B.PHARM SEMESTER IV · BP402T

BP402T Medicinal Chemistry

Unit II — Drugs Acting on the Autonomic Nervous System

Final Unit Notes

Chapters 3–8 · Adrenergic agents · Anti-adrenergic agents · Cholinergic agents · Anti-cholinergic agents · Local anesthetic agents · Synthesis handbook

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Chapter 3 — Adrenergic (Sympathomimetic) Agents

BP402T Medicinal Chemistry (Theory) | Unit II Language: very simple English, taught from absolute zero

This chapter studies **adrenergic drugs** — medicines that copy the action of the body's own "fight-or-flight" chemicals, adrenaline and noradrenaline. For every one of the 18 drugs in this chapter 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. Two starred drugs (Phenylephrine *and Salbutamol*) have their full **syntheses** given in **Chapter 8 (Synthesis Handbook)**, where all syntheses are consolidated — so no synthesis steps appear in this chapter. The chapter closes with the structure–activity rules that explain *why* small structural changes switch a drug from the heart to the lungs.

1. Learning Objectives

After studying this chapter, you will be able to:

- Define the sympathetic nervous system, sympathomimetic, adrenergic receptor, agonist, catecholamine, and the fight-or-flight response in simple words.
- Draw and explain the alpha vs beta receptor table (α1, α2, β1, β2 — location and effect).
- Classify sympathomimetics chemically into catecholamines vs non-catecholamines, with the definition of the catechol group.
- Classify sympathomimetics by action into direct-acting, indirect-acting and mixed-acting, with examples from the 18-drug list.
- Build the receptor-selectivity table: which drugs are mainly α1, α2, β1 or β2 agonists.
- Describe the chemical structure (scaffold + key substituents) of all 18 drugs in the list.
- State 1–3 therapeutic uses of each of the 18 drugs.
- Explain why the two catechol –OH groups cause poor oral activity (COMT metabolism), what the β–OH does, and how N-substituent size shifts selectivity from alpha to beta.
- Distinguish epinephrine vs norepinephrine vs phenylephrine by structure and use.
- Draw the phenethylamine scaffold, the classification flowchart, and the direct-vs-indirect mechanism flowchart.
- Answer MCQs, viva questions and application-based questions on this chapter.

2. Definitions

Sympathetic nervous system. The sympathetic nervous system is one of the two branches of the *autonomic* (automatic, not under our conscious control) nervous system. It is the body's **"emergency branch"** — it switches ON when you face danger, fear, exercise or stress. Its chemical messengers are **noradrenaline (norepinephrine)** released from nerve endings and **adrenaline (epinephrine)** released from the adrenal glands (two small glands sitting on top of the kidneys).

Fight-or-flight response. The fight-or-flight response is the body's emergency programme: heart beats faster and stronger, airways widen, blood moves to muscles, pupils widen, digestion slows. "Fight" = stay and face the danger; "flight" = run away. Both need extra energy, so the sympathetic system prepares the body in seconds.

Sympathomimetic. A sympathomimetic is a drug that **mimics (copies)** the sympathetic nervous system — it produces fight-or-flight effects. "Sympatho" = sympathetic, "mimetic" = imitator. Example: salbutamol copies adrenaline's airway-widening effect to relieve asthma.

Adrenergic drug / adrenergic receptor. "Adrenergic" means "acting like adrenaline." An **adrenergic receptor** is a protein switch on the cell surface that adrenaline and noradrenaline turn ON. An **adrenergic drug** is any drug that acts on these receptors. (Sympathomimetic and adrenergic agonist mean the same thing in this chapter.)

Agonist. An agonist is a drug that **binds to a receptor and switches it ON**, producing the receptor's natural effect. All 18 drugs in this chapter are agonists. (The opposite — a drug that blocks the receptor — is an *antagonist*, e.g., propranolol; antagonists are not in this chapter.)

Alpha (α) and beta (β) receptors. Adrenergic receptors come in two big families, **alpha** and **beta**, each with sub-types. Which sub-type a drug switches on decides what the drug does: α1 mainly tightens blood vessels, α2 in the brain lowers blood pressure, β1 mainly stimulates the heart, β2 mainly relaxes the airways. The full table is in Section 4.

Vasoconstriction / vasodilation. Vasoconstriction = narrowing of blood vessels ("constrict" = squeeze tight). Vasodilation = widening of blood vessels. α1 agonists cause vasoconstriction → blood pressure rises.

Bronchodilation. Bronchodilation = widening (relaxation) of the bronchi, the air tubes in the lungs. β2 agonists cause bronchodilation → easier breathing in asthma.

Mydriasis. Mydriasis = widening (dilation) of the pupil of the eye. α1 agonists cause mydriasis — used by eye doctors to examine the inside of the eye.

Pressor. A pressor is a drug that **presses blood pressure upward** — it raises low blood pressure. Norepinephrine, phenylephrine and metaraminol are pressors, given by IV drip in shock.

Decongestant. A decongestant is a drug that relieves a blocked ("congested") nose. α1 agonists shrink the swollen nasal lining → the nose opens up. Used in colds and allergies.

Tocolytic. A tocolytic is a drug that relaxes the uterus (womb) to **stop premature labour** (labour starting too early). β2 agonists like terbutaline and salbutamol are tocolytics.

Anaphylaxis. Anaphylaxis is a sudden, life-threatening allergic reaction — blood pressure crashes, airways close, the patient can die in minutes. **Epinephrine is the drug of choice** (the single best drug) for anaphylaxis.

Shock. Shock is a medical emergency in which blood pressure falls so low that organs stop receiving enough blood. Pressor sympathomimetics (norepinephrine, dopamine, dobutamine) are given by IV infusion to keep patients alive.

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 phenethylamine chain is the scaffold of most drugs in this chapter.
Substituent	A group of atoms attached to the scaffold, e.g., –OH, $–CH_3$, $–NHCH_3$. Substituents fine-tune what the drug does.
Catechol	A benzene ring carrying **two –OH groups next to each other** (adjacent positions, 1,2). The full name is benzene-1,2-diol. The two adjacent –OH groups are the "catechol" signature.
Phenethylamine	Phenyl (benzene ring) + ethyl (2-carbon chain) + amine (nitrogen) — the common scaffold of this chapter: ring–CH_2–CH_2–NH–. Almost every drug here is a substituted phenethylamine.
β-carbon / β–OH	In the phenethylamine chain, the carbon **next to the ring** is the α-carbon and the one **next to the nitrogen** is the β-carbon. A –OH on the β-carbon (β–OH) is found in adrenaline, noradrenaline and many others, and helps direct receptor binding.
Resorcinol	A benzene ring with two –OH groups **separated by one carbon** (positions 1,3 — meta to each other), NOT adjacent. Terbutaline has a resorcinol ring — this single change makes it resist COMT and act longer.
Imidazoline	A five-membered ring containing two nitrogens and one double bond — the scaffold of naphazoline, oxymetazoline, xylometazoline and clonidine.
Prodrug	An inactive (or less active) compound that the body converts into the active drug. Example: bitolterol → colterol; methyldopa → α-methylnorepinephrine.
COMT	**Catechol-O-methyltransferase** — an enzyme that attaches a methyl ($–CH_3$) group to one –OH of the catechol ring, switching the drug OFF. It is the main reason catecholamines cannot be given orally.
MAO	**Monoamine oxidase** — an enzyme that destroys amine drugs by removing the nitrogen part. A second reason catecholamines are short-acting.
Bioavailability	How much of a swallowed drug actually reaches the blood. Catecholamines have very poor oral bioavailability (COMT + MAO destroy them in the gut and liver).
Blood–brain barrier	The tight wall of blood vessels in the brain that keeps most drugs out. Catecholamines cannot cross it; clonidine and methyldopa's metabolite can — that is why they act in the brain.
Selectivity	When a drug switches on mainly ONE receptor sub-type (e.g., salbutamol is β2-selective), it is called selective. Selective drugs have fewer side effects.
Enantiomer	One of a pair of mirror-image forms of a molecule (left-hand vs right-hand). Many drugs here are used as a single enantiomer (the R-form of adrenaline).
Tachyphylaxis	Rapid loss of drug effect with repeated doses — seen with indirect-acting drugs (hydroxyamphetamine, propylhexedrine) because the stored noradrenaline runs out.

4. Explanation: the sympathetic system, fight-or-flight, and the receptor map

Technical concept. Danger signals reach the brain → sympathetic nerves fire → nerve endings release **norepinephrine** and the adrenal medulla releases **epinephrine** into blood → these bind adrenergic receptors (α1, α2, β1, β2) on target organs → each receptor produces its own effect. Sympathomimetic drugs copy this by binding the same receptors.

Simple explanation. Imagine a fire alarm in a building. The sympathetic system is the alarm network: sensors (nerves) detect fire (danger), the control room (brain/adrenal gland) sounds the alarm (releases adrenaline/noradrenaline), and every room has a different type of bell (α1, α2, β1, β2 receptors) that rings a different response — the heart room beats faster, the lung room opens its windows, the blood-vessel room tightens its pipes. A sympathomimetic drug is like a **spare alarm key** that can ring any chosen bell directly, without a real fire.

Example. In an asthma attack the lung's airways tighten (bronchospasm). Salbutamol is a spare key cut only for the β2 bell in the lungs — it rings bronchodilation, the airways relax, and breathing eases, without strongly ringing the heart's β1 bell.

Key takeaway. Sympathomimetics = spare keys for the body's emergency bells (adrenergic receptors); the bell type (α1/α2/β1/β2) decides the effect.

The alpha vs beta receptor table (learn this by heart)

Receptor	Main locations	What switching it ON does	Simple memory hook
α1	Blood-vessel walls, eye (iris radial muscle), nasal lining	Vessels **constrict** → blood pressure rises; pupil **dilates** (mydriasis); nasal lining shrinks → nose unblocks	"α1 = tightens"
α2	Brain (nerve centres), nerve endings	In the brain: **reduces sympathetic outflow** → blood pressure **falls**; on nerve endings: reduces noradrenaline release	"α2 = calms the brain"
β1	Heart (mainly)	Heart beats **faster and stronger** → more blood pumped	"β1 = **1 heart**"
β2	Lungs (bronchi), uterus, liver	Airways **relax/widen** (bronchodilation); uterus relaxes; liver releases glucose	"β2 = **2 lungs**"

How to read a drug's effect from this table: find which receptors it switches on, then read across. Example: phenylephrine = pure α1 → vessels constrict (BP rises, nose unblocks) + pupil dilates, but heart and lungs are untouched. Salbutamol = β2 → airways widen, uterus relaxes.

Fight-or-flight flowchart (draw as 6 boxes with arrows)

Box 1: "Danger / stress / exercise sensed" → Box 2: "Brain activates sympathetic nerves + adrenal glands" → Box 3: "Norepinephrine released at nerve endings; epinephrine released into blood" → Box 4: "They bind α1, α2, β1, β2 receptors" → Box 5: "Organ responses: heart faster/stronger (β1), airways widen (β2), vessels constrict (α1), pupils dilate (α1)" → Box 6: "Body ready to fight or run — a sympathomimetic drug enters at Box 4, skipping Boxes 1–3."

5. Chemical classification of sympathomimetics

Technical concept. The 18 drugs are classified three ways: (a) by the **ring chemistry** — does the molecule carry a catechol ring or not; (b) by **how** it produces the effect — binding the receptor directly, or forcing nerves to release stored noradrenaline; (c) by **which receptor** it prefers.

Simple explanation. Think of three different attendance registers for the same class of 18 students: Register A groups them by uniform (catechol ring or not), Register B groups them by behaviour (direct talkers, indirect whisperers, or both), and Register C groups them by favourite subject (α1, α2, β1 or β2).

Key takeaway. Every drug in this chapter has three labels — e.g., salbutamol = non-catecholamine + direct-acting + β2-selective.

(a) Catecholamines vs non-catecholamines

Technical concept. A **catecholamine** is a phenethylamine whose benzene ring carries the **catechol** group — two adjacent –OH groups (benzene-1,2-diol). A **non-catecholamine** sympathomimetic has any other ring pattern (one –OH, resorcinol 1,3-diol, saligenin-type, imidazoline, or no phenolic –OH at all).

Simple explanation. The catechol ring is like a double handle — two –OH groups side by side. Drugs carrying this double handle are the body's own chemicals and their closest copies; they are powerful but fragile (the body's COMT enzyme snips the handle off quickly). Drugs with a different ring pattern are tougher — they survive in the gut and last longer.

Catecholamines (6): Norepinephrine, Epinephrine, Dopamine, Dobutamine, Isoproterenol, Bitolterol (its active form colterol carries the catechol, hidden under ester "covers" in the prodrug).

Non-catecholamines (12): Phenylephrine (single meta –OH), Methyldopa (catechol ring but acts via a non-catecholamine metabolite — grouped here by its central α2 action; note it for exams), Clonidine (imidazoline), Terbutaline (resorcinol ring), Salbutamol (saligenin-type ring: one –OH + one –CH_2OH), Naphazoline, Oxymetazoline, Xylometazoline (imidazolines), Hydroxyamphetamine (single para –OH), Pseudoephedrine (no phenolic –OH), Propylhexedrine (cyclohexane ring, no benzene –OH at all), Metaraminol (single meta –OH).

Example. Adrenaline (epinephrine) has the double –OH handle → catecholamine → destroyed by COMT in the gut → must be injected. Salbutamol replaced one –OH with –CH_2OH → no catechol → survives the gut and the lung → works as an inhaler and tablet.

Key takeaway. Catechol = two adjacent ring –OH groups = body's own pattern = potent but short-acting and injectable; non-catechol = modified ring = orally active and longer-acting.

(b) Direct-acting vs indirect-acting vs mixed-acting

Technical concept. A **direct-acting** sympathomimetic binds the adrenergic receptor itself and switches it ON. An **indirect-acting** sympathomimetic does not touch the receptor — it enters the nerve ending and **forces the release of stored noradrenaline**, which then switches the receptor ON. A **mixed-acting** drug does both.

Simple explanation. Direct drugs knock on the door themselves. Indirect drugs don't knock — they push someone already inside the house (stored noradrenaline) to open the door. Mixed drugs do a bit of both.

Type	How it works	Drugs from our list of 18
Direct-acting (14)	Binds the receptor itself	Norepinephrine, Epinephrine, Phenylephrine, Dopamine*, Dobutamine, Isoproterenol, Terbutaline, Salbutamol, Bitolterol (as colterol), Methyldopa (as α-methylnorepinephrine), Clonidine, Naphazoline, Oxymetazoline, Xylometazoline, Metaraminol
Indirect-acting (2)	Releases stored noradrenaline from nerve endings; little/no direct receptor binding	Hydroxyamphetamine, Propylhexedrine
Mixed-acting (2)	Both direct binding AND noradrenaline release	Pseudoephedrine, Dopamine*

*Dopamine is counted in both rows because it directly stimulates D/β/α receptors AND releases noradrenaline — the classic mixed-acting catecholamine.

Example. Hydroxyamphetamine eye drops widen the pupil without touching the eye's receptors directly — they make the eye's own nerves dump noradrenaline, which then dilates the pupil. If the nerve is damaged (Horner syndrome), no noradrenaline is stored → the drops fail — and that failure is itself the diagnostic test.

Key takeaway. Direct = binds the receptor; indirect = releases stored noradrenaline (shows tachyphylaxis — effect fades as stores empty); mixed = both (pseudoephedrine, dopamine).

(c) Receptor-selectivity table

Technical concept. Selectivity = which receptor sub-type the drug switches on most strongly at ordinary doses. High doses can spill over to other receptors.

Main receptor target	Drugs (from our 18)
α1 (mainly)	Phenylephrine, Metaraminol, Naphazoline, Oxymetazoline, Xylometazoline
α2 — central (brain)	Clonidine, Methyldopa (via its metabolite α-methylnorepinephrine)
β1 (mainly)	Dobutamine
β2 (mainly)	Salbutamol, Terbutaline, Bitolterol (as colterol)
α + β (non-selective, mixed)	Epinephrine (α1, α2, β1, β2 — everything), Norepinephrine (α1, α2, β1; very little β2), Dopamine (D1/D2 + β1 + α1, dose-dependent)
β1 + β2 (pure beta, non-selective)	Isoproterenol

How selectivity changes with dose — the dopamine ladder (classic exam point):

- Low dose → **D1/D2 (dopamine) receptors** → kidney and gut vessels dilate.
- Medium dose → **β1** → heart beats stronger.
- High dose → **α1** → vessels constrict → blood pressure rises. Simple hook: "Dopamine climbs the ladder D → β → α as the dose rises."

6. Key structural features (SAR highlights — why small changes matter)

Technical concept. SAR = structure–activity relationship: how each part of the phenethylamine molecule controls receptor binding, metabolism and selectivity. Four features rule this chapter.

Rule 1 — The two catechol –OH groups: the COMT problem. The catechol –OH groups grip the receptor tightly (hydrogen bonds), giving strong activity — but the enzyme **COMT methylates one –OH**, and **MAO** attacks the amine, so catecholamines are destroyed in the gut and liver within minutes. Result: **poor oral bioavailability, short duration, must be injected or inhaled**, and they cannot cross the blood–brain barrier. *Simple version:* the double –OH handle is a great grip but also a bright target for the body's security enzymes — the drug is caught and destroyed before it can work by mouth. *Example:* adrenaline works brilliantly by injection but is useless as a swallowed tablet.

