanently jams bacterial scissors, rescuing the partner penicillin.

Inhibitor	Structure note	Partner drug (combination)	Uses of the combination
Clavulanic acid	Oxapenam — penicillin-like fused rings but with OXYGEN replacing sulfur in the 5-ring; made by *Streptomyces clavuligerus*	Amoxicillin (co-amoxiclav)	Respiratory infections, UTI, animal/human bite wounds, dental infections
Sulbactam	Penicillanic acid sulfone (S oxidised to SO_2)	Ampicillin	Intra-abdominal, gynaecological, and skin infections
Tazobactam	Sulbactam analogue with a triazole ring	Piperacillin	Life-threatening hospital infections — ventilator pneumonia, sepsis, febrile neutropenia

Clavulanic acid — structure and uses (syllabus drug)

Structure (textual): A fused two-ring system like penicillin, but the 5-membered ring contains an oxygen atom instead of sulfur (an "oxapenam"), with a –CH=CH–CH_2OH side arm at position 2 and the usual β-lactam carbonyl. It is isolated from the soil bacterium *Streptomyces clavuligerus*.

Uses: Never used alone (too weak). Combined with amoxicillin (co-amoxiclav): sinusitis, otitis media, lower respiratory infections, urinary infections, infected animal bites, and dental abscesses.

5.5.5 MONOBACTAMS

Technical concept: Monobactams contain a lone (monocyclic) β-lactam ring bearing an N-sulfonic acid group (–SO_3H) and a 3-acylamino side chain; aztreonam is the clinical member, active only against aerobic Gram-negative bacteria.

Simple explanation: Just the square weapon, all alone, with a sulfonic-acid tail on its nitrogen. It is a sniper rifle that only shoots Gram-negative bacteria — completely useless against Gram-positive ones.

Example: A patient allergic to penicillin who catches a *Pseudomonas* urinary infection can receive aztreonam, because its lonely-ring shape rarely triggers penicillin allergy.

Key takeaway: Aztreonam = single β-lactam ring + N–SO_3H; Gram-negative-only; the safe β-lactam for penicillin-allergic patients.

Aztreonam — structure and uses: Monocyclic β-lactam with an N-sulfonic acid group; at C-3 it carries the same aminothiazole-oxime side chain seen in 3rd-generation cephalosporins. Uses: Gram-negative hospital infections including *Pseudomonas aeruginosa* (UTI, pneumonia, septicaemia), especially in patients with penicillin allergy. No activity against Gram-positive bacteria or anaerobes.

5.5.6 Comparison table: the four β-lactam families

Feature	Penicillins	Cephalosporins	β-lactamase inhibitors	Monobactams
Core	6-APA: β-lactam + 5-ring (S)	7-ACA: β-lactam + 6-ring (S)	Oxapenam / penam sulfone	Single β-lactam ring + N–SO_3H
Tunable positions	C-6	C-7 and C-3	—	C-3
Main target	Gram-positive (early); broad (amino); *Pseudomonas* (ureido)	Gen 1: Gram+; Gen 3–4: Gram; Gen 5: MRSA	β-lactamase enzyme (not bacteria)	Gram-negative aerobes only
Used alone?	Yes	Yes	No — always with a penicillin	Yes
Example	Amoxicillin	Ceftriaxone	Clavulanic acid	Aztreonam

5.6 AMINOGLYCOSIDES

Technical concept: Aminoglycosides are amino sugars linked by glycosidic bonds to a central aminocyclitol ring (streptidine or 2-deoxystreptamine). They bind the 30S ribosomal subunit, cause misreading of mRNA, and are bactericidal; uptake needs oxygen, so they fail against anaerobes.

Simple explanation: These are sugar-based drugs built around a central amino ring. They sit on the bacterium's small protein-reading machine (30S) and scramble the message — wrong proteins get made, the membrane leaks, and the bacterium dies. Because they need oxygen to enter the cell, they cannot touch bacteria that live without oxygen.

Example: Streptomycin scrambles the protein code of the tuberculosis bacterium so badly that the cell poisons itself.

Key takeaway: Amino-sugar drugs jam the 30S reader wrong proteins bacterial death. Oxygen needed; ears and kidneys are the side-effect watch points.

The three syllabus drugs

Drug	Structure (textual)	Source	Uses
Streptomycin	Three units: a central **streptidine** ring (guanidino groups) linked to **streptose** (a branched sugar) and **N-methyl-L-glucosamine**	*Streptomyces griseus*	Tuberculosis (with other anti-TB drugs), plague, brucellosis, tularemia
Neomycin	**Neamine** (2-deoxystreptamine + neosamine) linked to **neobiosamine** (ribose + neosamine) — the most amino groups, hence most toxic	*Streptomyces fradiae*	Topical only (creams/ointments for skin infections, eye/ear drops) — too toxic for injection; oral form sterilises the gut before bowel surgery
Kanamycin	Central **2-deoxystreptamine** linked to **kanosamine** and 6-amino-6-deoxy-D-glucose	*Streptomyces kanamyceticus*	Multidrug-resistant tuberculosis, serious Gram-negative infections

Mechanism of action

Technical concept: Aminoglycosides bind irreversibly to the 30S subunit (16S rRNA), distort the A-site, cause mistranslation (wrong amino acids inserted), and produce faulty membrane proteins that increase drug uptake — a lethal positive-feedback loop.

Simple explanation: The drug sits in the proofreading seat of the 30S machine and switches the proofreader off. Every protein comes out with wrong parts — including the bacterium's own wall proteins. The damaged wall lets in even more drug. Death spiral.

Example: In TB treatment, streptomycin-damaged mycobacterial proteins make the cell wall leaky, pulling in more streptomycin until the bacillus dies.

Key takeaway: Aminoglycosides don't just stop the factory — they make it manufacture poison (faulty proteins), which is why they KILL rather than merely stop growth.

Pharmacy relevance: Ototoxicity (hearing loss, ringing) and nephrotoxicity (kidney damage) are dose-related — pharmacists monitor drug levels, hydration, and avoid combining two aminoglycosides or with loop diuretics.

5.7 TETRACYCLINES

Technical concept: Tetracyclines share a four-fused-ring naphthacene skeleton (rings A–B–C–D) with a C-4 dimethylamino group and a C-1–C-3 keto-enol system; they bind the 30S subunit reversibly, blocking aminoacyl-tRNA attachment — bacteriostatic.

Simple explanation: Picture four hexagonal rings fused in a straight row like a train of four coaches (A-B-C-D). These drugs park on the 30S machine and physically block the delivery truck (tRNA) carrying new amino-acid parts — the protein chain simply cannot grow. Unlike aminoglycosides, they don't scramble anything; they just pause the line, and the effect reverses when the drug leaves.