Rule 2 — The β–OH group. A –OH on the β-carbon (the carbon next to the nitrogen) adds a hydrogen-bond grip that **favours direct receptor binding** (adrenaline, noradrenaline, ephedrine-type drugs all carry it). Removing it (dopamine, dobutamine) is tolerated but changes the profile. *Simple version:* the β–OH is an extra finger that helps the key turn directly in the receptor lock.

Rule 3 — The size of the N-substituent: the alpha → beta slide. This is the single most-tested SAR rule in this chapter. On the nitrogen, as the alkyl group grows larger, **alpha activity falls and beta activity rises**:

- **N–H (no substituent, primary amine)** — norepinephrine: strong α + β1, almost no β2.
- **N–CH_3 (methyl)** — epinephrine: full α + β (β2 appears).
- **N–$CH(CH_3)_2$ (isopropyl)** — isoproterenol: pure β (α lost).
- **N–$C(CH_3)_3$ (tert-butyl)** — salbutamol, terbutaline: **β2-selective** (β1 weak). *Simple version:* the nitrogen wears a cap; a small cap fits the alpha lock, a big bulky cap only fits the beta lock — and the biggest cap (tert-butyl) fits the β2 lock best. *Memory hook:* "Bigger the N-cap, more the beta."

Rule 4 — Ring changes that beat COMT. Replacing the catechol ring defeats COMT because the enzyme only recognises the adjacent double –OH:

- **Resorcinol ring (1,3-diol)** — terbutaline: COMT-resistant → oral activity, longer action.
- **Saligenin-type ring (–OH + –CH_2OH)** — salbutamol: COMT-resistant → inhaler/tablet, longer action.
- **Single phenolic –OH** — phenylephrine, metaraminol: COMT-resistant, orally active, α1-selective.
- **Imidazoline ring instead of phenethylamine** — naphazoline, oxymetazoline, xylometazoline, clonidine: totally different scaffold, α-active, long-acting. *Simple version:* change the ring pattern and the COMT security guard no longer recognises the drug — it survives to work by mouth or as a long-acting nasal spray.

Key takeaway of this section. Catechol –OH = strong but COMT-destroyed (inject only); β–OH = direct binding helper; bigger N-alkyl = alpha → beta shift (tert-butyl = β2); non-catechol rings = COMT-proof = oral/long-acting.

7. Diagrams (describe textually so they can be drawn)

Diagram 1 — The phenethylamine scaffold (the mother structure). Draw a hexagon (benzene ring) on the left. From its right side draw a 2-carbon chain: label the carbon next to the ring "α-carbon" and the next one "β-carbon". Attach –NH–R to the β-carbon. Write the general formula beneath: **ring–CH_2–CH(β-OH)–NH–R** (most active drugs carry the β–OH). Mark with arrows: "catechol –OH groups go here (positions 3,4 of the ring)", "N-substituent R goes here — size decides α vs β".

Diagram 2 — The catechol ring close-up. Draw a benzene hexagon; at two adjacent corners draw –OH groups and circle them together with the label "**catechol = benzene-1,2-diol (two adjacent –OH)**". Beside it draw a resorcinol ring (OH groups separated by one carbon, labelled "NOT catechol — COMT-resistant") and a phenol ring (single –OH, labelled "NOT catechol").

Diagram 3 — The N-substituent ladder (draw as 4 rungs). Rung 1: "–H (norepinephrine) → α + β1". Rung 2: "–CH_3 (epinephrine) → α + β1 + β2". Rung 3: "–$CH(CH_3)_2$ (isoproterenol) → β1 + β2 only". Rung 4: "–$C(CH_3)_3$ (salbutamol, terbutaline) → β2 selective". Title: "Bigger N-cap → more beta".

Diagram 4 — Direct vs indirect action (two panels). Panel A (direct): draw a receptor (Y-shape) on a cell; an arrow from a drug capsule straight to the receptor labelled "drug binds receptor itself — e.g., phenylephrine → α1". Panel B (indirect): draw a nerve ending containing dots (stored noradrenaline); an arrow from a drug capsule into the nerve ending, then dots flying out to the receptor, labelled "drug releases stored noradrenaline — e.g., hydroxyamphetamine; stores can run out → tachyphylaxis".

8. Infographic concept box — "The Adrenergic Family Tree"

One-page visual for revision: draw a tree. The **trunk** is the phenethylamine scaffold (ring–CH_2–CH_2–NH–). The trunk splits into two big branches: **Catecholamines** (left branch, 6 leaves: NE, Epi, Dopamine, Dobutamine, Isoproterenol, Bitolterol — paint the leaves with the double –OH "handle" icon and a syringe icon = injectable) and **Non-catecholamines** (right branch, 12 leaves grouped into 4 twigs: single-OH twig — phenylephrine, metaraminol, hydroxyamphetamine; resorcinol/saligenin twig — terbutaline, salbutamol with a tablet icon = orally active; imidazoline twig — naphazoline, oxymetazoline, xylometazoline, clonidine with a nose-spray icon; no-ring-OH twig — pseudoephedrine, propylhexedrine, methyldopa). Across the top, hang four coloured receptor balloons — α1 (red: vessels), α2 (blue: brain), β1 (orange: heart), β2 (green: lungs) — with strings connecting each leaf to its balloon(s). At the tree's roots write the golden rule: "Bigger N-cap → more beta; catechol –OH → COMT eats it."

9. Drug-by-drug profiles — structure and uses

A. CATECHOLAMINES (direct-acting; carry the double –OH handle)

1. Norepinephrine (noradrenaline, NE)

- **Chemical classification:** Catecholamine; endogenous neurotransmitter; direct-acting mixed α + β agonist.
- **Structure: Catechol ring** (benzene with adjacent –OH at 3,4) + side chain **–CH(OH)–CH_2–NH_2**: a β–OH on the β-carbon and a **primary amine** (N–H, no N-substituent). The small N-cap explains its profile: strong α1/α2 and β1, almost no β2. Used as the bitartrate salt; the natural (R)-enantiomer is active.
- **Uses:** (1) **Septic shock and severe hypotension** — IV infusion, the first-choice pressor in ICUs (α1 vasoconstriction raises BP; β1 supports the heart); (2) hypotension after spinal anaesthesia.

2. Epinephrine (adrenaline)

- **Chemical classification:** Catecholamine; endogenous adrenal hormone; direct-acting **non-selective** α + β agonist (switches on α1, α2, β1 and β2).
- **Structure: Catechol ring** + side chain **–CH(OH)–CH_2–NH–CH_3**: β–OH plus an **N-methyl (secondary amine)**. Compared with norepinephrine, the single extra methyl on nitrogen adds full β2 activity ("methyl = the β2 ticket"). Active form is the (R)-enantiomer.
- **Uses:** (1) **Anaphylaxis** — IM injection, the drug of choice (α1 raises crashed BP, β2 opens closed airways, β1 restarts a failing heart — one drug fixes all three emergencies); (2) **cardiac arrest** — IV/IO during CPR; (3) **status asthmaticus** (severe asthma attack, when inhalers fail); (4) with local anaesthetics (e.g., lignocaine + adrenaline) — vasoconstriction keeps the anaesthetic at the site longer and reduces bleeding; (5) open-angle glaucoma and nasal/surgical haemostasis.

3. Dopamine

- **Chemical classification:** Catecholamine; endogenous neurotransmitter; **mixed-acting** (direct receptor stimulation + releases noradrenaline); dose-dependent receptor profile.
- **Structure: Catechol ring** + side chain **–CH_2–CH_2–NH_2**: a **primary amine with NO β–OH** — the simplest catecholamine, the metabolic precursor of norepinephrine. Given as dopamine hydrochloride IV infusion.
- **Uses:** (1) **Shock with hypotension** (cardiogenic/septic) — IV infusion; low dose acts on dopamine D1/D2 receptors (kidney vessels dilate), medium dose on β1 (heart stronger), high dose on α1 (BP rises); (2) acute heart failure with low output.

4. Dobutamine

- **Chemical classification:** Synthetic catecholamine; direct-acting, **β1-selective** agonist (the heart-selective catecholamine).
- **Structure: Catechol ring** + ethylamine chain **without β–OH**, carrying a very **bulky N-substituent**: –NH–CH(CH_3)–CH_2–CH_2–(4-hydroxyphenyl), i.e., an N-[1-methyl-3-(4-hydroxyphenyl)propyl] group. The big N-cap (Rule 3) wipes out α activity and the molecule is used as the racemate — the (+) enantiomer drives β1 stimulation. Dobutamine hydrochloride IV infusion.
- **Uses:** (1) **Cardiogenic shock and acute decompensated heart failure** — strengthens the heartbeat (β1) with less BP rise and less arrhythmia than dopamine; (2) **pharmacologic cardiac stress testing** — dobutamine stress echo, for patients who cannot exercise on a treadmill.

5. Isoproterenol (isoprenaline)

- **Chemical classification:** Synthetic catecholamine; direct-acting **pure β agonist** (β1 + β2, no α activity).
- **Structure: Catechol ring** + side chain **–CH(OH)–CH_2–NH–CH(CH_3)$_2$**: β–OH plus an **N-isopropyl group**. The isopropyl cap is the textbook example of Rule 3 — bigger than methyl, so α activity is completely lost and only β remains.
- **Uses:** (1) **Bradycardia and heart block** — emergency IV to speed a dangerously slow heart before a pacemaker is fitted (β1); (2) historically **status asthmaticus** (β2) — now replaced by selective β2 drugs like salbutamol.

6. Bitolterol

- **Chemical classification:** Catecholamine **prodrug**; direct-acting **β2-selective** agonist (after activation).
- **Structure:** The active molecule **colterol** is a catecholamine with an **N-tert-butyl** side chain — **4-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,2-diol**. In bitolterol the two catechol –OH groups are **masked as di-p-toluate esters** (each –OH is esterified with p-toluic acid). Body esterases hydrolyse the esters → colterol is released in the lung. The ester mask protects the catechol from COMT during delivery.
- **Uses:** (1) **Bronchospasm in asthma and COPD** — inhaled bronchodilator (β2). Largely superseded by salbutamol/terbutaline in current practice — remember it as the classic prodrug example.

B. NON-CATECHOLAMINE DIRECT-ACTING AGENTS

7. Phenylephrine*

- **Chemical classification:** Non-catecholamine phenethylamine; direct-acting **selective α1 agonist**.
- **Structure:** A benzene ring with a **single phenolic –OH at the meta position (position 3)** — NOT a catechol (only one –OH, so COMT cannot touch it) + side chain **–CH(OH)–CH_2–NH–CH_3**: β–OH and N-methyl, exactly like epinephrine's side chain, but the ring has lost one –OH. Losing that –OH costs all β activity → pure α1. Used as phenylephrine hydrochloride.
- **Uses:** (1) **Nasal decongestant** — oral tablets/syrups and nasal drops for cold and allergy (α1 shrinks swollen nasal lining); (2) **mydriatic eye drops** — dilates the pupil for eye examination; (3) **hypotension** — IV bolus/infusion to raise BP in anaesthesia and shock; (4) prolongs local anaesthesia and treats priapism.
- > **NOTE — synthesis:** Phenylephrine* synthesis is given in full in **Chapter 8 (Synthesis Handbook)**. All syntheses are consolidated there; no steps are repeated in this chapter.

8. Methyldopa

- **Chemical classification:** α-Methyl analogue of DOPA (a substituted phenylalanine); **prodrug** converted in the body to a **central α2 agonist**.
- **Structure:** A **catechol ring** attached to an α-methyl amino-acid side chain: **3-(3,4-dihydroxyphenyl)-2-methylalanine** — i.e., DOPA with an extra methyl on the α-carbon. The L-isomer (levorotatory) is used. In the brain, dopa decarboxylase → **α-methyldopamine**, then dopamine β-hydroxylase → **α-methylnorepinephrine**, which stimulates central α2 receptors → sympathetic outflow falls → BP falls.
- **Uses:** (1) **Hypertension in pregnancy** — the drug of choice (long safety record for mother and baby); (2) chronic hypertension (older first-line drug, now mostly reserved).

9. Clonidine

- **Chemical classification:** Imidazoline derivative; direct-acting **central α2 agonist** (non-catecholamine).
- **Structure:** Scaffold = **2-imidazoline ring** (five-membered, two nitrogens) joined through an **–NH– bridge** to a **2,6-dichlorophenyl ring** (benzene with chlorine atoms at both ortho positions). No phenethylamine chain, no phenolic –OH at all — a completely different scaffold that still fits adrenergic receptors. Lipophilic enough to cross the blood–brain barrier → acts in the brain. Clonidine hydrochloride tablets/patch.
- **Uses:** (1) **Hypertension** — central α2 action reduces sympathetic outflow; (2) **ADHD** in children; (3) **opioid/alcohol withdrawal** — calms sympathetic overactivity; (4) menopausal flushing, Tourette syndrome, and as an adjunct in pain management.

10. Terbutaline

- **Chemical classification:** Non-catecholamine phenethylamine; direct-acting **β2-selective** agonist.
- **Structure:** A **resorcinol ring** — benzene with two –OH groups at **positions 1 and 3 (meta to each other, NOT adjacent)** — + side chain **–CH(OH)–CH_2–NH–$C(CH_3)_3$**: β–OH and a bulky **N-tert-butyl** group. Two COMT-defeating tricks in one molecule: the resorcinol ring (COMT needs adjacent –OH) and the tert-butyl N-cap (Rule 3 → β2 selectivity). Orally active and longer-acting than catecholamines. Terbutaline sulphate tablets/injection.
- **Uses:** (1) **Asthma and COPD** — bronchodilator (β2); (2) **premature labour** — tocolytic, relaxes the uterus (β2); (3) hyperkalaemia (shifts potassium into cells).

11. Salbutamol* (albuterol)

- **Chemical classification:** Non-catecholamine phenethylamine (saligenin-type); direct-acting **β2-selective** agonist — the world's most-used asthma reliever.
- **Structure:** A benzene ring carrying **one phenolic –OH (position 4) and one –CH_2OH group (position 3)** — the saligenin pattern, NOT a catechol — + side chain **–CH(OH)–CH_2–NH–$C(CH_3)_3$**: β–OH and bulky **N-tert-butyl**. Like terbutaline it defeats COMT (no adjacent double –OH) and gains β2 selectivity from the tert-butyl cap; unlike terbutaline it keeps only one ring –OH. The (R)-enantiomer (levosalbutamol) carries most activity. Salbutamol sulphate inhaler/tablet/syrup.
- **Uses:** (1) **Asthma** — reliever inhaler for acute attacks and exercise-induced asthma (β2 bronchodilation within minutes); (2) **COPD** — maintenance bronchodilation; (3) **premature labour** (tocolytic); (4) **hyperkalaemia** — nebulised/IV salbutamol drives potassium into cells.
- > **NOTE — synthesis:** Salbutamol* synthesis is given in full in **Chapter 8 (Synthesis Handbook)**. All syntheses are consolidated there; no steps are repeated in this chapter.

12. Naphazoline

- **Chemical classification:** Imidazoline derivative; direct-acting **α agonist** (α1 + α2).
- **Structure: 2-imidazoline ring** joined through a **–CH_2– bridge** to a **1-naphthyl group** (naphthalene — two fused benzene rings). The bulky naphthalene gives strong local vasoconstriction. Naphazoline hydrochloride/nitrate.
- **Uses:** (1) **Nasal decongestant** — nasal drops/spray for colds and sinusitis; (2) **ophthalmic drops** — relieves red, irritated eyes (conjunctival vasoconstriction).

13. Oxymetazoline

- **Chemical classification:** Imidazoline derivative; direct-acting **α1/α2 agonist** (long-acting decongestant).
- **Structure: 2-imidazoline ring** joined through a **–CH_2– bridge** to a heavily substituted phenol ring carrying **one phenolic –OH, two methyl groups and one tert-butyl group**. The tert-butyl + methyl shields make the molecule lipophilic and very long-acting (up to 12 hours). Oxymetazoline hydrochloride nasal spray.
- **Uses:** (1) **Nasal congestion** — long-acting (12-hour) nasal spray for colds, allergies, sinusitis; (2) ophthalmic drops for eye redness.

14. Xylometazoline

- **Chemical classification:** Imidazoline derivative; direct-acting **α agonist** (nasal decongestant).
- **Structure: 2-imidazoline ring** joined through a **–CH_2– bridge** to a phenyl ring carrying a **para-tert-butyl group and two ortho-methyl groups** (4-tert-butyl-2,6-dimethylphenyl). No phenolic –OH. Close cousin of oxymetazoline minus the ring –OH. Xylometazoline hydrochloride nasal drops/spray.
- **Uses:** (1) **Nasal congestion** — nasal drops/spray for colds, allergic rhinitis, sinusitis (the decongestant in Otrivin).

15. Metaraminol

- **Chemical classification:** Non-catecholamine phenethylamine (α-methyl analogue); direct-acting **α1 agonist** (some β activity).
- **Structure:** A benzene ring with a **single meta –OH** (like phenylephrine — NOT a catechol) + side chain **–CH(OH)–CH(CH_3)–NH_2**: a β–OH, a **primary amine**, and an extra **methyl on the α-carbon**. The α-methyl blocks MAO attack → longer-acting than noradrenaline. Metaraminol bitartrate IV.
- **Uses:** (1) **Hypotension and shock** — IV pressor that raises BP (α1 vasoconstriction); (2) priapism (intracavernosal injection).

C. INDIRECT-ACTING AND MIXED-ACTING AGENTS

16. Hydroxyamphetamine

- **Chemical classification:** Non-catecholamine phenethylamine (p-hydroxyamphetamine); **indirect-acting** sympathomimetic.
- **Structure:** A benzene ring with a **single para –OH** + side chain **–CH_2–CH(CH_3)–NH_2**: an α-methyl (amphetamine skeleton) with a para-hydroxy on the ring. It enters sympathetic nerve endings and **displaces stored noradrenaline**, which then acts on receptors — it has almost no direct receptor action itself. Hydroxyamphetamine hydrobromide eye drops.
- **Uses:** (1) **Mydriatic for diagnosis** — dilates the pupil to test for **Horner syndrome** (if the nerve is damaged, no noradrenaline is stored → the pupil does NOT dilate → diagnosis confirmed); (2) nasal decongestant (older use).

17. Pseudoephedrine

- **Chemical classification:** Non-catecholamine phenethylamine (ephedrine diastereomer); **mixed-acting** (direct receptor binding + noradrenaline release).
- **Structure:** A **plain phenyl ring (no phenolic –OH)** + side chain **–CH(OH)–CH(CH_3)–NH–CH_3**: β–OH, an **α-methyl** and an **N-methyl**. The (1S,2S) stereoisomer; ephedrine is its (1R,2S) diastereomer. The α-methyl blocks MAO → orally active and long-acting; the lack of ring –OH lets it cross the blood–brain barrier → mild CNS stimulation. Pseudoephedrine hydrochloride tablets.
- **Uses:** (1) **Nasal and sinus decongestion** — the decongestant in cold/flu combination remedies (with paracetamol, antihistamines); (2) Eustachian-tube congestion. (Pharmacy note: regulated precursor — sales are recorded because it can be misused to make methamphetamine.)

18. Propylhexedrine

- **Chemical classification:** Cyclohexylamine analogue of methamphetamine; **indirect-acting** sympathomimetic.
- **Structure:** A **cyclohexane ring (fully saturated — no benzene, no –OH)** + side chain **–CH_2–CH(CH_3)–NH–CH_3**: an α-methyl and an N-methyl, exactly the methamphetamine skeleton with the benzene ring hydrogenated to cyclohexane. It releases stored noradrenaline from nerve endings; the saturated ring keeps action local and short. Used in a nasal **inhaler** device.
- **Uses:** (1) **Nasal congestion** — vapour inhaler (Benzedrex-type) for blocked nose in colds.

10. Master summary table (all 18 drugs)

#	Drug	Chemical class	Key structural features	Receptor action	Main uses
1	Norepinephrine	Catecholamine	Catechol + β–OH + primary amine (N–H)	α1, α2, β1	Septic shock, hypotension (IV pressor)
2	Epinephrine	Catecholamine	Catechol + β–OH + N–CH_3	α1, α2, β1, β2	Anaphylaxis, cardiac arrest, status asthmaticus, with local anaesthetics
3	Dopamine	Catecholamine (mixed)	Catechol, NO β–OH, primary amine	D1/D2 → β1 → α1 (dose ladder)	Shock, acute heart failure
4	Dobutamine	Catecholamine	Catechol + bulky N-(1-methyl-3-(4-hydroxyphenyl)propyl)	β1 selective	Cardiogenic shock, heart failure, cardiac stress test
5	Isoproterenol	Catecholamine	Catechol + β–OH + N-isopropyl	β1 + β2 (pure beta)	Bradycardia/heart block
6	Bitolterol	Catecholamine prodrug	Colterol catechol masked as di-p-toluate ester; N-tert-butyl	β2 (as colterol)	Bronchospasm (asthma/COPD)
7	Phenylephrine*	Non-catecholamine (single meta –OH)	3-OH phenyl + β–OH + N–CH_3	α1 selective	Nasal decongestant, mydriatic, hypotension
8	Methyldopa	α-Methyl DOPA prodrug	Catechol + α-methyl amino-acid side chain	Central α2 (as α-methylnorepinephrine)	Hypertension in pregnancy
9	Clonidine	Imidazoline	Imidazoline–NH–(2,6-dichlorophenyl)	Central α2	Hypertension, ADHD, opioid withdrawal
10	Terbutaline	Non-catecholamine (resorcinol)	1,3-diol ring + β–OH + N-tert-butyl	β2 selective	Asthma/COPD, premature labour
11	Salbutamol*	Non-catecholamine (saligenin-type)	4-OH + 3-CH_2OH ring + β–OH + N-tert-butyl	β2 selective	Asthma reliever inhaler, COPD, premature labour, hyperkalaemia
12	Naphazoline	Imidazoline	Imidazoline–CH_2–(1-naphthyl)	α1 + α2	Nasal decongestant, eye redness
13	Oxymetazoline	Imidazoline	Imidazoline–CH_2–(phenol with 2×CH_3 + tert-butyl)	α1/α2	Nasal decongestant (12-hour)
14	Xylometazoline	Imidazoline	Imidazoline–CH_2–(4-tert-butyl-2,6-dimethylphenyl)	α agonist	Nasal decongestant
15	Metaraminol	Non-catecholamine (single meta –OH)	3-OH phenyl + β–OH + α–CH_3 + primary amine	α1	Hypotension/shock (IV pressor)
16	Hydroxyamphetamine	Non-catecholamine (indirect)	4-OH phenyl + α–CH_3 + primary amine	Indirect (releases NE)	Diagnostic mydriatic (Horner syndrome)
17	Pseudoephedrine	Non-catecholamine (mixed)	Phenyl (no –OH) + β–OH + α–CH_3 + N–CH_3	Mixed (direct + releases NE)	Nasal/sinus decongestant in cold remedies
18	Propylhexedrine	Cyclohexylamine (indirect)	Cyclohexane + α–CH_3 + N–CH_3	Indirect (releases NE)	Nasal decongestant inhaler

Phenylephrine and Salbutamol *syntheses are given in full in Chapter 8 (Synthesis Handbook).*

11. Flowcharts

Flowchart 1 — Classification of the 18 sympathomimetics (draw as a tree). Top box: "SYMPATHOMIMETICS (18 drugs)". Two branches: LEFT — "Catecholamines (catechol ring present): Norepinephrine, Epinephrine, Dopamine, Dobutamine, Isoproterenol, Bitolterol (prodrug of colterol)". RIGHT — "Non-catecholamines (12)" splitting into four twigs: (i) "Phenethylamines, single ring –OH: Phenylephrine*, Metaraminol, Hydroxyamphetamine"; (ii) "Phenethylamines, modified diol ring: Terbutaline (resorcinol), Salbutamol* (saligenin-type), Pseudoephedrine (no ring –OH)"; (iii) "Imidazolines: Naphazoline, Oxymetazoline, Xylometazoline, Clonidine"; (iv) "Miscellaneous: Methyldopa (α-methyl DOPA prodrug), Propylhexedrine (cyclohexylamine)". Beneath, a second band: "By action: Direct (14) | Indirect (Hydroxyamphetamine, Propylhexedrine) | Mixed (Pseudoephedrine, Dopamine)".

Flowchart 2 — How each type produces its effect (draw 3 columns). Column 1 "DIRECT": "Drug → binds receptor → receptor ON → effect (e.g., salbutamol → β2 → bronchodilation)". Column 2 "INDIRECT": "Drug → enters nerve ending → pushes OUT stored noradrenaline → noradrenaline binds receptor → effect (e.g., hydroxyamphetamine → NE release → mydriasis). Note: repeated use empties stores → tachyphylaxis". Column 3 "MIXED": "Drug does BOTH — binds receptor itself AND releases noradrenaline (e.g., pseudoephedrine → decongestant + mild stimulation)".

12. Worked examples

Example 1 — Anaphylaxis: why epinephrine and not phenylephrine? *Problem:* A patient collapses after a bee sting — BP crashing, airways closing, weak pulse. Which drug, and why does its chemistry fit? *Solution:* Three emergencies need three receptor actions: crashed BP needs α1 vasoconstriction, closed airways need β2 bronchodilation, failing heart needs β1 stimulation. **Epinephrine** switches on α1 + β1 + β2 (its N-methyl catecholamine structure hits all receptors). Phenylephrine is pure α1 — it would raise BP but leave the airways closed. *Answer:* Epinephrine IM — the only drug whose receptor profile covers all three failures at once.

Example 2 — Asthma inhaler: why salbutamol, not isoproterenol? *Problem:* Two β-agonists exist — isoproterenol (pure β) and salbutamol (β2-selective). Which is the better asthma reliever, and what structural feature explains it? *Solution:* Asthma needs airway (β2) relaxation WITHOUT heart (β1) stimulation — isoproterenol's β1 action causes palpitations and tremor. **Salbutamol's N-tert-butyl cap** (Rule 3) makes it β2-selective, and its saligenin-type ring resists COMT, so it lasts 4–6 hours by inhaler versus minutes for catecholamines. *Answer:* Salbutamol — tert-butyl N-cap gives β2 selectivity; non-catechol ring gives duration.

Example 3 — Predict from structure. *Problem:* A new drug has a catechol ring, a β–OH, and an N-ethyl group (–CH_2CH_3). Predict: (a) oral activity? (b) receptor profile? *Solution:* (a) Catechol ring → COMT + MAO destroy it → **poor oral activity, injectable, short-acting**. (b) N-ethyl is between methyl and isopropyl in size → expect **α + β activity** (like epinephrine), shifting toward beta versus norepinephrine. *Answer:* Poor orally; mixed α + β agonist.

13. Analogies (to lock the concepts)

- **Receptors as doorbells:** α1 is the red bell (tightens vessels), β1 the orange bell (heart), β2 the green bell (lungs). Each drug is a key cut for specific bells — salbutamol's key fits only the green bell.
- **COMT as a paper shredder:** Catecholamine molecules are documents with a bright double –OH stamp; the COMT shredder in the gut recognises the stamp and shreds the document. Non-catecholamines removed the stamp → they pass through safely.
- **The N-substituent as a shoe size:** The alpha receptor is a small shoe, the beta receptor a big shoe. N–H and N–CH_3 (small feet) fit the alpha shoe; N-isopropyl and N-tert-butyl (big feet) only fit the beta shoe.
- **Indirect drugs as a firecracker in a matchbox:** Hydroxyamphetamine doesn't light the fire itself — it shakes the matchbox (nerve ending) until the stored matches (noradrenaline) fall out and ignite. Shake too often and the box is empty (tachyphylaxis).
- **Prodrugs as a gift in wrapping paper:** Bitolterol's catechol is wrapped in ester paper; esterases in the lung unwrap it to reveal active colterol.

14. Pharmacy relevance (what you will actually do as a pharmacist)

- **Storage — catecholamines oxidise:** Adrenaline/noradrenaline/dopamine injections darken (pink → brown) on exposure to air/light as the catechol oxidises. Discoloured ampoules must be discarded; formulations contain antioxidants (sodium metabisulphite) and are packed in amber ampoules. Counsel: "never use a darkened adrenaline ampoule."
- **Inhaler counselling:** Salbutamol inhalers (Asthalin) need correct technique — shake, exhale fully, seal lips, inhale slowly while pressing, hold breath 10 seconds. Rinse mouth after use to reduce tremor/throat irritation. Overuse (>2 days/week for symptoms) means asthma is uncontrolled — refer to the doctor.
- **Decongestant rebound:** Nasal sprays (oxymetazoline, xylometazoline, naphazoline) must not be used beyond **3 days** — longer use causes *rhinitis medicamentosa* (rebound congestion, the nose becomes "addicted" to the spray). Counsel every buyer.
- **Pseudoephedrine control:** It is a controlled precursor — record sales, check ID, and never sell bulk quantities; diversion to methamphetamine manufacture is a criminal offence.
- **Pressor infusions:** Norepinephrine, dopamine and dobutamine are given only as IV infusions with BP/heart monitoring — extravasation (leakage outside the vein) causes tissue necrosis; phenylephrine is the antidote infiltrated locally.

15. India context

- **Asthalin (salbutamol) inhaler** — Cipla's brand is in nearly every Indian home with an asthma patient; the 100 mcg rotacap/inhaler is the standard reliever taught in every pharmacy college.
- **Otrivin (xylometazoline)** and **oxymetazoline sprays** — the most-sold nasal decongestants in Indian pharmacies; pharmacists must give the 3-day warning at every sale.
- **Cold remedies** — pseudoephedrine + paracetamol + antihistamine combinations (Sinarest, D'Cold Total) are OTC bestsellers during monsoon/winter; watch for hypertensive and elderly patients.
- **Aldomet (methyldopa)** — still the first-choice antihypertensive in **pregnancy** across Indian obstetric practice because of its unmatched fetal safety record.
- **Emergency trays** — every Indian hospital casualty keeps **adrenaline 1 mg/mL ampoules** for anaphylaxis and cardiac arrest; **noradrenaline, dopamine and dobutamine infusions** run in every ICU for shock.
- **Clonidine** — widely available and inexpensive; used for hypertension and increasingly for ADHD in Indian paediatric practice.

16. Key points (rapid revision)

1. Sympathomimetics copy the fight-or-flight chemicals (adrenaline/noradrenaline) by switching on α1, α2, β1, β2 receptors.
2. α1 = vessels constrict + pupil dilates; α2 (brain) = sympathetic outflow falls; β1 = heart faster/stronger ("1 heart"); β2 = airways widen ("2 lungs").
3. Catechol = benzene with two adjacent –OH groups; catecholamines (6) are potent but COMT/MAO-destroyed → injectable, short-acting.
4. Non-catecholamine rings (resorcinol, saligenin-type, single –OH, imidazoline) resist COMT → oral/inhaled, longer-acting.
5. Direct = binds receptor; indirect = releases stored noradrenaline (hydroxyamphetamine, propylhexedrine; tachyphylaxis); mixed = both (pseudoephedrine, dopamine).
6. Bigger N-substituent → alpha lost, beta gained: H (NE) → CH_3 (epi) → isopropyl (isoproterenol, pure β) → tert-butyl (salbutamol/terbutaline, β2-selective).
7. Epinephrine = anaphylaxis + cardiac arrest; norepinephrine = septic shock pressor; phenylephrine = pure α1 (decongestant/mydriatic/pressor).
8. Dobutamine = β1-selective (cardiogenic shock, stress test); dopamine = dose ladder D → β1 → α1.
9. Methyldopa → α-methylnorepinephrine → central α2 → hypertension in pregnancy; clonidine = central α2 (hypertension, ADHD, withdrawal).
10. Imidazoline decongestants: naphazoline, oxymetazoline (12-hour), xylometazoline — max 3 days (rebound congestion).
11. Bitolterol = ester prodrug of colterol (β2); hydroxyamphetamine = indirect mydriatic diagnosing Horner syndrome.
12. Phenylephrine *and Salbutamol* syntheses are in Chapter 8 (Synthesis Handbook).

17. Common confusions (cleared)

- **Epinephrine vs norepinephrine vs phenylephrine:** Epinephrine (catechol + N–CH_3) = α + β everything → anaphylaxis/cardiac arrest. Norepinephrine (catechol + N–H) = α + β1, almost no β2 → septic-shock pressor. Phenylephrine (single meta –OH + N–CH_3, NOT a catechol) = pure α1 → decongestant/mydriatic/pressor. Hook: "Epi = Everything, Nor = No β2, Phenyl = Pure α1."
- **Salbutamol vs terbutaline:** Both β2-selective with N-tert-butyl; differ only in the ring — salbutamol = saligenin-type (one –OH + one –CH_2OH), terbutaline = resorcinol (two –OH meta). Same uses (asthma, tocolytic).
- **Dopamine vs dobutamine:** Dopamine = natural catecholamine, dose-ladder D → β1 → α1, shock. Dobutamine = synthetic, bulky N-substituent, β1-selective, cardiogenic shock + stress test. Hook: "Dobutamine has the big 'B' — big N-substituent, big β1 selectivity."
- **Clonidine vs methyldopa:** Both lower BP via central α2, but clonidine IS an α2 agonist itself (imidazoline), while methyldopa is a PRODRUG converted to α-methylnorepinephrine. Methyldopa is preferred in pregnancy.
- **Direct vs indirect:** If the drug name ends in "-terol"/"-butamol" or is a catecholamine, think direct; hydroxyamphetamine and propylhexedrine are the only two pure indirect drugs in this chapter.