Example: Doxycycline parks on the 30S of the malaria parasite's cousin machinery and of acne bacteria, pausing their growth long enough for immunity to clear them.

Key takeaway: Four-ring train blocks the tRNA delivery dock on 30S growth paused (bacteriostatic), not killed.

The four syllabus drugs

Drug	Structural difference from tetracycline	Uses
Tetracycline	The parent: OH at C-5 and C-6, H at C-7	Acne, cholera, rickettsial fevers, *H. pylori* regimens
Oxytetracycline	Extra –OH at C-5	Acne, and widely used in veterinary medicine
Minocycline	Dimethylamino group at C-7; no OH at C-5/C-6 very lipid-soluble, enters brain	Acne (deep), MRSA skin infections, rheumatoid arthritis adjunct
Doxycycline	No –OH at C-6 (only at C-5) longest half-life, once-daily	Malaria prophylaxis, scrub typhus, rickettsia, chlamydia, acne, Lyme disease

SAR of Tetracyclines — Rule Table (positions 4, 5, 6, 7, D-ring)

Rule #	Position / feature	Rule (what happens)
1	C-4 dimethylamino (–$N(CH_3)_2$), α/β orientation	Essential — removal or epimerisation destroys activity
2	C-1–C-3 keto-enol system	Essential for metal chelation and ribosome binding; must stay intact
3	C-5 substituent	Tolerates –OH (oxytetracycline) or –H; affects solubility
4	C-6 substituent	–OH present in tetracycline/oxytetracycline; ABSENT in doxycycline longer half-life, better absorption
5	C-7 substituent (D-ring)	Tolerates –Cl (chlortetracycline), –$N(CH_3)_2$ (minocycline) minocycline is the most lipid-soluble and potent
6	D-ring (aromatic)	Must stay aromatic; substituents at C-7 to C-9 fine-tune potency and pharmacokinetics
7	C-11–C-12 β-diketone	Needed for chelation with Mg^{2+}/Ca^{2+} (also the reason milk reduces absorption)
8	Stereochemistry at C-4a, C-5a, C-12a	Natural configuration required; wrong stereoisomers are inactive

Key takeaway from the SAR: C-4 dimethylamino + keto-enol + stereochemistry are untouchable; positions 5, 6, 7 and the D-ring are the chemist's playground (doxycycline and minocycline are the proof).

Pharmacy relevance: Tetracyclines chelate calcium — never give with milk, antacids, or iron; they stain growing teeth, so they are avoided in children under 8 and in pregnancy.

5.8 MACROLIDES

Technical concept: Macrolides contain a large macrocyclic lactone ring (14- or 15-membered) decorated with deoxy sugars (desosamine, cladinose); they bind the 50S subunit near the peptidyl transferase centre, blocking translocation — bacteriostatic.

Simple explanation: Imagine a big bracelet (the lactone ring) with two sugar charms hanging off it. The bracelet wedges into the bacterium's large protein machine (50S) and blocks the conveyor belt that moves the growing protein along. The chain stalls.

Example: Erythromycin's bracelet stalls protein production in the bacteria causing whooping cough and atypical pneumonia.

Key takeaway: Big-ring bracelet + sugar charms jams the 50S conveyor belt protein chain stalls.

Structure differences among the three

Drug	Ring	Key structural difference	Consequence
Erythromycin	14-membered lactone + desosamine + cladinose sugars	Parent molecule	Destroyed by stomach acid poor oral absorption; short half-life (multiple daily doses)
Clarithromycin	14-membered	6-O-methyl ether (a $-OCH_3$ caps the C-6 hydroxyl)	Acid-stable excellent oral absorption; longer acting
Azithromycin	15-membered **azalide** (nitrogen inserted at position 9a, N-methylated)	Ring expanded with a nitrogen atom	Very long half-life (once daily, 3-day course), huge tissue penetration, best vs atypical organisms

Diagram (textual): Draw a large circle of 14 atoms with one –C(=O)–O– ester link (the lactone). Hang two small hexagons (sugars) off the circle — one is desosamine (with a dimethylamino group), the other cladinose. For clarithromycin, put a small $-OCH_3$ flag on carbon-6. For azithromycin, redraw the circle with 15 atoms and mark one atom as $N–CH_3$ (the azalide nitrogen).

Uses

- **Erythromycin:** respiratory infections, whooping cough (pertussis), diphtheria, acne (topical), and the substitute for penicillin-allergic patients with streptococcal infection.
- **Clarithromycin:** *H. pylori* eradication (with amoxicillin + PPI), respiratory infections, atypical mycobacterial infections.
- **Azithromycin:** single-dose chlamydia treatment, typhoid fever, traveller's diarrhoea, community-acquired (atypical) pneumonia, 3-day respiratory courses.

5.9 CHLORAMPHENICOL, CLINDAMYCIN, CLAVULANIC ACID

5.9.1 Chloramphenicol (full synthesis required)

Structure (textual): A p-nitrophenyl ring ($–C_6H_4–NO_2$, para) attached to a 3-carbon chain: $–CH(OH)–CH(NH–CO–CHCl_2)–CH_2OH$. Only the **D-threo** stereoisomer is active — the two chiral centres must have the correct handedness. The dichloroacetamide ($–CO–CHCl_2$) tail is essential.

Simple explanation: A nitro-benzene head, a sweet 3-carbon middle carrying two –OH groups, and a chlorine-rich tail. The molecule is like a right-handed glove — only the D-threo "hand" fits the bacterial 50S target; the mirror image is useless.

Mechanism: Binds the 50S subunit, blocks peptidyl transferase — the enzyme that links amino acids together. Protein chain cannot elongate. Bacteriostatic (bactericidal for a few organisms like *H. influenzae*).

Uses: Bacterial meningitis (where penicillin cannot be used), typhoid fever (historical first-choice), rickettsial fevers, and eye infections (chloramphenicol eye drops/ointment — still widely used in India).
Caution: rare but fatal aplastic anaemia (bone-marrow failure) — use is restricted.

Complete synthesis of Chloramphenicol (Controulis route)

Overall plan: build the 3-carbon amino-diol skeleton by a nitroaldol (Henry) reaction between p-nitrobenzaldehyde and 2-nitroethanol reduce the nitro group to an amine resolve the correct D-threo stereoisomer attach the dichloroacetyl tail.

Step 1 — Nitroaldol (Henry) condensation. Reagents & conditions: p-nitrobenzaldehyde + 2-nitroethanol ($HO–CH_2–CH_2–NO_2$), catalytic aqueous NaOH (or NaOMe), methanol, 0–5 °C. Intermediate: 1-(p-nitrophenyl)-2-nitropropane-1,3-diol — $p\text{-}NO_2–C_6H_4–CH(OH)–CH(NO_2)–CH_2OH$ (mixture of threo/erythro diastereomers). What happens: the base removes a proton next to the nitro group of 2-nitroethanol, forming a carbanion that attacks the aldehyde carbonyl; protonation gives the β-nitro alcohol.