18. Common mistakes (don't make these in exams)

1. Calling phenylephrine a catecholamine — it has only ONE ring –OH; it is a non-catecholamine.
2. Saying catecholamines are orally active — COMT + MAO destroy them; they are injected/inhaled.
3. Writing that salbutamol is β1-selective — it is β2-selective (that's why it doesn't strongly stimulate the heart).
4. Confusing the dopamine dose ladder order — it is D → β1 → α1 with rising dose, not the reverse.
5. Saying isoproterenol has alpha activity — the N-isopropyl makes it a PURE β (β1 + β2) agonist.
6. Forgetting that bitolterol and methyldopa are prodrugs — name their active forms (colterol; α-methylnorepinephrine).
7. Mixing up ephedrine and pseudoephedrine stereochemistry — pseudoephedrine is the (1S,2S) diastereomer.
8. Recommending nasal decongestant sprays for more than 3 days — rebound congestion (rhinitis medicamentosa).

19. Mnemonics

- **Catecholamines (6):** "Never Eat Doughnuts During Intense Battles" → **N**orepinephrine, **E**pinephrine, **D**opamine, **D**obutamine, **I**soproterenol, **B**itolterol.
- **N-cap rule:** "Bigger the N-cap, more the beta" — H → CH_3 → isopropyl → tert-butyl.
- **Receptor hooks:** "β1 = 1 heart; β2 = 2 lungs; α1 = tightens; α2 = calms the brain."
- **Epi/Nor/Phenyl:** "Epi = Everything (α+β), Nor = No β2, Phenyl = Pure α1."
- **Imidazoline decongestants (3):** "NOX" → **N**aphazoline, **O**xymetazoline, **X**ylometazoline (plus Clonidine the brain one).
- **Indirect-only (2):** "Hi Prof" → **H**ydroxyamphetamine, **P**ropylhexedrine are **p**urely indirect.
- **Dopamine ladder:** "Doctors Build Arteries" → **D**opamine receptors → **B**eta-1 → **A**lpha-1 as dose rises.

20. Exam summary (one page)

Sympathomimetics = adrenergic agonists copying fight-or-flight. Receptors: α1 (vasoconstriction, mydriasis), α2 central (↓sympathetic outflow), β1 (heart), β2 (bronchodilation). **Catechol** = benzene-1,2-diol; 6 catecholamines (NE, epi, dopamine, dobutamine, isoproterenol, bitolterol-prodrug) — potent, COMT/MAO-destroyed, injectable. 12 non-catecholamines — COMT-resistant, oral/inhaled, longer. Action: direct (14), indirect (hydroxyamphetamine, propylhexedrine), mixed (pseudoephedrine, dopamine). Selectivity: α1 — phenylephrine, metaraminol, naphazoline, oxymetazoline, xylometazoline; central α2 — clonidine, methyldopa (→ α-methylnorepinephrine); β1 — dobutamine; β2 — salbutamol, terbutaline, bitolterol; mixed α+β — epi, NE, dopamine; pure β — isoproterenol. SAR: catechol –OH → COMT target; β–OH → direct binding; N-substituent size H → CH_3 → iPr → tBu slides α → β (tBu = β2). Uses: epi — anaphylaxis/cardiac arrest; NE — septic shock; salbutamol — asthma reliever; terbutaline — asthma/tocolytic; phenylephrine — decongestant/mydriatic/pressor; clonidine/methyldopa — hypertension (methyldopa in pregnancy); imidazolines — nasal decongestion (≤3 days); hydroxyamphetamine — Horner test; pseudoephedrine — cold remedies (controlled); propylhexedrine — inhaler; dobutamine — cardiogenic shock/stress test. Syntheses of Phenylephrine *and Salbutamol* are in Chapter 8.

21. One-minute revision (read aloud before entering the exam hall)

"Fight-or-flight keys: α1 tightens vessels and dilates pupils, α2 in the brain calms BP down, β1 is one heart beating harder, β2 is two lungs opening up. Catechol means two adjacent OH — six drugs, injectable, COMT eats them. Bigger N-cap means more beta: methyl is epi, isopropyl is pure beta, tert-butyl is beta-2. Epi fixes anaphylaxis, noradrenaline fixes shock, salbutamol fixes asthma, phenylephrine unblocks noses, methyldopa is safe in pregnancy, dopamine climbs D-beta-alpha with dose. Two indirect only: hydroxyamphetamine and propylhexedrine. Syntheses live in Chapter 8."

22. Exam questions

A. MCQs (10) — with answer key

Q1. The catechol group is defined as: (a) Benzene with two –OH groups at adjacent positions (b) Benzene with two –OH groups at meta positions (c) Benzene with one –OH and one –CH_2OH group (d) Benzene with three –OH groups *Answer: (a)*

Q2. Which of the following is a prodrug that is hydrolysed by esterases to the active β2 agonist colterol? (a) Terbutaline (b) Bitolterol (c) Dobutamine (d) Metaraminol *Answer: (b)*

Q3. As the N-alkyl substituent of a phenethylamine increases in size (H → CH_3 → isopropyl → tert-butyl), the pharmacological profile shifts: (a) From beta to alpha (b) From alpha to beta (c) From direct to indirect (d) It does not change *Answer: (b)*

Q4. Which drug is a pure β (β1 + β2) agonist with NO alpha activity? (a) Epinephrine (b) Norepinephrine (c) Isoproterenol (d) Phenylephrine *Answer: (c)*

Q5. The active metabolite of methyldopa responsible for its antihypertensive action is: (a) α-Methyldopamine (b) α-Methylnorepinephrine (c) Normetanephrine (d) Colterol *Answer: (b)*

Q6. Which of the following is an INDIRECT-acting sympathomimetic? (a) Salbutamol (b) Xylometazoline (c) Hydroxyamphetamine (d) Dobutamine *Answer: (c)*

Q7. Terbutaline contains which ring system that makes it resistant to COMT? (a) Catechol (b) Resorcinol (c) Imidazoline (d) Naphthalene *Answer: (b)*

Q8. Which drug shows a dose-dependent receptor ladder D1/D2 → β1 → α1? (a) Dobutamine (b) Dopamine (c) Clonidine (d) Pseudoephedrine *Answer: (b)*

Q9. Oxymetazoline, xylometazoline and naphazoline share which common scaffold? (a) Phenethylamine (b) Catecholamine (c) Imidazoline (d) Phenylalanine *Answer: (c)*

Q10. The drug of choice for anaphylactic shock is: (a) Norepinephrine (b) Phenylephrine (c) Epinephrine (d) Metaraminol *Answer: (c)*

B. Viva questions (5) — with short answers

V1. Define a sympathomimetic with one example. A drug that mimics the sympathetic nervous system by stimulating adrenergic receptors — e.g., salbutamol stimulates β2 receptors causing bronchodilation in asthma.

V2. Why are catecholamines not given orally? Their catechol –OH groups are methylated by COMT and the amine is attacked by MAO in the gut and liver, so almost none reaches the blood — poor oral bioavailability and very short action; they must be injected or inhaled.

V3. What is the difference between direct- and indirect-acting sympathomimetics? Direct-acting drugs bind the adrenergic receptor themselves (e.g., phenylephrine → α1); indirect-acting drugs release stored noradrenaline from nerve endings, which then stimulates the receptor (e.g., hydroxyamphetamine) — repeated use depletes stores causing tachyphylaxis.

V4. Why is salbutamol β2-selective while epinephrine is not? Salbutamol carries a bulky N-tert-butyl group — big N-substituents shift selectivity from alpha to beta, and tert-butyl specifically favours β2; epinephrine's small N-methyl fits both alpha and beta receptors.

V5. How does methyldopa lower blood pressure? It is a prodrug: in the brain it is converted to α-methyldopamine and then α-methylnorepinephrine, which stimulates central α2 receptors, reducing sympathetic outflow and lowering blood pressure — safe in pregnancy.

C. Application-based questions (3)

A1. A 24-year-old develops anaphylaxis after an insect sting — BP 70/40, wheezing, weak rapid pulse. The intern suggests phenylephrine IV. Is this correct? Justify using receptor chemistry. *Expected answer:* No — epinephrine IM is the drug of choice. Anaphylaxis needs α1 (raise BP) + β1 (support heart) + β2 (open airways); epinephrine's N-methyl catecholamine structure stimulates all three, while phenylephrine is pure α1 and would leave bronchospasm untreated.

A2. A hypertensive patient on clonidine asks for "something for my blocked nose" and picks oxymetazoline spray. What two counselling points will you give, and why is the combination generally acceptable short-term? *Expected answer:* (1) Use for maximum 3 days — longer use causes rebound congestion (rhinitis medicamentosa). (2) It acts locally on nasal α receptors with minimal systemic absorption, so short-term use rarely disturbs BP control; but prolonged/overuse could raise BP — if congestion persists beyond 3 days, see the doctor.

A3. Two bronchodilator structures are shown: Drug X has a catechol ring + N-isopropyl; Drug Y has a resorcinol ring + N-tert-butyl. Which is better for a chronic asthma inhaler and why? *Expected answer:* Drug Y (the terbutaline pattern). The resorcinol ring resists COMT → longer action and oral/inhaled activity, and the tert-butyl N-cap gives β2 selectivity (fewer cardiac β1 side effects). Drug X (the isoproterenol pattern) is a catecholamine — short-acting, non-selective β (cardiac stimulation), and injectable only.

23. References

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UNIT II — Adrenergic System Drugs

Chapter 4 — Anti-adrenergic (Sympatholytic) Agents

Learning Objectives

After studying this chapter, you should be able to:

1. Define a sympatholytic agent and explain what it does to the "fight-or-flight" signals of the body.
2. Classify the 14 drugs of this chapter as alpha-blockers or beta-blockers, and as selective or non-selective.
3. Describe the structure of each drug in words as a scaffold plus its key substituents, and name its chemical class.
4. State the therapeutic uses of each of the 14 drugs (1–3 uses each).
5. Explain why phenoxybenzamine is called an irreversible alpha-blocker (the nitrogen-mustard-like aziridinium ion forming a covalent bond).
6. Write all eight SAR rules of beta adrenergic blockers, each with a drug example.
7. Explain what an aryloxypropanolamine scaffold is (Ar–O–CH2–CH(OH)–CH2–NH–R) and why the –OH and the bulky nitrogen substituent are essential.
8. Correctly expand the syllabus typos "Metibranolol" → metipranolol and "Betazolol" → betaxolol.

Definitions

- **Sympatholytic agent** — A drug that blocks the action of the sympathetic nervous system. Simple meaning: it blocks the "fight-or-flight" messages that adrenaline (epinephrine) and noradrenaline (norepinephrine) carry to organs.
- **Anti-adrenergic agent** — A drug that acts against adrenaline-like signals. It either blocks the receptors that adrenaline binds to, or reduces the amount of adrenaline available. (Sympatholytic and anti-adrenergic are used almost interchangeably.)
- **Fight-or-flight response** — The body's emergency mode: heart beats faster and harder, blood vessels tighten, pupils widen, airways open. It is switched on by adrenaline acting on adrenergic receptors.
- **Adrenergic receptor** — A protein "lock" on the surface of cells that adrenaline or noradrenaline (the "keys") fit into. The two big families are **alpha receptors** and **beta receptors**.
- **Alpha receptor** — An adrenergic receptor type found mainly on blood vessel walls. When switched on, blood vessels tighten (constrict) and blood pressure rises. There are two subtypes you must know: **alpha1** (on vessels — tightening) and **alpha2** (on nerve endings and in the brain — a feedback brake).
- **Beta receptor** — An adrenergic receptor type with three subtypes: **beta1** (mainly on the heart — makes it beat faster and harder), **beta2** (on airways/lungs and blood vessels of muscles — opens airways, relaxes vessels), **beta3** (on fat cells — not important for this chapter).
- **Antagonist (blocker)** — A drug that sits in the receptor like a key that fits the lock but cannot turn it, so the real key (adrenaline) cannot enter. Simple meaning: a plug that stops the signal.
- **Selective blocker** — A blocker that plugs only ONE receptor subtype (e.g., only alpha1, or only beta1) and leaves the others alone.
- **Non-selective blocker** — A blocker that plugs more than one subtype (e.g., both alpha1 and alpha2, or both beta1 and beta2).
- **Reversible blocker** — A blocker that sits on the receptor but can be washed away; when the drug leaves, the receptor works again.
- **Irreversible blocker** — A blocker that chemically glues itself to the receptor with a strong covalent bond; the receptor stays dead until the body makes a new one.

Terminology (Words You Must Know)

- **Catecholamine** — The family name of adrenaline, noradrenaline and dopamine. They all have a catechol (benzene ring with two –OH groups side by side) attached to an ethylamine chain.
- **Aryloxypropanolamine** — The classic chemical backbone (scaffold) of most beta-blockers: an aromatic ring (Ar) joined through an oxygen to a three-carbon chain bearing –OH and –NH– groups: Ar–O–CH2–CH(OH)–CH2–NH–R. Almost every beta-blocker in this chapter is built on it.
- **Scaffold** — The basic ring skeleton of a molecule on which substituents hang (like the frame of a building).
- **Substituent** — A group of atoms attached to the main scaffold (like –CH3, –OCH3, –CONH2). Changing substituents changes the drug's behaviour.
- **Cardioselective** — Means "chooses the heart": a beta1-selective blocker, because beta1 receptors live mainly on the heart. Safer for asthma patients than non-selective beta-blockers.
- **Pheochromocytoma** — A rare tumour of the adrenal gland that pours out huge amounts of adrenaline/noradrenaline, causing dangerous high blood pressure. Alpha-blockers are used to control it.
- **Hypertension** — High blood pressure. Blood pushing too hard against artery walls.
- **Angina** — Chest pain that comes when the heart muscle does not get enough oxygen (usually because coronary arteries are narrowed).
- **Arrhythmia** — An abnormal heart rhythm (too fast, too slow, or irregular).
- **Benign prostatic hyperplasia (BPH)** — Non-cancerous enlargement of the prostate gland in older men; alpha1-blockers relax the prostate/bladder-neck muscle and improve urine flow.
- **Raynaud's phenomenon** — Fingers and toes turn white/blue and painful in the cold because tiny blood vessels spasm shut.
- **Glaucoma** — High pressure inside the eye that can damage the optic nerve and cause blindness. Beta-blockers given as eye drops reduce the eye's fluid production.
- **Migraine** — A severe one-sided headache, often with nausea and sensitivity to light. Dihydroergotamine and propranolol are both used (one to treat attacks, one to prevent them).
- **Orthostatic (postural) hypotension** — A fall in blood pressure on standing up, causing dizziness. A common side effect of alpha-blockers ("first-dose effect").
- **Ergot alkaloid** — A natural product from the fungus *Claviceps purpurea* (ergot) that grows on rye. Ergot alkaloids have complex ring structures and act on several receptors, including alpha-adrenergic ones.
- **Covalent bond** — A very strong chemical bond where atoms share electrons. Phenoxybenzamine forms one with the receptor — that is why it is irreversible.
- **Aziridinium ion** — A tiny, highly reactive three-membered ring (two carbons + one positively charged nitrogen). Phenoxybenzamine converts into this inside the body, like a nitrogen-mustard, and it attacks the receptor.
- **Nitrogen mustard** — A family of reactive chemicals that form aziridinium ions and permanently attach to proteins/DNA. Phenoxybenzamine is "nitrogen-mustard-like" in its chemistry.
- **Intrinsic sympathomimetic activity (ISA)** — Partial agonist activity: a beta-blocker that blocks the receptor but also weakly stimulates it, so resting heart rate does not fall as much. (None of the 14 drugs here is famous for ISA, but the term appears in exams.)
- **Tachycardia** — Abnormally fast heartbeat.

Explanations (Concept → Simple Explanation → Example → Takeaway)

1. What do sympatholytic (anti-adrenergic) drugs do?

- *Concept:* The sympathetic nervous system is the body's "fight-or-flight" wiring. Its chemical messengers — adrenaline and noradrenaline — switch on alpha and beta receptors to raise heart rate, tighten blood vessels and raise blood pressure.
- *Simple explanation:* Imagine the body as a house with an alarm system (sympathetic nerves). Adrenaline is the guard shouting "Emergency!" through loudspeakers (receptors) in the heart and blood vessels. A sympatholytic drug puts earplugs in those loudspeakers — the guard still shouts, but the heart and vessels cannot hear him, so they stay calm.
- *Example:* Propranolol plugs beta receptors on the heart, so even during stress the heart beats slower and gentler — useful in hypertension and angina.
- *Takeaway:* Sympatholytics = earplugs for fight-or-flight signals. Alpha-blockers calm blood vessels; beta-blockers calm the heart.

2. Why do we need both alpha-blockers and beta-blockers?

- *Concept:* Alpha receptors (mainly alpha1) control blood-vessel tightening; beta1 receptors control heart rate and force. Blocking one system lowers blood pressure by relaxing vessels; blocking the other lowers it by calming the heart.
- *Simple explanation:* Blood pressure is like water pressure in a garden pipe. Alpha-blockers widen the pipe (vessels relax); beta-blockers turn down the pump (heart beats slower and softer). Both reduce pressure, but through different handles.
- *Example:* Prazosin (alpha1-blocker) widens vessels and is used in hypertension and BPH. Atenolol (beta1-blocker) slows the heart and is used in hypertension and angina.
- *Takeaway:* Alpha-blockers = widen the pipes. Beta-blockers = calm the pump. Know which handle each drug turns.

3. What does "selective" vs "non-selective" mean, and why does it matter?

- *Concept:* A selective blocker fits only one receptor subtype; a non-selective one fits two or more. Because beta2 receptors keep airways open, a non-selective beta-blocker can narrow the airways — dangerous for asthma patients.
- *Simple explanation:* A selective blocker is a key cut for ONE specific lock; a non-selective blocker is a master key that opens several locks, wanted or not.
- *Example:* Atenolol is beta1-selective (cardioselective): it calms the heart but mostly leaves the lung's beta2 receptors alone, so it is safer in patients with mild asthma. Propranolol is non-selective: it blocks beta1 AND beta2, so it can trigger breathing difficulty in asthmatics.
- *Takeaway:* Selective = fewer unwanted locks opened = fewer side effects. Non-selective = broader action but more side-effect risk.

4. What is special about phenoxybenzamine (the irreversible blocker)?

- *Concept:* Most blockers sit on the receptor reversibly (they come and go). Phenoxybenzamine converts in the body into a reactive aziridinium ion — a nitrogen-mustard-like species — that forms a permanent covalent bond with the alpha receptor. The blockade lasts for days, until the body builds new receptors.
- *Simple explanation:* Most blockers are like a cork pushed into a bottle — you can pull it out. Phenoxybenzamine is like superglue poured into the lock — the lock is dead until a new lock is installed.
- *Example:* In pheochromocytoma (adrenaline-secreting tumour), phenoxybenzamine is given for 1–2 weeks before surgery so that the massive adrenaline surges during the operation cannot cause a fatal blood-pressure spike.
- *Takeaway:* Reversible = temporary plug. Irreversible (phenoxybenzamine) = chemical superglue, very long-lasting blockade.

> **Note box:** Tolazoline *and Propranolol* syntheses are given in full in Chapter 8 (Synthesis Handbook). No syntheses are given in this chapter — only structures (described in text), chemical classes and uses.

Classifications

Table 1 — Alpha-adrenergic blockers (drugs in this chapter)

Drug	Selectivity	Chemical class	Simple note
Tolazoline	Non-selective alpha (alpha1 + alpha2)	Imidazoline derivative	Vessel widener; also stimulates the gut
Phentolamine	Non-selective alpha (alpha1 + alpha2)	Imidazoline derivative	Short-acting, injectable alpha-blocker
Phenoxybenzamine	Non-selective alpha (alpha1 + alpha2)	Haloalkylamine (nitrogen-mustard-like)	IRREVERSIBLE — covalent bond via aziridinium ion
Prazosin	Alpha1-selective	Quinazoline (piperazinyl-quinazoline) derivative	First-dose hypotension; also used in BPH
Dihydroergotamine	Partial alpha-blocking (plus serotonin/dopamine actions)	Ergot alkaloid (hydrogenated ergotamine)	Migraine drug with alpha-blocking activity

Table 2 — Beta-adrenergic blockers (drugs in this chapter)

Drug	Selectivity	Chemical class	Simple note
Propranolol	Non-selective (beta1 + beta2)	Aryloxypropanolamine (naphthyloxy)	The prototype beta-blocker
Metipranolol	Beta1-selective (cardioselective)	Aryloxypropanolamine	Used as eye drops in glaucoma
Atenolol	Beta1-selective (cardioselective)	Aryloxypropanolamine (para-amide)	Once-daily, water-soluble
Betaxolol	Beta1-selective (cardioselective)	Aryloxypropanolamine (para-substituted)	Eye drops for glaucoma; also oral for hypertension
Bisoprolol	Beta1-selective (highly cardioselective)	Aryloxypropanolamine	Heart-failure and hypertension use
Esmolol	Beta1-selective (cardioselective)	Aryloxypropanolamine ester	Ultra-short-acting — IV only, for ICUs
Metoprolol	Beta1-selective (cardioselective)	Aryloxypropanolamine (ortho/para-substituted)	Angina, hypertension, post-heart-attack
Labetalol	Mixed alpha1 + beta (alpha1:beta ≈ 1:3 oral, 1:7 IV)	Aryloxypropanolamine with salicylamide moiety	Hypertension in pregnancy; IV for emergencies
Carvedilol	Mixed alpha1 + beta (non-selective beta)	Aryloxypropanolamine with carbazole ring	Heart failure; the carbazole adds alpha-blocking

Name note (syllabus typo): The syllabus prints "Metibranolol" — this is a typo. The real drug is **metipranolol**, a beta1-selective beta-blocker used as eye drops in glaucoma. This chapter covers metipranolol.

Name note (syllabus typo): The syllabus prints "Betazolol" — this is a typo. The real drug is **betaxolol**, a beta1-selective (cardioselective) beta-blocker used in glaucoma (eye drops) and hypertension (oral). This chapter covers betaxolol.

Drug Profiles — Alpha-Adrenergic Blockers

1. Tolazoline

- *Chemical class:* Imidazoline derivative (non-selective alpha-blocker).
- *Structure in words:* The scaffold is a five-membered **imidazoline ring** (a ring with two nitrogens and one double bond — think of a pentagon with N at two corners). Attached to the carbon between the two ring nitrogens is a **benzyl group** (–CH2–phenyl): a phenyl ring joined to the imidazoline carbon through a single –CH2– bridge. That is the whole molecule: imidazoline–C(–CH2–phenyl). Tolazoline looks like a "mini-adrenaline": the imidazoline ring imitates adrenaline's amine end and the benzyl phenyl imitates adrenaline's aromatic ring, but the shape is wrong for activation — so it plugs the receptor instead of switching it on.
- *Therapeutic uses:* (1) Persistent pulmonary hypertension of the newborn — injected to widen the lung's blood vessels in newborn babies whose lungs stay clamped shut after birth. (2) Treatment of peripheral vascular spasm (e.g., Raynaud's phenomenon) — relaxes tight small vessels in fingers and toes. (3) Reversal of adrenaline/noradrenaline extravasation injury — injected around the site where a noradrenaline drip leaked into tissue, to stop the tissue dying from vessel spasm.

2. Phentolamine

- *Chemical class:* Imidazoline derivative (non-selective alpha-blocker).
- *Structure in words:* Again an **imidazoline ring** as the scaffold, but much more decorated than tolazoline. The carbon between the two ring nitrogens carries a benzyl-type carbon bearing TWO substituents: a **para-tolyl group** (a phenyl ring with a –CH3 at the para position) and a **meta-hydroxyphenyl group** (a phenyl ring with –OH at the meta position) — so it is a diarylmethyl group, N-substituted with a methyl. Think: imidazoline ring with a "two-ringed umbrella" hanging off it. The two phenolic/hydrophobic rings fill the receptor's binding pocket and block both alpha1 and alpha2.
- *Therapeutic uses:* (1) Diagnosis and short-term management of **pheochromocytoma** — an IV injection drops the dangerously high blood pressure caused by the tumour's adrenaline surges. (2) Treatment of noradrenaline **extravasation necrosis** — injected into the skin around a leaked vasopressor drip to reopen vessels and save the tissue. (3) Management of hypertensive crisis during surgery on a pheochromocytoma.

3. Phenoxybenzamine

- *Chemical class:* Haloalkylamine — a **nitrogen-mustard-like** irreversible alpha-blocker (non-selective: alpha1 + alpha2).
- *Structure in words:* The molecule has three parts. (a) A **phenoxy group**: a phenyl ring joined through an oxygen (–O–) — this is the part that first docks into the receptor pocket. (b) An **isopropyl-substituted nitrogen**: –N(isopropyl)–CH2–. (c) A **2-chloroethyl arm**: –CH2–CH2–Cl hanging off the nitrogen. In the body, the nitrogen attacks its own chloroethyl carbon, kicking out chloride and forming a three-membered **aziridinium ion** (two carbons + positively charged nitrogen in a strained triangle — exactly like nitrogen mustards). This super-reactive triangle is attacked by a nucleophilic group on the alpha receptor, forming a permanent **covalent bond**. The receptor is glued shut.
- *Therapeutic uses:* (1) Long-term control of hypertension in **pheochromocytoma** — given orally for 1–2 weeks before tumour-removal surgery so adrenaline surges cannot cause fatal blood-pressure spikes. (2) Chronic management when the tumour cannot be removed by surgery. (3) Sometimes used in peripheral vascular disorders with severe vasospasm.

4. Prazosin

- *Chemical class:* Quinazoline derivative (alpha1-**selective** blocker).
- *Structure in words:* The scaffold is a **quinazoline ring** (a benzene ring fused to a pyrimidine — two nitrogens in the second ring; think of a double-ring like naphthalene but with nitrogens). At position 2 of the quinazoline there is an **amino group** (–NH2), and at position 4 a **piperazine ring** (a six-membered ring with two nitrogens opposite each other). The piperazine's second nitrogen carries a **2-furoyl group** (a five-membered furan ring attached via a carbonyl C=O). So: quinazoline–piperazine–C(=O)–furan. The quinazoline core is the alpha1-recognition piece; the furoyl-piperazine tail fills a side pocket that gives alpha1 selectivity.
- *Therapeutic uses:* (1) **Hypertension** — relaxes blood vessels (alpha1 on vessel walls); famous for the "first-dose effect" (severe dizziness on the first tablet, so it is started at bedtime in a low dose). (2) **Benign prostatic hyperplasia (BPH)** — relaxes smooth muscle in the prostate and bladder neck, improving urine flow in older men. (3) Raynaud's phenomenon and peripheral vascular disease (less common now).

5. Dihydroergotamine

- *Chemical class:* **Ergot alkaloid** — a hydrogenated (dihydro) derivative of ergotamine, from the fungus *Claviceps purpurea*. Has partial alpha-adrenergic blocking activity along with serotonin (5-HT) and dopamine actions.
- *Structure in words:* The scaffold is the classic **ergoline ring system**: a complex four-fused-ring core (an indole fused to a tricyclic system — imagine three six-membered rings fused in a row with an indole hanging off one end, containing nitrogens). The "dihydro" part means the double bond between positions 9–10 of ergotamine is hydrogenated (saturated), which makes it less of a vasoconstrictor and more of an alpha-blocker than ergotamine. Attached to the ergoline core is a **tripeptide-like side chain** (proline-containing cyclic peptide fragment). The bulky peptide tail is what lets it grip several receptors at once.
- *Therapeutic uses:* (1) **Acute migraine attacks** — constricts the dilated cranial vessels and blocks neurogenic inflammation (given as nasal spray or injection; the alpha-blocking plus 5-HT1 agonist actions abort the headache). (2) **Cluster headache** — same mechanism, for this severe one-sided headache. (3) Postural hypotension (in some countries, oral forms are used to tighten vessels on standing).

Drug Profiles — Beta-Adrenergic Blockers

6. Propranolol

- *Chemical class:* Aryloxypropanolamine — **non-selective** beta-blocker (beta1 + beta2). The prototype of the whole class.
- *Structure in words:* The aromatic part is a **naphthalene ring** (two fused benzene rings — a bigger, flatter aromatic system than a single phenyl). Position 1 of the naphthalene carries the –O–CH2–CH(OH)–CH2–NH– side chain (the aryloxypropanolamine backbone), and the nitrogen at the end carries an **isopropyl group** (–CH(CH3)2). So: naphthyl–O–CH2–CH(OH)–CH2–NH–CH(CH3)2. The large naphthalene ring fills the receptor pocket of BOTH beta1 and beta2 — hence non-selective. The –OH on the middle carbon and the bulky isopropyl on nitrogen are the two classic beta-blocker features (see SAR below).
- *Therapeutic uses:* (1) **Hypertension and angina** — slows the heart and reduces its oxygen demand. (2) **Migraine prevention** (prophylaxis) — taken daily to reduce attack frequency. (3) Essential tremor, anxiety-related palpitations, and thyrotoxicosis symptoms (calms the racing heart of an overactive thyroid).

> **Note box:** Propranolol* synthesis is given in full in Chapter 8 (Synthesis Handbook). No synthesis is given here.

7. Metipranolol

- *Chemical class:* Aryloxypropanolamine — **beta1-selective** (cardioselective) beta-blocker.
- *Structure in words:* A single **phenyl ring** (not naphthalene) carrying the standard –O–CH2–CH(OH)–CH2–NH– side chain, with the nitrogen bearing a **tert-butyl group** (–C(CH3)3, bulkier than isopropyl). On the phenyl ring there is an **ortho substituent**: a –O–CO–CH(CH3)2 (isobutyryloxy ester) group at the ortho position relative to the ether oxygen. The smaller single-ring aromatic plus the ortho ester gives it beta1 preference.
- *Therapeutic uses:* (1) **Glaucoma** — as eye drops, it reduces the production of aqueous humour (eye fluid), lowering intra-ocular pressure. This is its main use. (2) Ocular hypertension (high eye pressure without nerve damage yet). (3) Occasionally oral forms were explored for hypertension, but the eye-drop use dominates.

8. Atenolol

- *Chemical class:* Aryloxypropanolamine — **beta1-selective** (cardioselective) beta-blocker.
- *Structure in words:* A single **phenyl ring** with the classic –O–CH2–CH(OH)–CH2–NH–isopropyl side chain. The key feature is a **para substituent**: –CH2–C(=O)–NH2 (an **acetamide** group, –CH2CONH2) at the para position of the phenyl ring. This para amide is the textbook example of a "beta1-selectivity handle" (see SAR rule vi). Atenolol is relatively **water-soluble (hydrophilic)** — it does not cross into the brain much, so it causes fewer central side effects (like nightmares) than propranolol.
- *Therapeutic uses:* (1) **Hypertension** — once-daily tablet, very widely used in India. (2) **Angina** — reduces heart workload. (3) Prevention of heart attack complications / arrhythmias after myocardial infarction.

9. Betaxolol

- *Chemical class:* Aryloxypropanolamine — **beta1-selective** (cardioselective) beta-blocker.
- *Structure in words:* A single **phenyl ring** with the standard –O–CH2–CH(OH)–CH2–NH–isopropyl side chain. The para substituent is a **–CH2–O–CH2–cyclopropyl** group (a cyclopropylmethoxy-methyl ether tail: phenyl–CH2–O–CH2–[three-membered cyclopropane ring]). This ether-linked para tail is the beta1-selectivity handle here.
- *Therapeutic uses:* (1) **Glaucoma / ocular hypertension** — as eye drops, lowers eye pressure (beta1-selective drops cause less breathing risk than non-selective drops like timolol). (2) **Hypertension** — oral tablets. (3) Angina (oral).

10. Bisoprolol

- *Chemical class:* Aryloxypropanolamine — **highly beta1-selective** (one of the most cardioselective) beta-blocker.
- *Structure in words:* A single **phenyl ring** with the –O–CH2–CH(OH)–CH2–NH–isopropyl side chain. The para substituent is a longer ether chain: –CH2–O–CH2–CH2–O–CH(CH3)2 (an **isopropoxy-ethoxymethyl** tail). The long, flexible para ether chain fits the beta1 receptor's side pocket perfectly but clashes with beta2 — giving very high beta1 selectivity.
- *Therapeutic uses:* (1) **Chronic heart failure** — one of the few beta-blockers proven to prolong life in heart failure (protects the failing heart from chronic adrenaline overstimulation). (2) **Hypertension**. (3) Angina and post-heart-attack protection.

11. Esmolol

- *Chemical class:* Aryloxypropanolamine **ester** — beta1-selective (cardioselective), **ultra-short-acting** beta-blocker.
- *Structure in words:* A single **phenyl ring** with the –O–CH2–CH(OH)–CH2–NH–isopropyl side chain. The para substituent is –CH2–CH2–C(=O)–O–CH3 (a **methyl ester** tail: phenyl–CH2–CH2–COOCH3). This ester is the whole point of esmolol: blood enzymes (**esterases**) chop the ester within minutes, destroying the drug. Half-life is about **9 minutes** — the shortest of any beta-blocker.
- *Therapeutic uses:* (1) **Emergency control of fast heart rhythms in the ICU/operation theatre** — given as a continuous IV drip; if anything goes wrong, you simply stop the drip and the effect vanishes in minutes. (2) Rapid control of blood pressure and heart rate during surgery. (3) Acute atrial fibrillation/flutter with fast ventricular rate — slows the heart within seconds to minutes.

12. Metoprolol

- *Chemical class:* Aryloxypropanolamine — **beta1-selective** (cardioselective) beta-blocker.
- *Structure in words:* A single **phenyl ring** with the –O–CH2–CH(OH)–CH2–NH–isopropyl side chain. It carries substituents at BOTH the ortho and para positions (relative to the ether oxygen): an **ortho methyl group** (–CH3) and a **para –CH2–CH2–O–CH3** (methoxyethyl) tail. The ortho substitution is tolerated without losing activity (SAR rule v), and the para methoxyethyl chain is the beta1-selectivity handle (SAR rule vi). Metoprolol is moderately fat-soluble, so it enters the brain more than atenolol.
- *Therapeutic uses:* (1) **Hypertension** — very widely prescribed in India, available as immediate- and extended-release tablets. (2) **Angina** and prevention of second heart attacks (post-myocardial infarction). (3) Heart failure (extended-release form) and certain arrhythmias.