Step 2 — Reduction of the aliphatic nitro group to a primary amine. Reagents & conditions: Zn dust / HCl (or catalytic hydrogenation, H_2–Pt), keeping the aromatic $–NO_2$ untouched by controlled conditions. Intermediate: 2-amino-1-(p-nitrophenyl)propane-1,3-diol — $p\text{-}NO_2–C_6H_4–CH(OH)–CH(NH_2)–CH_2OH$ (racemic threo + erythro mixture). The aromatic nitro group survives because aliphatic nitro reduces faster under these conditions.

Step 3 — Resolution to the D-threo isomer. Reagents & conditions: d-camphoric acid (or L-tartaric acid) in ethanol; fractional crystallisation. Intermediate: pure D-threo-2-amino-1-(p-nitrophenyl)propane-1,3-diol (as the resolved salt, then freed with base). What happens: the resolving acid forms diastereomeric salts with the (±)-threo amine; the D-threo salt crystallises out selectively. (Only the D-threo amine leads to active chloramphenicol.)

Step 4 — Dichloroacetylation of the amine. Reagents & conditions: methyl dichloroacetate ($Cl_2CH–CO_2Me$) in methanol, room temperature; (alternative: dichloroacetyl chloride in dry conditions). Product: Chloramphenicol — $p\text{-}NO_2–C_6H_4–CH(OH)–CH(NH–CO–CHCl_2)–CH_2OH$ (D-threo). What happens: the primary amine attacks the ester carbonyl, displacing methanol and forming the dichloroacetamide linkage. The two –OH groups do not react under these mild conditions.

> **Key takeaway:** Aldehyde + nitroethanol nitro-diol amino-diol resolve D-threo cap the amine with $–CO–CHCl_2$. Four steps, and stereochemistry is the whole game.

5.9.2 Clindamycin

Structure (textual): A chlorinated derivative of the natural antibiotic lincomycin: a sulfur-linked amino-acid (propylhygric acid) joined to an amino sugar (methylthiolincosamide) in which the 7-hydroxyl group is replaced by chlorine with inversion of configuration (7-chloro-7-deoxylincomycin).

Simple explanation: Scientists took the natural drug lincomycin and swapped one –OH for a –Cl atom — a tiny change that made it far better absorbed and stronger.

Mechanism: Binds the 50S subunit (same neighbourhood as macrolides), blocks translocation — bacteriostatic.

Uses: Anaerobic infections (dental abscess, intra-abdominal), skin/soft-tissue infections including MRSA, acne (topical), and toxoplasmosis (with pyrimethamine). **Caution:** can cause pseudomembranous colitis (*Clostridioides difficile* overgrowth) — stop the drug if severe diarrhoea appears.

5.9.3 Clavulanic acid — (covered in 5.5.4; summary for exams)

Weak antibacterial on its own; suicide inhibitor of β-lactamases; always combined (co-amoxiclav with amoxicillin). Uses: respiratory, urinary, bite-wound, and dental infections where β-lactamase-producing bacteria are suspected.

5.9.4 Infographic concept box — "The Antibiotic Battlefield"

BACTERIA vs DRUGS — who hits what **WALL SMASHERS** (kill growing bacteria): Penicillins · Cephalosporins · Aztreonam — handcuff the wall builders (PBPs). Protected by bodyguards: Clavulanic acid · Sulbactam · Tazobactam (they jam the bacterial scissors). **FACTORY JAMMERS — small machine (30S)**: Aminoglycosides KILL (scramble the code — need oxygen) · Tetracyclines PAUSE (block the delivery truck). **FACTORY JAMMERS — large machine (50S)**: Macrolides · Chloramphenicol · Clindamycin PAUSE the conveyor belt. **FOOD SUPPLY CUTTERS**: Sulfa drugs (fake PABA) + Trimethoprim — double blockade of folic acid; together = Cotrimoxazole synergy. **SPECIALIST**: Dapsone — leprosy bacteria's folic-acid blocker. **WATCH OUT**: Aminoglycosides ears + kidneys · Chloramphenicol bone marrow (rare, fatal) · Clindamycin *C. difficile* diarrhoea · Tetracyclines teeth + milk interaction.

5.10 SULFA DRUGS (SULFONAMIDES)

5.10.1 Core chemistry

Technical concept: All sulfonamides share the p-aminobenzenesulfonamide scaffold: $H_2N–C_6H_4–SO_2–NHR$ (para relationship). They are structural analogues of p-aminobenzoic acid (PABA, $H_2N–C_6H_4–COOH$) — the $–SO_2NHR$ group mimics the –COOH of PABA.

Simple explanation: Draw a benzene ring. Put $–NH_2$ at the top (position 4, the "N4" amino) and $–SO_2–NH–R$ at the bottom (position 1, the "N1" end). This molecule is a near-twin of PABA, a raw material bacteria need to build folic acid. The bacterium's enzyme cannot tell the twin from the real thing, grabs the drug, and the folic-acid assembly line jams.

Diagram (textual): Benzene hexagon, $–NH_2$ at 12 o'clock (para amino, "N4"), $–SO_2–NH–R$ at 6 o'clock (sulfonamido, "N1"). Beside it draw PABA: same hexagon, $–NH_2$ at 12 o'clock, –COOH at 6 o'clock. The two 6-o'clock groups ($–SO_2NHR$ vs –COOH) are similar in size and charge — that is the mimicry.

Key takeaway: Sulfonamide = PABA look-alike; the para-NH_2 and the $–SO_2NH–$ are both non-negotiable.

Mechanism of action — sequential blockade

Technical concept: Sulfonamides competitively inhibit dihydropteroate synthase (the enzyme that joins PABA to pteridine), blocking dihydrofolate tetrahydrofolate thymidine/DNA synthesis. Trimethoprim inhibits the NEXT enzyme, dihydrofolate reductase. Together (cotrimoxazole) they block two consecutive steps — synergistic and bactericidal.

Simple explanation: Making folic acid is a two-step recipe: Step 1 (needs PABA) Step 2. Sulfa drugs spoil Step 1 with a fake ingredient; trimethoprim padlocks Step 2. One blockade slows bacteria (bacteriostatic); the double blockade starves them completely (often bactericidal) — like cutting both the water pipe AND the backup tank.

Example: In a urinary infection, sulphamethoxazole alone would only stall *E. coli*; with trimethoprim (cotrimoxazole), the combination kills it — which is why the fixed 5:1 combination is the standard tablet.

Key takeaway: Sulfa = fake PABA (Step 1); Trimethoprim = Step 2 blocker; together = sequential blockade = synergy.