13. Labetalol

- *Chemical class:* Aryloxypropanolamine with a **salicylamide** moiety — **mixed alpha1 + beta blocker** (blocks alpha1 AND beta1/beta2).
- *Structure in words:* The aromatic ring is a **phenyl ring bearing an ortho –C(=O)–NH2 (amide) group** — this ortho-amide-phenol-like arrangement is called a **salicylamide** piece (it resembles salicylic acid's layout). The side chain is a modified propanolamine: –CH(OH)–CH2–NH– attached to a **1-methyl-3-phenylpropyl** group (nitrogen carries a bulky –CH(CH3)–CH2–CH2–phenyl tail instead of simple isopropyl). The salicylamide aromatic portion is believed to contribute the **alpha1-blocking** part, while the propanolamine backbone gives the **beta-blocking** part. Oral ratio alpha:beta ≈ 1:3; IV ratio ≈ 1:7.
- *Therapeutic uses:* (1) **Hypertension in pregnancy (including pre-eclampsia)** — one of the safest blood-pressure drugs in pregnancy because the combined blockade lowers pressure without reducing blood flow to the placenta as much. (2) **Hypertensive emergencies** — IV labetalol lowers blood pressure rapidly in hospital. (3) Chronic hypertension, especially when a single drug with both actions is desired.

14. Carvedilol

- *Chemical class:* Aryloxypropanolamine with a **carbazole** ring — **mixed alpha1 + beta blocker** (blocks alpha1 plus beta1/beta2 non-selectively on the beta side).
- *Structure in words:* The aromatic end is a **carbazole ring** (three fused rings — two benzene rings fused to a central five-membered nitrogen ring; think of a wide, flat triple-decker aromatic system). One end of the carbazole carries an **ortho –O–CH2–CH(OH)–CH2–NH–** side chain whose nitrogen is joined through a –CH2–CH2– spacer to a **para-methoxyphenyl (guaiacol-like) group**: –NH–CH2–CH2–(phenyl–OCH3). The large carbazole system is the SAR-famous feature: it reaches into an extra pocket of the receptor and adds **alpha1-blocking** activity on top of beta-blockade (SAR rule viii).
- *Therapeutic uses:* (1) **Chronic heart failure** — a cornerstone drug; prolongs life by blocking both the heart-stimulating (beta) and vessel-tightening (alpha1) effects of chronic adrenaline excess. (2) **Hypertension**. (3) Left-ventricular dysfunction after heart attack.

Mechanisms (How Each Drug Works — In Simple Words)

1. **Tolazoline and Phentolamine** — Sit on alpha1 receptors (vessel walls) and alpha2 receptors (nerve endings), blocking noradrenaline from tightening vessels. Vessels relax → blood pressure falls. Because alpha2 (the "brake" on noradrenaline release) is also blocked, extra noradrenaline spills out — which is why these drugs can paradoxically stimulate the heart and gut.
2. **Phenoxybenzamine** — First docks reversibly on the alpha receptor, then its aziridinium ion forms a permanent covalent bond. The receptor is permanently switched off; only newly made receptors restore the response. Longest-acting alpha-blocker.
3. **Prazosin** — Selectively plugs alpha1 receptors on blood-vessel walls and in the prostate/bladder neck. Vessels widen (blood pressure falls); prostate muscle relaxes (urine flows better). It does NOT block alpha2, so the nerve-ending brake stays working — less reflex tachycardia than non-selective alpha-blockers.
4. **Dihydroergotamine** — A "dirty" drug in a good way: it partially blocks alpha receptors while stimulating serotonin 5-HT1 receptors on cranial vessels. In migraine, cranial vessels are painfully dilated and inflamed; dihydroergotamine tightens them back and calms the nerve inflammation, aborting the attack.
5. **Propranolol** — Plugs beta1 (heart) and beta2 (lungs, vessels) receptors. Heart: slower rate, weaker squeeze → less oxygen needed (good in angina), lower blood pressure. Lungs: beta2 blockade can narrow airways → avoid in asthma.
6. **Metipranolol, Atenolol, Betaxolol, Bisoprolol, Esmolol, Metoprolol** — Prefer beta1 over beta2 (cardioselective). They calm the heart (lower rate, force, blood pressure; less oxygen demand) while mostly sparing the lung's beta2 receptors. In the eye (metipranolol, betaxolol drops), beta-blockade reduces aqueous humour production → eye pressure falls → glaucoma controlled.
7. **Esmolol (special mechanism note)** — Same beta1 blockade as above, but blood esterases destroy it in ~9 minutes. It is given as an IV drip, so the doctor controls the effect second-by-second like a tap.
8. **Labetalol and Carvedilol** — Block beta receptors (calm the heart) AND alpha1 receptors (widen vessels) at the same time. Two handles, one tablet: the heart pumps more gently into wider pipes → blood pressure falls smoothly with less reflex speeding of the heart.

SAR of Beta Adrenergic Blockers (Structure–Activity Relationship)

First, the scaffold every rule refers to. Almost all beta-blockers in this chapter are built on the **aryloxypropanolamine** backbone:

Ar–O–CH2–CH(OH)–CH2–NH–R

Read it left to right: an **aromatic ring (Ar)** — joined through an **oxygen** — to a **CH2** — to a **CH(OH)** (the carbon carrying the –OH; this carbon is chiral, meaning it has four different groups and exists in left/right mirror forms) — to another **CH2** — to an **NH** — carrying a bulky group **R** (usually isopropyl or tert-butyl).

Why this shape? Adrenaline itself is Ar–CH(OH)–CH2–NH–CH3. The beta-blocker scaffold is adrenaline's "evil twin": it is similar enough to fit the same receptor pocket, but the extra –O–CH2– spacer changes the angle so the receptor cannot be switched on — the drug just sits there and blocks.

Rule No.	SAR Rule (what the chemistry says)	Simple meaning	Drug example from this chapter
(i)	The **–OH on the beta carbon** (the CH(OH) middle carbon) is **essential** — it forms hydrogen bonds with the receptor. Remove it or replace it and activity collapses.	The –OH is the hand that grips the receptor. No hand, no grip.	Propranolol — its –CH(OH)– is the hydrogen-bond anchor; analogues without it are nearly inactive.
(ii)	The **S-enantiomer is the more active** form. The CH(OH) carbon is chiral; the S mirror-image fits the receptor far better than the R form.	Left glove vs right glove: only one hand shape fits. Most beta-blockers are sold as the racemic (50:50) mixture, but the S half does most of the work.	Metoprolol — the S-enantiomer carries almost all the beta-blocking activity.
(iii)	The **–CH2– between the ether oxygen and the chiral carbon** is needed — it sets the correct distance and angle between the aromatic ring and the –OH/NH groups. Shorten or lengthen the chain and the fit is ruined.	Like the right length of a key shaft: too short or too long and the key won't turn (here, won't even fit).	Atenolol — its –O–CH2–CH(OH)– spacing is exactly the two-carbon gap the receptor pocket demands.
(iv)	**Bulky N-substituents increase beta-blocking activity.** Isopropyl (–CH(CH3)2) and tert-butyl (–C(CH3)3) on the nitrogen are optimal; a small methyl (as in adrenaline itself) gives agonist (stimulant) character instead.	A fat group on the nitrogen wedges the receptor in the "off" position. Small group = switch ON; big group = switch OFF.	Propranolol (N-isopropyl), Metipranolol (N-tert-butyl) — both bulky; compare adrenaline (N-methyl), which stimulates.
(v)	**Ortho substitution on the aromatic ring is tolerated.** Groups placed next to (ortho to) the ether oxygen do not destroy activity.	The receptor has spare room beside the ring — you can hang a group there and the drug still fits.	Metoprolol — has an ortho methyl group and is still a potent beta1-blocker. Labetalol — its salicylamide has an ortho amide.
(vi)	**Para substituents decide beta1-selectivity.** The group placed opposite (para to) the ether oxygen reaches into a side pocket that differs between beta1 and beta2 — the right para group makes the drug prefer beta1 (cardioselective).	The para position is the "selectivity dial": turn it and the drug chooses heart over lungs.	Atenolol — para –CH2CONH2 (acetamide) → beta1-selective. Metoprolol — para –CH2CH2OCH3 → beta1-selective. Bisoprolol — long para ether chain → highly beta1-selective.
(vii)	**Larger fused rings give non-selective blockers.** Replacing the single phenyl with a big flat system like naphthalene fills both beta1 and beta2 pockets equally — selectivity is lost.	A bigger key fills every lock — heart and lungs both blocked.	Propranolol — naphthalene ring → blocks beta1 AND beta2 (non-selective).
(viii)	**The carbazole ring in carvedilol adds alpha-blocking.** Carvedilol's triple-fused carbazole system reaches an extra receptor pocket, giving alpha1-blocking activity on top of beta-blockade.	An extra ring = an extra talent: the same molecule now also widens blood vessels.	Carvedilol — carbazole ring → mixed alpha1 + beta blocker, unlike every other aryloxypropanolamine here.

SAR summary in one line: Keep the –OH (rule i) on a chiral carbon in the S form (rule ii), keep the two-carbon spacer (rule iii), put a fat group on nitrogen (rule iv); then tune the aromatic ring — ortho is free real estate (rule v), para is the selectivity dial (rule vi), big fused rings kill selectivity (rule vii), and a carbazole buys you alpha-blocking too (rule viii).

Diagrams (Describe So They Can Be Drawn)

Diagram 1 — The fight-or-flight circuit and where sympatholytics cut it Draw the brain at top with an arrow down the spinal cord to the adrenal gland and sympathetic nerves. From the nerves draw two messenger arrows labelled "adrenaline / noradrenaline" reaching: (a) the heart with beta1 receptors (draw as Y-shaped locks) labelled "faster + harder beat"; (b) blood-vessel walls with alpha1 receptors labelled "tighten"; (c) lung airways with beta2 receptors labelled "open wide". Now draw a beta-blocker tablet as a plug sitting in the heart's beta1 locks (× over the signal), and an alpha-blocker plug in the vessel's alpha1 locks. Caption: "Sympatholytics do not remove the messengers — they plug the locks."

Diagram 2 — The aryloxypropanolamine scaffold, labelled Draw: Ar–O–CH2–CH(OH)–CH2–NH–R as a zigzag chain. Circle the –OH and label "Rule i: ESSENTIAL — hydrogen bonds to receptor". Put a star on the CH(OH) carbon and label "Rule ii: chiral — S form is active". Bracket the –O–CH2– section and label "Rule iii: this two-carbon spacer sets the fit". Circle the R on nitrogen and label "Rule iv: must be BULKY (isopropyl / tert-butyl)". Draw the Ar ring with ortho and para positions marked: ortho = "Rule v: tolerated", para = "Rule vi: selectivity dial". Below, draw propranolol's version with a naphthalene ring and label "Rule vii: big fused ring = non-selective".

Diagram 3 — Phenoxybenzamine: from reversible docking to permanent glue Three panels left to right. Panel 1: draw phenoxybenzamine (phenoxy–N(isopropyl)–CH2–CH2–Cl) sitting loosely in the alpha-receptor pocket, labelled "docks reversibly first". Panel 2: zoom into the –N–CH2–CH2–Cl tail curling into a triangle (aziridinium ion, N+ in a three-membered ring) with Cl− leaving, labelled "forms aziridinium ion — like a nitrogen mustard". Panel 3: the triangle opened and bonded to the receptor wall with a thick line labelled "covalent bond — PERMANENT. Receptor dead until replaced."

Diagram 4 — Selective vs non-selective beta-blockade (heart vs lungs) Draw two organs: heart (with beta1 locks) and lungs (with beta2 locks). For atenolol: draw plugs only in the heart's locks, lungs' locks empty and open, caption "beta1-selective (atenolol): heart calmed, airways safe". For propranolol: draw plugs in BOTH organs' locks, caption "non-selective (propranolol): heart calmed BUT airways narrowed — avoid in asthma".

Diagram 5 — Esmolol's self-destruct timer Draw esmolol's para –CH2–CH2–C(=O)–O–CH3 ester tail with scissors labelled "blood esterases" cutting the ester bond. Show the molecule splitting into an inactive acid fragment, with a clock showing "≈ 9 minutes half-life". Below draw an IV drip bag with a tap: "Drip ON = effect; drip OFF = gone in minutes."

Diagram 6 — Labetalol vs carvedilol: two handles, one drug Draw a blood-pressure gauge. For labetalol: two hands on it — one labelled "beta-block: calmer heart" and one labelled "alpha1-block: wider vessels". For carvedilol: the same two hands, but the alpha1 hand is drawn larger (carvedilol's alpha blockade is relatively stronger) and a heart-failure shield icon beside it labelled "heart-failure cornerstone".

Flowcharts

Flowchart 1 — Is it an alpha-blocker or a beta-blocker? (exam rescue chart)

```
Drug name given in exam
        |
Does it end in -ZOSIN (prazosin)? ──Yes──→ Alpha1-selective blocker
        | No
Does it end in -OLOL (propranolol, atenolol, metoprolol…)? ──Yes──→ Beta-blocker
        | No
Is it tolazoline / phentolamine / phenoxybenzamine? ──Yes──→ Non-selective alpha-blocker
        | No
Is it dihydroergotamine? ──Yes──→ Ergot alkaloid with alpha-blocking activity
        |
Is it labetalol / carvedilol? ──Yes──→ MIXED alpha + beta blocker
        (both end in -olol BUT block alpha1 too — the exam's favourite trap)
```

Flowchart 2 — Choosing among beta-blockers (clinical logic)

```
Need a beta-blocker
        |
Asthma / breathing problem? ──Yes──→ Pick a BETA1-SELECTIVE one
        |                                (atenolol, metoprolol, bisoprolol — NOT propranolol)
       No
        ↓
Emergency / ICU, need second-by-second control? ──Yes──→ Esmolol IV drip (9-min half-life)
        | No
        ↓
Heart failure? ──Yes──→ Bisoprolol or Carvedilol (proven to prolong life)
        | No
        ↓
Glaucoma (eye drops)? ──Yes──→ Metipranolol or Betaxolol eye drops
        | No
        ↓
Pregnancy hypertension? ──Yes──→ Labetalol (drug of choice)
        |
       Otherwise ──→ Atenolol / Metoprolol (standard hypertension, angina)
```

Flowchart 3 — SAR decision path (designing a beta-blocker)

```
Start: Ar-O-CH2-CH(OH)-CH2-NH-R
        |
Keep -OH? ──No──→ DEAD molecule (rule i) ──→ STOP
  | Yes
S-enantiomer? ──No──→ weak (rule ii) ──→ resolve or accept racemate
  | Yes
Bulky N-group (isopropyl / tert-butyl)? ──No──→ becomes agonist-like (rule iv) ──→ STOP
  | Yes
        ↓
Want beta1-selective? ──Yes──→ single phenyl + smart PARA group (rule vi)
        |                          (atenolol's -CH2CONH2, metoprolol's -CH2CH2OCH3)
       No (want non-selective) ──→ big fused ring, e.g. naphthalene (rule vii)
        |
Want alpha-blocking too? ──Yes──→ add carbazole (rule viii) = carvedilol;
        |                            or salicylamide design = labetalol
       No ──→ done: classic beta-blocker
```

Infographic Concept Box — "The Beta-Blocker Family Tree" (one-page visual idea)

- **Trunk:** the aryloxypropanolamine scaffold Ar–O–CH2–CH(OH)–CH2–NH–R, drawn large across the middle.
- **Left branch (NON-SELECTIVE):** a big naphthalene leaf labelled Propranolol — "blocks beta1 + beta2; the prototype; avoid in asthma".
- **Middle branch (BETA1-SELECTIVE / cardioselective):** six leaves — Atenolol (para –CH2CONH2), Metoprolol (para –CH2CH2OCH3 + ortho CH3), Bisoprolol (long para ether — "most selective"), Betaxolol and Metipranolol (eye-drop leaves, glaucoma icon), Esmolol (leaf with a scissors icon — "ester tail, 9-minute life, IV only").
- **Right branch (MIXED alpha + beta):** two leaves — Labetalol (pregnancy-safe icon) and Carvedilol (carbazole triple-ring icon, heart-failure shield).
- **Roots (alpha-blockers, separate small tree):** Tolazoline & Phentololamine as imidazoline roots, Phenoxybenzamine as a root wrapped in chains ("irreversible — covalent glue"), Prazosin as a quinazoline root ("alpha1-selective"), Dihydroergotamine as an ergot-fungus root.
- **Footer strip:** the 8 SAR rules as numbered icons ①–⑧ along the bottom.

Worked Examples

Example 1 — Exam-style: "Classify propranolol, atenolol, labetalol and prazosin."

- Step 1: Look at the ending. Propranolol, atenolol, labetalol end in -olol → beta-blocker family. Prazosin ends in -zosin → alpha1-blocker.
- Step 2: Check selectivity. Propranolol has a naphthalene (big fused) ring → non-selective (beta1 + beta2). Atenolol has a single phenyl with para –CH2CONH2 → beta1-selective. Labetalol ends in -olol BUT has the salicylamide piece → mixed alpha1 + beta (the trap — always mention both).
- Step 3: Write the answer: Propranolol — non-selective beta-blocker (aryloxypropanolamine); Atenolol — beta1-selective beta-blocker (aryloxypropanolamine); Labetalol — mixed alpha1 + beta blocker; Prazosin — alpha1-selective blocker (quinazoline).
- *Takeaway:* Ending (-olol/-zosin) first, then the ring/para-group check, then remember the two mixed-blocker exceptions.