Flowchart: folic acid pathway blockade

```
Pteridine + PABA ──(dihydropteroate synthase)──▶ Dihydrofolate ──(dihydrofolate reductase)──▶
Tetrahydrofolate ──▶ DNA building blocks
                   ▲ BLOCKED by sulfonamides                                    ▲ BLOCKED by
trimethoprim
                   (fake PABA)                                                  (fake folate
                                        ═══════════════════════════════
                                        BOTH TOGETHER = COTRIMOXAZOLE (sequential blockade → synergy)
Humans: NOT affected — we absorb ready-made folic acid from food; we don't run this pathway.
```

5.10.2 Classification of sulfonamides (by use/site)

Group	Drugs	Character	Uses
Short/intermediate-acting systemic	Sulphamethizole, Sulfisoxazole, Sulphadiazine	Absorbed, excreted in urine	Urinary tract infections (sulphamethizole, sulfisoxazole); sulphadiazine also for toxoplasmosis
Long-acting systemic	Sulphapyridine (historical), Sulphadimethoxine-type	Long half-life	Dermatitis herpetiformis (sulphapyridine); rheumatic fever prophylaxis (sulphadiazine)
Topical	Sulphathiazole, Sulfacetamide, Mafenide	Local action	Sulphathiazole: skin; Sulfacetamide: eye infections (drops/ointment); Mafenide: burn wounds (penetrates dead tissue)
Gut-acting (azo prodrug)	Sulfasalazine	Split by colonic bacteria 5-aminosalicylic acid + sulphapyridine	Ulcerative colitis, Crohn's disease, rheumatoid arthritis

Group	Drugs	Character	Uses
Non-classical (DHFR inhibitor)	Trimethoprim	Not a sulfonamide chemically — a diaminopyrimidine	With sulphamethoxazole = cotrimoxazole
Sulfone	Dapsone	–SO_2– between two aniline rings (no N1 side chain)	Leprosy (MDT), dermatitis herpetiformis, PCP prophylaxis

5.10.3 Uses of EACH sulfa drug (exam-ready one-liners)

- **Sulphamethizole:** N1-(5-methyl-1,3,4-thiadiazol-2-yl); short-acting — acute urinary tract infections.
- **Sulfisoxazole:** N1-(3,4-dimethyl-5-isoxazolyl); urinary tract infections and middle-ear infections (otitis media) in children.
- **Sulphapyridine:** N1-(2-pyridyl); the original pneumonia sulfa — now mainly dermatitis herpetiformis (blistering skin disease).
- **Sulphathiazole:** N1-(2-thiazolyl); topical antibacterial for skin infections and wounds.
- **Sulfacetamide:** N1-acetyl; eye infections — bacterial conjunctivitis (drops and ointment); the acetyl group makes it gentle for the eye.
- **Sulphamethoxazole:** N1-(5-methyl-3-isoxazolyl); intermediate-acting — the sulfa half of cotrimoxazole (UTI, respiratory infections, PCP treatment).
- **Sulphadiazine:** N1-(2-pyrimidinyl); toxoplasmosis (with pyrimethamine), rheumatic fever prophylaxis, and (as silver sulphadiazine cream) burn wounds.
- **Mafenide:** p-aminomethyl-benzenesulfonamide (the –NH_2 is on a –CH_2– spacer, not directly on the ring); burn-wound cream that penetrates dead eschar tissue where other drugs cannot reach.
- **Sulfasalazine:** sulphapyridine linked via an azo (–N=N–) bond to 5-aminosalicylic acid; colonic bacteria cut the azo bond, releasing 5-ASA exactly in the colon — ulcerative colitis, Crohn's disease, rheumatoid arthritis.
- **Trimethoprim:** 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine; selective bacterial dihydrofolate reductase inhibitor — urinary infections, and combined as cotrimoxazole.
- **Cotrimoxazole:** fixed 5:1 combination of sulphamethoxazole + trimethoprim; urinary tract infections, *Pneumocystis* pneumonia (PCP) treatment/prophylaxis, traveller's diarrhoea, nocardiosis.
- **Dapsone:** 4,4′-diaminodiphenyl sulfone; leprosy multidrug therapy (with rifampicin + clofazimine), dermatitis herpetiformis, PCP prophylaxis in sulfa-allergic patients.

SAR of Sulfonamides — Rule Table

Rule #	Structural feature	Rule (what happens)
1	Free para-amino group (–NH_2 at N4)	Absolutely essential — it mimics PABA's amino group; N4-acylated forms are inactive prodrugs (e.g., sulfacetamide releases the free amine… note: sulfacetamide is N1-acetyl, active as eye drug)
2	Para relationship of –NH_2 and –SO_2NH–	Required; ortho/meta isomers are inactive

Rule #	Structural feature	Rule (what happens)
3	–SO_2NH– linker	Essential; replacing –SO_2– with –CO– destroys the PABA mimicry
4	N1 substitution (–SO_2–NH–R)	Heterocyclic R (pyrimidine, isoxazole, thiazole, thiadiazole) increases potency, lipid solubility, and half-life vs unsubstituted sulfanilamide
5	pKa of the N1–H (acidity)	Optimum ~6.5–7.4: at blood pH part of the drug is ionised (soluble) and part unionised (penetrates bacteria) — the best balance of solubility and penetration
6	Electron-withdrawing N1 heterocycle	Lowers the N1–H pKa into the optimum window and improves protein binding longer action
7	Ortho substituents on the benzene ring	Reduce activity (distort the flat PABA-like shape)
8	N4 substitution	Generally kills activity UNLESS the substituent is cleaved in the body to free the –NH_2 (prodrug strategy, e.g., sulfasalazine's azo bond)
9	Lipid solubility of R	Higher lipophilicity better tissue penetration and longer half-life (long-acting sulfas)
10	Sulfone variant (dapsone)	Two p-aminophenyl rings on one –SO_2– keep the PABA mimicry without an N1–H — still blocks the same enzyme

Key takeaway: Free para-NH_2 + para-SO_2NH– + well-chosen N1 heterocycle with pKa 7 = an effective sulfa drug.

5.10.4 Dapsone (full synthesis required)

Structure (textual): Two para-aminophenyl rings joined by a sulfone bridge: H_2N–C_6H_4–SO_2–C_6H_4–NH_2 (4,4′-diaminodiphenyl sulfone). No N1 side chain — it is a sulfone, not a sulfonamide, but it keeps the two free para-amino groups that mimic PABA.

Mechanism: Same as sulfonamides — competes with PABA at dihydropteroate synthase in *Mycobacterium leprae*; bacteriostatic for leprosy bacilli.

Uses: Leprosy multidrug therapy (with rifampicin and clofazimine — the WHO/NLEP regimen), dermatitis herpetiformis, and PCP prophylaxis.