Example 2 — SAR application: "Why is esmolol ultra-short-acting while metoprolol is long-acting?"

- Step 1: Draw both scaffolds. Both are aryloxypropanolamines with para substituents.
- Step 2: Compare the para tails. Esmolol: para –CH2–CH2–C(=O)–O–CH3 — an **ester**. Metoprolol: para –CH2–CH2–O–CH3 — an **ether**.
- Step 3: Blood contains esterase enzymes that hydrolyse (cut) esters in minutes but cannot touch ethers. So esmolol is chopped into an inactive acid almost as fast as it is infused (half-life ≈ 9 min), while metoprolol survives for hours.
- *Takeaway:* Ester in the side chain = built-in self-destruct button. This is deliberate drug design, not an accident.

Example 3 — Clinical reasoning: "A hypertensive patient has asthma. Which beta-blocker is safe, and why?"

- Step 1: Asthma airways depend on beta2 receptors to stay open. A non-selective beta-blocker (propranolol) would plug beta2 and risk a severe asthma attack.
- Step 2: Choose a beta1-selective (cardioselective) agent — atenolol, metoprolol or bisoprolol — which prefers the heart's beta1 and mostly spares lung beta2.
- Step 3: Even then, use the lowest effective dose and watch breathing, because selectivity is dose-dependent (at high doses, "selective" drugs start blocking beta2 too).
- *Takeaway:* Asthma + hypertension → cardioselective beta1-blocker, never propranolol; and selectivity fades at high doses.

Analogies (to lock the concepts in memory)

- **Sympatholytic = earplugs for the fight-or-flight alarm.** The alarm (adrenaline) still rings; the organs just can't hear it.
- **Selective blocker = a key cut for one lock; non-selective = a master key.** The master key opens doors you didn't want opened (like the lung's beta2 doors).
- **Phenoxybenzamine = superglue in the lock.** Other blockers are corks you can pull out; phenoxybenzamine glues the lock shut permanently.
- **Esmolol = a sparkler, metoprolol = a candle.** Both give light (beta-blockade), but the sparkler burns out in minutes (ester chopped by blood enzymes) while the candle burns for hours.
- **Para substituent = the selectivity dial on a radio.** Turn the dial (change the para group) and you tune from "all stations" (non-selective) to "one station" (beta1-selective).
- **Labetalol/carvedilol = a player who bats and bowls.** One drug, two skills: calms the heart AND widens the vessels.

Pharmacy Relevance (why a pharmacist must know this)

- **Dispensing vigilance:** Never dispense propranolol to an asthmatic without checking with the prescriber — a non-selective beta-blocker can precipitate a life-threatening asthma attack. Recommend a cardioselective alternative.
- **First-dose counselling:** A patient starting prazosin must be warned about the "first-dose effect" — take the first tablet at bedtime, rise slowly — to prevent fainting from sudden blood-pressure fall.
- **Eye-drop technique:** For metipranolol/betaxolol glaucoma drops, teach punctal occlusion (press the inner corner of the eye for a minute) so less drug drains into the nose and bloodstream — reducing systemic beta-blockade side effects like slow pulse.
- **Esmolol in ICU:** It comes as an IV infusion that must be titrated (dose adjusted drop by drop) with continuous heart-rate and blood-pressure monitoring — a classic hospital-pharmacist preparation and monitoring role.
- **Stopping safely:** Beta-blockers must never be stopped suddenly after long use — rebound hypertension, angina or even heart attack can follow. Counsel every patient on tapering.
- **Pregnancy:** Labetalol is the go-to antihypertensive in pregnancy — a pharmacist should know it is preferred over many other blood-pressure drugs for the expectant mother.

India Context

- **Propranolol and atenolol are among the most widely used blood-pressure and heart drugs in India** — cheap, available as generics in every pharmacy, and listed in standard treatment guidelines for hypertension and angina. Atenolol 50 mg once daily is a staple prescription across Indian clinics.
- **Metoprolol (especially the extended-release form)** is hugely prescribed in Indian cardiology practice for hypertension, angina and post-heart-attack care.
- **Esmolol's ultra-short action makes it the ICU favourite in Indian tertiary hospitals** — during cardiac surgery or in hypertensive emergencies, anaesthetists run it as a titratable IV drip because it can be switched off in minutes if the pressure falls too far.
- **Prazosin remains in use in India for hypertension and BPH**, valued for being inexpensive; pharmacists routinely counsel on its first-dose bedtime rule.
- **Glaucoma burden:** India has millions of glaucoma patients; beta-blocker eye drops (betaxolol, and timolol — a cousin not in this chapter) are first-line, affordable therapy, and correct drop technique counselling is a daily community-pharmacy task.
- **Pheochromocytoma surgery** in Indian endocrine-surgery centres still follows the classic protocol: oral phenoxybenzamine for 1–2 weeks before tumour removal to tame adrenaline surges.

Key Points (must-remember list)

1. Sympatholytics block fight-or-flight signals: alpha-blockers relax blood vessels; beta-blockers calm the heart.
2. Alpha-blockers here: tolazoline, phentolamine, phenoxybenzamine (all non-selective, imidazoline/imidazoline/haloalkylamine), prazosin (alpha1-selective, quinazoline), dihydroergotamine (ergot alkaloid, migraine).
3. Phenoxybenzamine is IRREVERSIBLE — its nitrogen-mustard-like aziridinium ion forms a covalent bond with the alpha receptor.
4. Beta-blockers here: propranolol (non-selective, prototype, naphthalene); atenolol, metoprolol, bisoprolol, esmolol, betaxolol, metipranolol (beta1-selective/cardioselective); labetalol, carvedilol (mixed alpha1 + beta).
5. Almost all beta-blockers share the aryloxypropanolamine scaffold: Ar–O–CH2–CH(OH)–CH2–NH–R.
6. SAR essentials: –OH essential (H-bonding); S-enantiomer active; –CH2– spacer needed; bulky N-substituent (isopropyl/tert-butyl) boosts blockade; ortho substitution tolerated; para substituent = beta1-selectivity dial; fused rings (naphthalene) = non-selective; carbazole = added alpha-blocking.
7. Esmolol has a para ester → chopped by blood esterases → half-life ≈ 9 min → IV drip for ICU emergencies.
8. Labetalol is the drug of choice for hypertension in pregnancy; carvedilol and bisoprolol prolong life in heart failure.
9. Never give propranolol (non-selective) to asthmatics; prefer cardioselective agents — and even those lose selectivity at high doses.
10. Syllabus typos corrected: "Metibranolol" = metipranolol; "Betazolol" = betaxolol.

Common Confusions (cleared up)

- **Selective vs non-selective:** Selective = blocks ONE subtype (e.g., atenolol → beta1 only). Non-selective = blocks two or more (e.g., propranolol → beta1 + beta2; phentolamine → alpha1 + alpha2). The confusion costs marks because the side-effect profile flips with it (asthma risk only with non-selective beta-blockers).
- **Labetalol vs carvedilol:** BOTH are mixed alpha1 + beta blockers and both end in -olol — but labetalol has a salicylamide ring and is the pregnancy-hypertension drug (IV/oral), while carvedilol has a carbazole ring and is the heart-failure drug. Different ring, different headline use.
- **Prazosin vs phenoxybenzamine:** Both are alpha-blockers, but prazosin is alpha1-SELECTIVE and reversible (quinazoline), while phenoxybenzamine is NON-selective and IRREVERSIBLE (covalent glue via aziridinium ion).
- **Metipranolol vs metoprolol:** Similar names, different drugs. Metipranolol = eye drops for glaucoma (beta1-selective). Metoprolol = oral tablets for hypertension/angina (beta1-selective). Don't swap them.
- **Esmolol vs "slow-lol":** The name sounds ordinary, but esmolol is the SHORTEST-acting beta-blocker (ester → 9-minute half-life), given only as IV drip — the opposite of a once-daily tablet.
- **Alpha-blocker effect on heart rate:** Alpha-blockers lower blood pressure by widening vessels, but the body may reflexly speed the heart (reflex tachycardia) — blocking alpha does NOT directly slow the heart the way beta-blockers do.

Common Mistakes (exam hall traps)

1. Writing "Betazolol" or "Metibranolol" — these are syllabus typos; the correct names are **betaxolol** and **metipranolol**. Examiners reward the correction.
2. Calling labetalol/carvedilol "pure beta-blockers" — they are MIXED alpha1 + beta blockers; missing the alpha1 part loses half the marks.
3. Saying phenoxybenzamine is reversible — it is the chapter's only IRREVERSIBLE blocker (covalent bond). Reversible vs irreversible is a favourite one-mark question.
4. Giving propranolol for a patient with asthma in a case question — non-selective beta-blockade narrows airways; choose a cardioselective agent.
5. Forgetting the –OH in the SAR: the beta-carbon –OH is ESSENTIAL for hydrogen bonding — a structure without it is inactive.
6. Mixing up which para groups give selectivity: atenolol = para –CH2CONH2; metoprolol = para –CH2CH2OCH3. Learn one example per rule.
7. Stating esmolol is oral — it is IV ONLY (ester would not survive, and the ultra-short action needs a drip).

Mnemonics

- **Beta1-selective ("cardioselective") agents — "A B C D E M": A**tenolol, **B**etaxolol, **B**isoprolol, **E**smolol, **M**etoprolol, **M**etipranolol. Memory hook: "A Big CarDiac EMergency" — the cardioselective team.
- **Non-selective alpha-blockers — "The 3 Ph's of Phenoxy": Ph**entolamine, **Ph**enoxybenzamine, plus **T**olazoline ("T joins the Ph club"). All block alpha1 + alpha2.
- **Mixed alpha + beta — "LAB CAR": Lab**etalol and **Car**vedilol — the two that do both jobs, like a lab car that carries two drivers.
- **Irreversible blocker:** "**Phenoxy** puts the **ph**one down forever" — phenoxybenzamine = permanent (covalent) blockade.
- **Esmolol's ester:** "**E**smolol = **E**ster = **E**mergency (IV, minutes)". Three E's, one ultra-short drug.
- **SAR –OH rule:** "No OH, no hold" — without the beta-carbon hydroxyl, the drug can't hydrogen-bond and can't hold the receptor.

Exam Summary (the whole chapter in one page)

- **Sympatholytic** = blocks sympathetic fight-or-flight signals (adrenaline/noradrenaline) at alpha or beta receptors.
- **Alpha-blockers:** tolazoline (imidazoline, non-selective), phentolamine (imidazoline, non-selective, injectable), phenoxybenzamine (haloalkylamine, non-selective, IRREVERSIBLE via aziridinium ion → covalent bond; pheochromocytoma surgery cover), prazosin (quinazoline, alpha1-selective; hypertension + BPH; first-dose hypotension), dihydroergotamine (ergot alkaloid; acute migraine).
- **Beta-blockers** (all aryloxypropanolamines except where noted): propranolol (non-selective, naphthalene, prototype; hypertension, angina, migraine prevention, tremor); atenolol (beta1-selective, para –CH2CONH2; hypertension); metoprolol (beta1-selective, ortho-CH3 + para –CH2CH2OCH3; hypertension, angina, post-MI); bisoprolol (highly beta1-selective; heart failure); esmolol (beta1-selective, para ester, t½ ≈ 9 min, IV only; ICU emergencies); betaxolol (beta1-selective; glaucoma drops + hypertension); metipranolol (beta1-selective; glaucoma drops).
- **Mixed blockers:** labetalol (salicylamide; alpha1 + beta; hypertension in pregnancy, IV emergencies); carvedilol (carbazole; alpha1 + beta; heart failure).
- **SAR (8 rules):** (i) beta-carbon –OH essential; (ii) S-enantiomer active; (iii) –CH2– spacer required; (iv) bulky N-substituent (isopropyl/tert-butyl) boosts activity; (v) ortho substitution tolerated; (vi) para substituent = beta1-selectivity dial; (vii) fused rings (naphthalene) = non-selective; (viii) carbazole = added alpha-blocking.
- **Name corrections:** Metibranolol → metipranolol; Betazolol → betaxolol.
- **Syntheses:** Tolazoline *and Propranolol* are in Chapter 8 (Synthesis Handbook), not here.

One-Minute Revision (read this just before the exam)

Alpha-blockers: tolazoline, phentolamine (imidazolines, non-selective); phenoxybenzamine (IRREVERSIBLE, aziridinium, covalent); prazosin (quinazoline, alpha1-selective, BPH + first-dose effect); dihydroergotamine (ergot, migraine). Beta-blockers: scaffold Ar–O–CH2–CH(OH)–CH2–NH–R. Propranolol = non-selective prototype (naphthalene). Cardioselective = atenolol, metoprolol, bisoprolol, esmolol, betaxolol, metipranolol ("A B C D E M"). Mixed = labetalol (pregnancy), carvedilol (heart failure, carbazole). SAR: OH essential, S active, spacer needed, bulky N good, ortho OK, para = selectivity, fused ring = non-selective, carbazole = alpha too. Esmolol = ester, 9 min, IV only. Typos: metipranolol, betaxolol. Never propranolol in asthma.

Exam Questions

MCQs (10) — with answer key

1. Which of the following is an IRREVERSIBLE alpha-adrenergic blocker? a) Prazosin b) Phenoxybenzamine c) Phentolamine d) Tolazoline
2. The aryloxypropanolamine scaffold of beta-blockers is: a) Ar–CH(OH)–CH2–NH–R b) Ar–O–CH2–CH(OH)–CH2–NH–R c) Ar–O–CH2–CH2–NH–R d) Ar–NH–CH2–CH(OH)–CH2–R
3. Which beta-blocker is ultra-short-acting due to a para ester group hydrolysed by blood esterases? a) Metoprolol b) Bisoprolol c) Esmolol d) Atenolol
4. The beta1-selectivity of atenolol is attributed to its para substituent: a) –CH2CONH2 b) –CH2CH2OCH3 c) naphthalene ring d) –CH2CH2COOCH3
5. Which drug is the DOC (drug of choice) for hypertension in pregnancy? a) Propranolol b) Labetalol c) Prazosin d) Phenoxybenzamine
6. The "nitrogen-mustard-like" reactive species formed by phenoxybenzamine is the: a) epoxide ion b) aziridinium ion c) carbonium ion d) nitrenium ion
7. Which statement about the SAR of beta-blockers is TRUE? a) The R-enantiomer is more active b) The –OH on the beta carbon is essential for hydrogen bonding c) A methyl group on nitrogen gives the best blockade d) Ortho substitution always destroys activity
8. Carvedilol differs from metoprolol mainly because its _____ ring adds alpha1-blocking activity: a) naphthalene b) quinazoline c) carbazole d) imidazoline
9. "Betazolol" in the syllabus is a typo for: a) betaxolol b) bisoprolol c) butoxamine d) bevantolol
10. Which beta-blocker should be AVOIDED in a hypertensive patient with asthma? a) Atenolol b) Bisoprolol c) Propranolol d) Esmolol

Answer key: 1-b, 2-b, 3-c, 4-a, 5-b, 6-b, 7-b, 8-c, 9-a, 10-c.

Viva Questions (5) — with short answers

1. *What is a sympatholytic agent?* — A drug that blocks the sympathetic (fight-or-flight) signals of adrenaline/noradrenaline at alpha or beta receptors, e.g., propranolol, prazosin.
2. *Why is phenoxybenzamine called irreversible?* — It forms an aziridinium ion (nitrogen-mustard-like) that makes a permanent covalent bond with the alpha receptor; blockade lasts until new receptors are synthesised.
3. *Name the scaffold of beta-blockers and its two essential features.* — Aryloxypropanolamine: Ar–O–CH2–CH(OH)–CH2–NH–R. Essential: the –OH on the beta carbon (hydrogen bonding) and a bulky N-substituent like isopropyl or tert-butyl.
4. *Which enantiomer of a beta-blocker is more active, and why does it matter?* — The S-enantiomer; the chiral CH(OH) carbon's S form fits the receptor pocket far better, so it carries most of the activity of the racemic mixture.
5. *Why is esmolol given only intravenously?* — Its para methyl-ester is hydrolysed by blood esterases within minutes (half-life ≈ 9 min); as an IV drip its effect can be titrated and switched off almost instantly in emergencies.