Complete synthesis of Dapsone

Overall plan: couple two molecules of p-chloronitrobenzene through a sulfur bridge oxidise the sulfide to a sulfone reduce both nitro groups to amines.

Step 1 — Thioether formation (nucleophilic aromatic substitution). Reagents & conditions: 2 equivalents of p-chloronitrobenzene + sodium sulfide (Na_2S), ethanol/water, reflux. Intermediate: 4,4′-dinitrodiphenyl sulfide — O_2N–C_6H_4–S–C_6H_4–NO_2. What happens: sulfide ion (S^{2-}) displaces chloride from two molecules of p-chloronitrobenzene; the para-nitro group activates the ring for this substitution.

Step 2 — Oxidation of sulfide to sulfone. Reagents & conditions: hydrogen peroxide (H_2O_2) in glacial acetic acid (or CrO_3/H_2SO_4), gentle heat. Intermediate: 4,4′-dinitrodiphenyl sulfone — $O_2N–C_6H_4–SO_2–C_6H_4–NO_2$. What happens: the sulfur is oxidised from oxidation state –2 (sulfide) to +4 (sulfone) via the sulfoxide; two oxygen atoms add to sulfur.

Step 3 — Reduction of both nitro groups to primary amines. Reagents & conditions: Sn/HCl (or Fe/AcOH, or catalytic hydrogenation H_2–Pd/C), then basify. Product: Dapsone — $H_2N–C_6H_4–SO_2–C_6H_4–NH_2$ (4,4′-diaminodiphenyl sulfone). What happens: each $–NO_2$ is reduced to $–NH_2$ (nitro nitroso hydroxylamine amine); the sulfone bridge is untouched by these reducing conditions.

Key takeaway: p-Cl–C_6H_4–NO_2 sulfide bridge oxidise to sulfone reduce nitro to amine. Three steps: couple, oxidise, reduce.

5.11 Master Comparison Tables

Table A — Protein-synthesis inhibitors: 30S vs 50S

Feature	Aminoglycosides	Tetracyclines	Macrolides	Chloramphenicol	Clindamycin
Subunit	30S	30S	50S	50S	50S
Action	Misreading faulty proteins	Blocks tRNA docking	Blocks translocation	Blocks peptidyl transferase	Blocks translocation
Cidal/static	Bactericidal	Bacteriostatic	Bacteriostatic	Bacteriostatic	Bacteriostatic
Needs oxygen?	Yes (uptake)	No	No	No	No
Key toxicity	Oto-/nephrotoxic	Teeth, photosensitivity	GI upset	Aplastic anaemia (rare)	*C. difficile* colitis
Star example	Streptomycin (TB)	Doxycycline (malaria prophylaxis)	Azithromycin (3-day course)	Eye drops	Dental/anaerobic

Table B — Cell-wall drugs at a glance

Drug class	Core	Spectrum highlight	Partner/protector
Natural penicillins	6-APA	Streptococci, syphilis	—
Penicillinase-resistant	6-APA + bulky R	Staph (penicillinase makers)	—
Aminopenicillins	6-APA + α-NH_2	+ Gram-negative	+ Clavulanic acid (co-amoxiclav)
Antipseudomonal	6-APA + acidic R	+ *Pseudomonas*	+ Tazobactam
Cephalosporins Gen 15	7-ACA	Gen 1: Gram+ Gen 4: Gram; Gen 5: MRSA	—
Monobactam	Lone β-lactam	Gram only	—

Table C — Folate-pathway drugs

Drug	Step blocked	Enzyme	Used as
Sulfonamides	Step 1	Dihydropteroate synthase	Cotrimoxazole component; UTI, toxoplasmosis
Trimethoprim	Step 2	Dihydrofolate reductase	Cotrimoxazole component; UTI
Dapsone	Step 1 (in *M. leprae*)	Dihydropteroate synthase	Leprosy MDT

5.12 Worked Examples

Example 1 — Penicillin allergy + Pseudomonas UTI. A patient allergic to penicillin develops a *Pseudomonas* urinary infection. Which β-lactam is safe and effective, and why? *Answer:* Aztreonam — it is a monobactam (single ring, no fused penicillin/cephalosporin shape), so penicillin allergy rarely cross-reacts, and it kills aerobic Gram-negative bacteria including *Pseudomonas*.

Example 2 — Why milk with doxycycline is a bad idea. A student takes doxycycline with a glass of milk and the acne does not improve. Why? *Answer:* The C-11–C-12 β-diketone of tetracyclines chelates (grabs) calcium in milk, forming an insoluble complex that cannot be absorbed — the drug never reaches the blood.

Example 3 — Sequential blockade in action. Why is cotrimoxazole (sulphamethoxazole + trimethoprim) stronger than either drug alone? *Answer:* Sulphamethoxazole fakes PABA and blocks Step 1 of folate synthesis; trimethoprim blocks Step 2 (dihydrofolate reductase). Two consecutive blocks in one pathway = synergy, turning two bacteriostatic drugs into a bactericidal combination.

Example 4 — Picking the cephalosporin generation. A case of bacterial meningitis needs a cephalosporin. Which generation and why? *Answer:* 3rd generation (ceftriaxone or cefotaxime) — they cross the blood–brain barrier, resist Gram-negative β-lactamases, and cover meningitis pathogens.

5.13 Analogies (for memory)

1. **Penicillin as a fake key:** The bacterium's wall-builder expects a D-Ala-D-Ala key; penicillin is a look-alike key that snaps off inside the lock — the builder is handcuffed forever.
2. **β-lactamase inhibitors as bodyguards:** Clavulanic acid jumps in front of the bacterial scissors and jams them with its own body so amoxicillin can pass safely.
3. **Sulfa drugs as duplicate ration cards:** The bacterial kitchen needs PABA ration cards to cook folic acid; sulfa drugs are forged cards — the kitchen accepts them and the whole meal fails.
4. **Aminoglycosides as a corrupted printer:** The 30S printer keeps printing proteins but with wrong letters — the faulty pages (proteins) tear the bacterium's own walls.
5. **Tetracyclines as a paused assembly line:** The delivery truck (tRNA) is blocked at the factory gate — nothing is built wrong, the line just waits.
6. **Cephalosporin generations as phone models:** Gen 1 is the sturdy basic phone (great for Gram-positive calls); each generation adds Gram-negative "network bands" until Gen 5 gets the MRSA "5G band".

7 **Aztreonam as a sniper:** One bullet, one target type — Gram-negative only; never wastes a shot on Gram-positive bacteria.

8 **Cotrimoxazole as a double roadblock:** Police block the road at kilometre 10 (sulfa) AND kilometre 11 (trimethoprim) — no folate truck gets through either way.

5.14 Pharmacy Relevance (what a pharmacist does with this)

1 **Allergy history before any β-lactam:** Ask every patient about penicillin allergy; keep aztreonam in mind as the Gram-negative alternative, and remember cephalosporin cross-allergy is possible.

2 **Counselling points:** Take amoxicillin-clavulanate with food (less stomach upset); finish the full course; take doxycycline with water (not milk/antacids) and avoid sunlight; warn about diarrhoea with clindamycin — report severe/bloody diarrhoea immediately.

3 **Monitoring:** Aminoglycosides — watch kidney function and hearing; chloramphenicol systemic use — watch blood counts (aplastic anaemia risk); sulfonamides — hydration (crystalluria) and rash (Stevens–Johnson warning signs).

4 **Rational combinations:** Dispense cotrimoxazole as the fixed 5:1 combination; never split it. For *H. pylori*, amoxicillin + clarithromycin + PPI is the classic triple therapy.

5 **Storage & stability:** Reconstituted amoxicillin/clavulanate suspensions need refrigeration and have short expiry — label the discard date. Clavulanate degrades in moisture.

6 **Antimicrobial stewardship:** Reserve 3rd/4th-generation cephalosporins, piperacillin-tazobactam, and carbapenem-sparing choices for genuine need; discourage OTC sale of antibiotics — a major driver of resistance in India.

5.15 India Context

- **Leprosy (NLEP):** India runs one of the world's largest leprosy programmes; dapsone remains part of the WHO multidrug therapy (rifampicin + clofazimine + dapsone) given free at government centres.
- **TB & streptomycin:** Streptomycin was once a mainstay of TB treatment under DOTS; it is now reserved for retreatment/drug-resistant cases because of resistance and injectable toxicity.
- **Typhoid:** Ceftriaxone/cefixime and azithromycin are frontline for typhoid in India, including extensively drug-resistant strains; chloramphenicol was the original typhoid drug in the 1950s–70s.
- **Co-amoxiclav overuse:** Amoxicillin-clavulanic acid is among the most sold (and most misused) antibiotics in Indian retail pharmacies — pharmacists are key to curbing unnecessary use.
- **Sulfa heritage:** Cotrimoxazole remains on India's essential medicines list and is used in national programmes (e.g., PCP prophylaxis in HIV care).
- **Scrub typhus:** Doxycycline is the drug of choice for scrub typhus, common in many Indian states during/after monsoon.

- **Burns:** Silver sulphadiazine cream and mafenide are stocked in Indian burn units; sulphadiazine's silver salt is the classic topical.

5.16 Key Points (rapid-fire)

1 Penicillins = 6-APA core; cephalosporins = 7-ACA core; monobactam = lone β-lactam + N–SO_3H.

2 C-6 side chain of penicillins decides spectrum: benzyl (natural), bulky ortho (penicillinase-resistant), α-amino (broad), α-carboxyl/ureido (antipseudomonal).

3 Cephalosporin generations 14: Gram-positive Gram-negative shift; 5th (ceftaroline) adds MRSA.

4 β-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam) are suicide decoys — never used alone.

5 Aminoglycosides: 30S misreading, bactericidal, need oxygen; oto-/nephrotoxic.

6 Tetracyclines: 30S tRNA blockade, bacteriostatic; C-4 dimethylamino essential; chelate calcium.

7 Macrolides: 50S translocation blockers; erythromycin 14-ring (acid-labile) clarithromycin (6-O-methyl, acid-stable) azithromycin (15-ring azalide, long half-life).

8 Chloramphenicol: 50S blocker; D-threo isomer only; rare fatal aplastic anaemia; synthesis = Henry reduce resolve dichloroacetylate.

9 Sulfonamides mimic PABA block dihydropteroate synthase; trimethoprim blocks dihydrofolate reductase; cotrimoxazole = sequential blockade (synergy).

10 Sulfa SAR: free para-NH_2 + para-SO_2NH– essential; N1 heterocycle tunes potency; N1–H pKa 6.5–7.4 optimal.

11 Dapsone = 4,4′-diaminodiphenyl sulfone; leprosy MDT; synthesis = couple oxidise reduce.

12 Clindamycin = 7-chloro lincomycin; anaerobes + MRSA skin; watch for *C. difficile* diarrhoea.

5.17 Common Confusions (don't mix these up)

Confusion	Clarification
Penicillin G vs Penicillin V	G = injectable, destroyed by acid; V = oral, acid-stable. Both natural, both penicillinase-sensitive.
Ampicillin vs Amoxicillin	Both aminopenicillins; amoxicillin is better absorbed orally (food-independent) — not stronger, just better behaved.
Sulbactam vs Tazobactam	Sulbactam pairs with ampicillin; tazobactam pairs with piperacillin. Don't swap the partners.
3rd vs 4th generation cephalosporins	3rd = ceftriaxone/cefotaxime/ceftazidime; 4th = cefepime (zwitterionic, porin-penetrating). Ceftaroline is 5th (MRSA).
Bactericidal vs bacteriostatic in this chapter	Cidal: penicillins, cephalosporins, aminoglycosides, cotrimoxazole (combo). Static: tetracyclines, macrolides, chloramphenicol, clindamycin, sulfonamides alone.

Confusion	Clarification
Sulphadiazine vs Sulfasalazine	Sulphadiazine = N1-pyrimidinyl sulfa (toxoplasmosis, burns as silver salt); sulfasalazine = azo prodrug for the colon (ulcerative colitis).
Mafenide vs other sulfas	Mafenide's $–NH_2$ sits on a $–CH_2–$ spacer (not directly on the ring) — it is NOT a PABA analogue in the strict sense; it works topically on burns.
Clavulanic acid vs penicillins	Clavulanate has almost no killing power alone — it is a protector, not a fighter.
Erythromycin vs Azithromycin ring	Erythromycin = 14-membered; azithromycin = 15-membered azalide (extra N).
Dapsone vs sulfonamides	Dapsone is a sulfone ($Ar–SO_2–Ar$), not a sulfonamide ($–SO_2NH–$), but blocks the same PABA enzyme.

5.18 Common Mistakes (exam hall errors)

1 Writing that cephalosporins have a 6-APA core — they have 7-ACA (6-membered dihydrothiazine ring).

2 Calling clavulanic acid an antibiotic used alone — it is always a combination partner.

3 Saying tetracyclines are bactericidal — they are bacteriostatic (aminoglycosides are the bactericidal 30S drugs).

4 Forgetting stereochemistry in chloramphenicol — only the D-threo isomer is active; mention the resolution step in synthesis.

5 Drawing dapsone with an –NH– in the sulfone bridge — it is $Ar–SO_2–Ar$, no nitrogen in the bridge.

6 Mixing up the two folate enzymes — sulfonamides block dihydropteroate synthase (Step 1); trimethoprim blocks dihydrofolate reductase (Step 2).

7 Stating sulfa drugs work in humans' folate pathway — humans don't synthesise folate; that's the selectivity.

8 Omitting reagents/conditions in synthesis answers — "Zn/HCl, then resolve with d-camphoric acid, then methyl dichloroacetate" earns marks; vague arrows don't.

9 Confusing "penicillinase-resistant" with "broad-spectrum" — cloxacillin is narrow (staph only); ampicillin is broad.

10 Writing aztreonam active against Gram-positive bacteria — it is strictly Gram-negative aerobes.

5.19 Mnemonics

- **Penicillin classes:** "**N**aughty **P**irates **A**te **A**ll **P**ears" — Natural, Penicillinase-resistant, Aminopenicillins, Antipseudomonal.
- **Cephalosporin generations 1–5:** "**L**ions **U**sually **T**ake **E**lephants **M**orningly" — cephaLexin, cefUroxime, cefTriaxone, cEfepime, ceftaroline (with **M** for MRSA at the end).

- **30S vs 50S:** "**Buy AT 30, CELL at 50**" — Aminoglycosides + Tetracyclines at 30S; Chloramphenicol, Erythromycin (macrolides), Linezolid-type, cLindamycin at 50S.
- **Cidal vs static:** "**Very Cidal AB**" — Very (cell-wall drugs: penicillins/cephalosporins), Cidal Aminoglycosides, Bactericidal combo (cotrimoxazole); the rest mostly static.
- **Sulfa SAR:** "**Para Pair, N1 with flair, pKa with care**" — para-NH_2 + para-SO_2NH essential; N1 heterocycle tunes; pKa ~7 optimal.
- **Chloramphenicol synthesis:** "**Henri Reduces Resolutions, then Caps**" — Henry (nitroaldol) → Reduce → Resolve → Cap with dichloroacetyl.
- **Dapsone synthesis:** "**Couple, Oxidise, Reduce**" — sulfide coupling → sulfone oxidation → nitro reduction.
- **β-lactamase inhibitor pairs:** "**CAM-SUL-TAZO**": Clavulanate-Amoxicillin, Sulbactam-Ampicillin, Tazobactam-piperacillin (alphabetical pairs: C-A, S-A, T-P).

5.20 Exam Summary (one page of everything)

β-lactams share a 4-membered β-lactam ring. **Penicillins** (6-APA: β-lactam + thiazolidine): natural (G, V) penicillinase-resistant (methicillin, oxacillin, cloxacillin — bulky ortho R) → aminopenicillins (ampicillin, amoxicillin — α-amino, broad) → antipseudomonal (carbenicillin, ticarcillin, piperacillin — acidic R). SAR: intact nucleus, cis C5–C6, free C3–COOH, C-6 R decides spectrum. MOA: fake D-Ala-D-Ala → acylate PBP transpeptidase → wall lysis (bactericidal). **Cephalosporins** (7-ACA: β-lactam + dihydrothiazine; tunable at C-7, C-3): Gen 1 (cephalexin, cefazolin — Gram+), Gen 2 (cefuroxime, cefoxitin — +Gram/anaerobes), Gen 3 (ceftriaxone, cefotaxime, ceftazidime — meningitis, typhoid, Pseudomonas), Gen 4 (cefepime — zwitterionic), Gen 5 (ceftaroline — MRSA). **β-lactamase inhibitors** (clavulanic acid — oxapenam from *S. clavuligerus*; sulbactam; tazobactam): suicide decoys, always combined (co-amoxiclav etc.). **Monobactam** aztreonam: lone β-lactam + N–SO_3H, Gram-negative only, penicillin-allergy-safe. **Aminoglycosides** (streptomycin: streptidine + streptose; neomycin: topical; kanamycin: MDR-TB): 30S misreading, bactericidal, oxygen-dependent; oto-/nephrotoxic. **Tetracyclines** (4-ring naphthacene; tetracycline, oxytetracycline, minocycline — C7-NMe_2, doxycycline — no C6-OH): 30S tRNA block, bacteriostatic; C4-NMe_2 and keto-enol essential; chelate Ca^{2+}. **Macrolides** (50S translocation blockers): erythromycin 14-ring acid-labile → clarithromycin 6-O-methyl acid-stable → azithromycin 15-ring azalide long half-life. **Chloramphenicol** (p-NO_2–C_6H_4–CH(OH)–CH($NHCOCHCl_2$)–CH_2OH, D-threo only): 50S peptidyl transferase blocker; meningitis/typhoid/eye; aplastic anaemia risk; synthesis: Henry condensation → nitro reduction → resolution → dichloroacetylation. **Clindamycin**: 7-chloro-lincomycin; anaerobes, MRSA skin; *C. difficile* risk. **Sulfonamides** (H_2N–C_6H_4–SO_2–NHR, para): PABA mimics → block dihydropteroate synthase; N1 heterocycle (sulphamethizole, sulfisoxazole, sulphapyridine, sulphathiazole, sulfacetamide — eye, sulphamethoxazole, sulphadiazine — toxoplasmosis/burns, mafenide — burns, sulfasalazine — azo prodrug for colon); SAR: free para-NH_2 essential, N1–H pKa 6.5–7.4 optimal. **Trimethoprim** blocks dihydrofolate reductase; **cotrimoxazole** (5:1) = sequential blockade, synergy. **Dapsone** (H_2N–C_6H_4–SO_2–C_6H_4–NH_2): leprosy MDT; synthesis: p-chloronitrobenzene + Na_2S → dinitro sulfide → oxidise to sulfone → reduce to diamine.

5.21 One-Minute Revision

Square ring = β-lactam. 6-APA + R at C-6 = penicillin (bulky R resists enzymes; amino R broadens; acidic R hits Pseudomonas). 7-ACA, Gens 1–5 = cephalosporins (later = more Gram-negative; 5th kills MRSA). Clavulanate/sulbactam/tazobactam = suicide bodyguards. Aztreonam = lone ring, Gram-negative only. 30S: aminoglycosides KILL by misreading (need O_2; ears/kidneys), tetracyclines PAUSE tRNA (4 rings; no milk). 50S: macrolides (1415 rings), chloramphenicol (D-threo; marrow risk), clindamycin (anaerobes; diarrhoea risk). Sulfa = fake PABA (para-NH_2 must be free) Step 1; trimethoprim Step 2; cotrimoxazole = double block = synergy. Dapsone = sulfone for leprosy (couple–oxidise–reduce). Chloramphenicol synthesis = Henry–reduce–resolve–cap.

5.22 Exam Questions

A. Short questions (2–5 marks)

1 Define 6-APA and 7-ACA. How do their fused ring systems differ?

2 Why is clavulanic acid never used alone?

3 Name two penicillinase-resistant penicillins and state the structural trick that gives resistance.

4 Which cephalosporin generation crosses the blood–brain barrier best? Give two examples.

5 Why do aminoglycosides fail against anaerobic bacteria?

6 What is sequential blockade? Which drug combination demonstrates it, and in what ratio?

7 Why should tetracyclines not be taken with milk or antacids?

8 State the structural difference between erythromycin and azithromycin and its clinical consequence.

9 Why is only the D-threo isomer of chloramphenicol active?

10 Write the structure (in words) of dapsone and give its two main uses.

B. Long questions (10–15 marks)

1 Classify penicillins with structures (describe scaffolds) and give one use of each drug. Add the SAR of penicillins as a rule table.

2 Describe the five generations of cephalosporins with two examples each, their spectra, and uses. Include the SAR of cephalosporins.

3 Write the complete synthesis of chloramphenicol with numbered steps, reagents, conditions, and intermediates. Explain why the resolution step is necessary.

4 Write the complete synthesis of dapsone. Explain its mechanism of action and its role in leprosy multidrug therapy.

5 Explain the mechanism of action of sulfonamides with a labelled flowchart of the folic acid pathway. Describe the SAR of sulfonamides as a rule table and explain the synergy of cotrimoxazole.

6 Compare aminoglycosides, tetracyclines, and macrolides under: core structure, ribosomal target, bactericidal/bacteriostatic nature, and one key toxicity each.

C. MCQs (with answer key)

1 The parent nucleus of penicillins is:

a) 7-ACA b) 6-APA c) Naphthacene d) Macrocyclic lactone — **Answer: b**

1 Which substituent makes a penicillin penicillinase-resistant?

a) α-amino group b) Bulky ortho-substituted aromatic ring c) α-carboxyl group d) N-sulfonic acid — **Answer: b**

1 Ceftaroline belongs to which cephalosporin generation?

a) 3rd b) 4th c) 5th d) 2nd — **Answer: c**

1 Clavulanic acid is best described as a:

a) Bactericidal antibiotic b) Suicide inhibitor of β-lactamase c) 30S binder d) Folate blocker — **Answer: b**

1 Aztreonam is active against:

a) Gram-positive cocci b) Anaerobes c) Aerobic Gram-negative bacteria only d) Fungi — **Answer: c**

1 Streptomycin kills bacteria by:

a) Blocking tRNA docking b) Causing misreading of mRNA at 30S c) Blocking translocation at 50S d) Inhibiting cell-wall synthesis — **Answer: b**

1 Which position's dimethylamino group is essential in tetracyclines?

a) C-5 b) C-4 c) C-7 d) C-6 — **Answer: b**

1 Clarithromycin differs from erythromycin by:

a) 15-membered ring b) 6-O-methyl group c) N-methyl at 9a d) Dichloroacetyl tail — **Answer: b**

1 The active stereoisomer of chloramphenicol is:

a) L-erythro b) D-threo c) D-erythro d) Racemic — **Answer: b**

1 Sulfonamides block which enzyme?

a) Dihydrofolate reductase b) Dihydropteroate synthase c) Transpeptidase d) DNA gyrase — **Answer: b**

1 Trimethoprim inhibits:

a) Dihydropteroate synthase b) Dihydrofolate reductase c) Peptidyl transferase d) β-lactamase — **Answer: b**

1 The ratio of sulphamethoxazole to trimethoprim in cotrimoxazole is:

a) 1:1 b) 5:1 c) 1:5 d) 2:1 — **Answer: b**

1 Dapsone is chemically a:

a) Sulfonamide b) Sulfone c) β-lactam d) Macrolide — **Answer: b**

1 Which sulfa drug is an azo prodrug acting in the colon?

a) Sulphadiazine b) Sulfasalazine c) Sulfacetamide d) Mafenide — **Answer: b**

1 Ototoxicity and nephrotoxicity are characteristic of:

a) Penicillins b) Aminoglycosides c) Macrolides d) Sulfonamides — **Answer: b**

D. Viva questions (with answers)

1 **Q: What is the β-lactam ring?** A: A four-membered cyclic amide; the shared weapon of penicillins, cephalosporins, monobactams, and β-lactamase inhibitors.

2 **Q: Why do penicillins kill only growing bacteria?** A: They block wall building (transpeptidase); resting bacteria aren't building walls, so there's nothing to block.

3 **Q: Name the β-lactamase inhibitor from a natural source.** A: Clavulanic acid, from *Streptomyces clavuligerus*.

4 **Q: Which aminoglycoside is only for topical use, and why?** A: Neomycin — too ototoxic/nephrotoxic for systemic injection.

5 **Q: Doxycycline vs tetracycline — one structural difference?** A: Doxycycline lacks the C-6 hydroxyl longer half-life, once-daily dosing.

6 **Q: Why is azithromycin given for only 3 days?** A: 15-membered azalide structure gives a very long half-life and deep tissue penetration.

7 **Q: What makes cotrimoxazole synergistic?** A: Sequential blockade — sulphamethoxazole blocks folate Step 1, trimethoprim blocks Step 2.

8 **Q: Which sulfa drug is used in the eye?** A: Sulfacetamide (drops/ointment for conjunctivitis).

9 **Q: Reagents for dapsone's final step?** A: Reduction of 4,4′-dinitrodiphenyl sulfone with Sn/HCl (or H_2–Pd/C) to the diamine.

10 **Q: Why don't sulfa drugs harm human folate metabolism?** A: Humans absorb ready-made folate from food; we don't synthesise it via the PABA pathway.

E. Application-based questions

1 **Case:** A 6-year-old with streptococcal pharyngitis is allergic to penicillin (rash). Which macrolide would you choose and why? *(Hint: acid-stable, good taste, paediatric suspension — consider erythromycin vs azithromycin dosing convenience.)*

2 **Case:** A farmer with a deep, dirty wound needs anaerobic cover but has a history of severe antibiotic-associated diarrhoea. Which drug from this chapter fits, and what warning would you give? *(Hint: clindamycin covers anaerobes but carries C. difficile risk — counsel and monitor.)*

3 **Case:** A traveller to a scrub-typhus-endemic district of India asks for prevention advice. Which drug from this chapter is relevant, and what counselling points apply? *(Hint: doxycycline prophylaxis; take with water not milk, sun protection.)*

4 **Case:** A leprosy patient is prescribed dapsone + rifampicin + clofazimine. Explain to a junior pharmacist why three drugs are used instead of dapsone alone. *(Hint: multidrug therapy prevents resistance — same principle as TB treatment.)*

5 **Case:** A hospital wants to reserve one β-lactam for penicillin-allergic patients with *Pseudomonas* pneumonia. Justify your choice from this chapter. *(Hint: aztreonam — monobactam, Gram-negative only, minimal cross-allergy.)*

5.23 References

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