Application-Based Questions (3)

1. A 55-year-old hypertensive man also suffers from bronchial asthma. His doctor considers a beta-blocker. Which agents are safe choices and which one must be avoided? Justify using selectivity and SAR. *(Expected: avoid propranolol — non-selective, naphthalene ring blocks beta2 → bronchospasm; choose cardioselective atenolol/metoprolol/bisoprolol — single phenyl with para selectivity handle, spares beta2; note selectivity is lost at high doses.)*
2. A patient with pheochromocytoma is scheduled for tumour-removal surgery in 10 days and has dangerously high blood pressure. Which alpha-blocker is started now, and what chemistry makes its effect last so long? *(Expected: phenoxybenzamine — non-selective alpha-blocker; its 2-chloroethyl group forms an aziridinium ion that covalently (irreversibly) bonds the alpha receptor, so adrenaline surges during surgery cannot spike blood pressure.)*
3. A drug-design team wants a beta-blocker for ICU use that can be "switched off" within minutes if blood pressure falls too far. Which structural feature would you build in, and which marketed drug proves the concept? *(Expected: a hydrolysable ester in the para side chain — blood esterases destroy it rapidly; esmolol, para –CH2CH2COOCH3, half-life ≈ 9 min, given as titratable IV drip.)*

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BP402T Medicinal Chemistry — Semester IV

Chapter 5: Cholinergic (Parasympathomimetic) Agents — Unit II

Learning Objectives

After studying this chapter, you should be able to:

1. Define parasympathomimetic agents and explain what the parasympathetic ("rest-and-digest") system does.
2. Distinguish muscarinic and nicotinic acetylcholine receptors (location and response).
3. Classify cholinergic drugs into direct-acting muscarinic agonists, indirect-acting anticholinesterases (reversible and irreversible), and cholinesterase reactivators.
4. Explain, in simple words, how carbamates and organophosphates block cholinesterase (carbamylation vs phosphorylation of the serine –OH).
5. Describe the structure, chemical class, and therapeutic uses of all 16 drugs in this chapter.
6. Explain how pralidoxime chloride reactivates cholinesterase in 3 simple steps.
7. Recall India-relevant clinical uses (neostigmine in myasthenia gravis, pralidoxime + atropine in organophosphate poisoning, pilocarpine in glaucoma).

1. Definitions

- **Cholinergic agent:** A drug that produces the same effects as acetylcholine (ACh), the body's main "rest-and-digest" messenger. Another word for cholinergic is **parasympathomimetic** — "mimetic" means *copying or mimicking*, so a parasympathomimetic is a drug that *mimics* the parasympathetic nervous system.
- **Agonist:** A drug that switches a receptor ON (like pressing the start button). Cholinergic agonists switch acetylcholine receptors ON.
- **Antagonist:** A drug that blocks a receptor (like putting a lock on the switch). Not the subject of this chapter, but you will meet them in anticholinergic chapters.
- **Cholinesterase (ChE):** An enzyme (a protein that speeds up chemical reactions) whose job is to destroy acetylcholine after it has done its work. There are two forms: **acetylcholinesterase (AChE)** at nerve endings, and **butyrylcholinesterase (BuChE)** in blood plasma.
- **Anticholinesterase:** A drug that blocks cholinesterase, so acetylcholine survives longer and its signal gets stronger. These are the **indirect-acting** cholinergic drugs — they don't touch the receptor directly; they just raise the level of the natural messenger.
- **Direct-acting:** Drugs that bind directly to the acetylcholine receptor and switch it on themselves (e.g., carbachol, pilocarpine).
- **Receptor:** A protein "switch" on a cell that receives a chemical signal. Acetylcholine works on two receptor families: **muscarinic** (letter "M") and **nicotinic** (letter "N").

Key takeaway: Cholinergic drugs either copy acetylcholine at the receptor (direct) or protect natural acetylcholine from being destroyed (indirect).

2. Terminology Word Bank

Term	Simple meaning	Example
Parasympathetic nervous system	The "rest-and-digest" branch of the automatic nervous system; slows the heart, makes saliva, helps digestion and urination	What is active after a heavy lunch
Sympathetic nervous system	The "fight-or-flight" branch; opposite of parasympathetic	What is active during an exam
Acetylcholine (ACh)	The chemical messenger used by the parasympathetic system	Released at nerve endings to slow the heart
Hydrolysis	Breaking a molecule using water (hydro = water, lysis = breaking)	Cholinesterase hydrolyses acetylcholine into choline + acetic acid
Serine –OH	A part of the enzyme's active site (the –OH group of the amino acid serine); the "handle" the drug grabs	Carbamates grab this –OH
Carbamylation	Attaching a carbamate group (–O–CO–N) to the enzyme's serine –OH	What physostigmine does — slow, reversible
Phosphorylation	Attaching a phosphate group to the enzyme's serine –OH	What organophosphates do — very strong, practically permanent
Oxime	A chemical group (C=N–OH) that can pull a phosphate off an enzyme	Pralidoxime contains an oxime
Muscarinic selectivity	Acting mostly on muscarinic receptors, not nicotinic ones	Bethanechol is muscarinic-selective
Quaternary ammonium	A nitrogen atom with four bonds carrying a permanent positive charge (written N^+); cannot cross the brain barrier	Neostigmine is a quaternary ammonium drug
Tertiary amine	A nitrogen with three bonds, uncharged; can enter the brain	Physostigmine is a tertiary amine
Glaucoma	Eye disease where fluid pressure inside the eye is dangerously high	Pilocarpine eye drops lower this pressure
Myasthenia gravis	Disease where muscles become weak because the body's own antibodies attack nicotinic receptors	Neostigmine and pyridostigmine treat it

3. The Parasympathetic System: Rest and Digest

Technical concept: The autonomic (automatic) nervous system has two branches — sympathetic ("fight or flight") and parasympathetic ("rest and digest"). The parasympathetic branch uses acetylcholine as its messenger at most of its endings.

Simple explanation: Think of the two branches as the accelerator and the brake of a car. The sympathetic system is the **accelerator** — it speeds the heart, opens the airways, and stops digestion when you are in danger. The parasympathetic system is the **brake and the kitchen staff** — it slows the heart, makes the pupils smaller, increases saliva and digestive juices, moves food through the gut, and empties the bladder. It is most active when you are relaxed, eating, and digesting — hence "rest and digest."

Example: After a heavy thali, your parasympathetic system is in charge: heart slow, digestion busy, bladder ready. A cholinergic drug produces similar effects — slow heart, more saliva, gut movement, urination.

Key takeaway: Cholinergic drugs copy the "rest-and-digest" system: ↓ heart rate, ↑ saliva/tears, ↑ gut movement, bladder emptying, pupil constriction.

4. Muscarinic vs Nicotinic Receptors — One Simple Table

Acetylcholine works on **two receptor families**. Muscarinic receptors were named because the mushroom poison **muscarine** switches them on; nicotinic receptors were named because **nicotine** (from tobacco) switches them on.

Feature	Muscarinic receptors (M_1–M_5)	Nicotinic receptors (N_m, N_n)
Switched on by	Muscarine, acetylcholine	Nicotine, acetylcholine
Where found	Heart, gut, glands, eye, bladder, brain	Muscle junctions (N_m), nerve ganglia and brain (N_n)
What happens when switched on	Slow heart, more saliva, gut squeezes, pupil shrinks	Skeletal muscle contracts; nerve signals pass on
Blocked by	Atropine	Curare (muscle type), hexamethonium (ganglion type)
Drug examples in this chapter	Pilocarpine, bethanechol, methacholine	Carbachol (acts on both), neostigmine effect is via more ACh

Simple memory hook: M = Mushroom (muscarine) and Mostly organs; N = Nicotine and Nerves/muscles.

Key takeaway: Most therapeutic effects in this chapter (glaucoma, gut/bladder stimulation) come from muscarinic action. Muscle-strengthening effects (myasthenia gravis) come from the nicotinic side.

5. Chemical Classification — Master Table

Cholinergic drugs are classified by **how** they raise cholinergic activity: directly at the receptor, or indirectly by saving acetylcholine from destruction.

Main class	Sub-class	Drugs	Simple identifying feature
A. Direct-acting muscarinic agonists	Choline esters	Acetylcholine, Carbachol, Bethanechol, Methacholine	Built on the choline skeleton (N^+–CH_2–CH_2–O–)
	Alkaloid	Pilocarpine	Plant alkaloid with an imidazole ring
B. Indirect-acting (anticholinesterases)	Reversible carbamates	Physostigmine, Neostigmine, Pyridostigmine	Carry a carbamate group; enzyme recovers in hours
	Other reversibles	Edrophonium chloride, Tacrine hydrochloride, Ambenonium chloride	No carbamate; block by short, weak binding
	Irreversible organophosphates	Isofluorphate, Echothiophate iodide, Parathion*, Malathion	Phosphorus compounds; enzyme blocked for days–weeks
C. Cholinesterase reactivator	Oxime	Pralidoxime chloride	Oxime (C=N–OH) that pulls phosphate off the enzyme

\Syllabus note:* The syllabus prints "Parathione" — this is a spelling error for **parathion**, the well-known organophosphate insecticide. This chapter covers parathion.

5A. The Choline Esters — Structural Tweaks Explained Simply

All four choline esters share the same skeleton: a **quaternary nitrogen (N^+)** connected through two CH_2 groups to an oxygen (N^+–CH_2–CH_2–O–CO–). Acetylcholine is destroyed by cholinesterase in a fraction of a second — useless as a medicine. The other three are **tweaked versions** that survive longer:

- **Carbachol:** The ester group (–O–CO–CH_3) is replaced by a **carbamate** (–O–CO–NH_2). Cholinesterase cannot easily break a carbamate, so carbachol is **stable to cholinesterase** and acts longer. Think of it as replacing a paper lock with a steel lock.
- **Bethanechol:** Has a **beta-methyl group** (an extra CH_3 on the carbon next to the nitrogen). This methyl group physically blocks the enzyme from reaching the molecule (like a shield), making it stable, and it also makes the drug **prefer muscarinic receptors** over nicotinic ones. Bethanechol = carbamate + beta-methyl.
- **Methacholine:** Has the **beta-methyl group** like bethanechol but keeps the normal **acetyl ester** (not a carbamate). So it is muscarinic-selective but still broken down by cholinesterase fairly quickly.

Flowchart — how the tweaks were designed:

```
Acetylcholine (natural, destroyed in seconds)
    │
    ├─ Replace ester with CARBAMATE ──► Carbachol (stable, longer acting)
    │
    ├─ Add BETA-METHYL to the chain ──► Bethanechol (stable + muscarinic selective)
    │
    └─ Beta-methyl + keep acetyl ester ─► Methacholine (muscarinic selective, short)
```

Key takeaway: Carbamate = stability against the enzyme; beta-methyl = muscarinic selectivity (+ some stability).

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6. Individual Drugs — Structure, Class, Uses

6.1 Acetylcholine (ACh)

- **Chemical class:** Direct-acting choline ester; the natural neurotransmitter.
- **Structure (described in text):** A simple straight-chain molecule: a quaternary ammonium head — nitrogen carrying three methyl groups and a permanent positive charge ($N^+(CH_3)_3$) — joined by a two-carbon (–CH_2–CH_2–) bridge to an **acetate ester** (–O–CO–CH_3). Formula feel: CH_3–CO–O–CH_2–CH_2–$N^+(CH_3)_3$.
- **Therapeutic uses:** (1) Rarely used as a drug because it is destroyed in seconds and acts everywhere (heart, gut, glands) — too messy. (2) Occasionally used as an eye solution during eye surgery to constrict the pupil quickly (miosis).

6.2 Carbachol

- **Chemical class:** Direct-acting choline ester (synthetic); acts on both muscarinic and nicotinic receptors.
- **Structure (described in text):** Same choline skeleton as acetylcholine ($N^+(CH_3)_3$–CH_2–CH_2–O–), but the acetyl ester is replaced by a **carbamate group** (–O–CO–NH_2). The –NH_2 (amino) part is the key change: the enzyme cannot hydrolyse a carbamate easily, so carbachol survives and acts for a long time. No beta-methyl group.
- **Therapeutic uses:** (1) Eye drops for glaucoma — constricts the pupil and drains eye fluid, lowering pressure. (2) Used during eye surgery to constrict the pupil.

> **Note box:** Carbachol* synthesis is given in full in Chapter 8 (Synthesis Handbook) — it is not repeated here.

6.3 Bethanechol

- **Chemical class:** Direct-acting choline ester; **muscarinic-selective** agonist.
- **Structure (described in text):** The carbachol skeleton (choline + carbamate, –O–CO–NH_2) **plus a beta-methyl group** — an extra CH_3 attached to the carbon next to (beta to) the nitrogen: $N^+(CH_3)_3$–$CH(CH_3)$–CH_2–O–CO–NH_2. The methyl "shield" gives enzyme stability and muscarinic preference.
- **Therapeutic uses:** (1) Stimulates the bladder to contract — used for **urinary retention** (when a patient cannot pass urine, e.g., after surgery). (2) Stimulates gut movement in postoperative or postpartum **paralytic ileus** (when the intestines have "gone to sleep").

6.4 Methacholine

- **Chemical class:** Direct-acting choline ester; muscarinic-selective agonist.
- **Structure (described in text):** The acetylcholine skeleton **plus a beta-methyl group** — $N^+(CH_3)_3$–$CH(CH_3)$–CH_2–O–CO–CH_3 — but it keeps the normal **acetyl ester** (not a carbamate). So it prefers muscarinic receptors but is still destroyed by cholinesterase (shorter action than bethanechol).
- **Therapeutic uses:** (1) **Diagnostic** — the methacholine challenge test: inhaled methacholine narrows airways; in asthma patients even a small dose causes measurable narrowing, so it is used to **diagnose bronchial hyperreactivity/asthma**. (Not used for this in patients with severe asthma — safety point.)

6.5 Pilocarpine

- **Chemical class:** Direct-acting muscarinic agonist; a **natural plant alkaloid** (from the leaves of *Pilocarpus* shrubs of South America).
- **Structure (described in text):** Not a choline ester at all. It has two ring systems joined together: a five-membered **imidazole ring** (a ring with two nitrogens — the part that mimics acetylcholine at the receptor) attached to a **lactone ring** (a cyclic ester). It is a tertiary amine (uncharged nitrogen), so unlike the choline esters it can cross into the eye tissues well and is stable enough for eye-drop use.
- **Therapeutic uses:** (1) **First-line eye drops for open-angle glaucoma** — constricts the pupil and opens the drainage channels, lowering eye pressure. (2) Treats **dry mouth (xerostomia)**, e.g., after radiation therapy of the head and neck — it stimulates saliva. (3) Used in diagnosis/testing of sweat glands in cystic fibrosis (sweat chloride test) — a classic exam point.

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7. Indirect-Acting Drugs — Anticholinesterases (Reversible)

Simple mechanism — how anticholinesterases work (numbered steps, very simple language)

Technical concept: Acetylcholinesterase has an active site with a serine amino acid whose –OH group attacks acetylcholine and breaks it. Anticholinesterases occupy this –OH so the enzyme cannot destroy acetylcholine — the natural messenger builds up.

Step-by-step:

1. **Normal working:** Acetylcholine arrives at the enzyme → the serine –OH grabs it, breaks it into choline + acetic acid → the enzyme is free again within milliseconds.
2. **Carbamate drugs (physostigmine, neostigmine, pyridostigmine):** The drug offers its carbamate group to the serine –OH instead. The enzyme becomes **carbamylated** — the –OH is capped with a carbamate "hat."
3. **Slow recovery:** Water removes a carbamate hat **very slowly** (hours). While the hat is on, the enzyme cannot destroy acetylcholine → acetylcholine piles up → stronger, longer signal. This is **reversible** — the enzyme eventually recovers.
4. **Organophosphate drugs (isofluorphate, parathion, malathion):** These put a **phosphate** "hat" on the same serine –OH (**phosphorylation**). The phosphate hat is almost impossible for water to remove — recovery takes days to weeks, and the body must make fresh enzyme. This is **irreversible** (practically permanent).
5. **Rescue (pralidoxime):** An oxime drug acts like a strong magnet that **pulls the phosphate hat off** the enzyme, but only if given early — after some hours the phosphate "sets" (a process called **ageing**) and even the oxime cannot remove it.

> **Analogy:** The enzyme is a dustbin that eats acetylcholine. A carbamate drug puts a lid on the dustbin that falls off after a few hours (reversible). An organophosphate **glues the lid shut** (irreversible) — only pralidoxime, applied quickly, can pry it open before the glue sets.

Textual diagram description (sketchable):

```
Normal:        Enzyme–OH  +  ACh  →  Enzyme–OH (free again) + choline + acetic acid
Carbamate:     Enzyme–OH  +  drug →  Enzyme–O–CO–NR₂  (blocked for hours) → slow recovery
Organophos.:   Enzyme–OH  +  drug →  Enzyme–O–PO(OR)₂  (blocked for days/weeks) → needs new
enzyme
Rescue:        Enzyme–O–PO(OR)₂ + pralidoxime → Enzyme–OH (free!) + oxime–phosphate
```

Key takeaway: Carbamylation = slow, reversible block (hours). Phosphorylation = near-permanent block (days–weeks); pralidoxime can reverse it only before "ageing."

7.1 Physostigmine (Eserine)

- **Chemical class:** Reversible carbamate anticholinesterase; **natural plant alkaloid** (from the Calabar bean, *Physostigma venenosum*).
- **Structure (described in text):** A complex three-ring (tricyclic) alkaloid skeleton carrying a **methylcarbamate group** (–O–CO–NH–CH_3) — this carbamate is the "warhead" that carbamylates the enzyme. The nitrogen in the ring system is a **tertiary amine** (uncharged), so physostigmine **crosses the blood–brain barrier** and works in the brain too.
- **Therapeutic uses:** (1) Eye drops for glaucoma (constricts pupil, lowers pressure). (2) **Antidote for atropine/belladonna poisoning** — because it enters the brain, it reverses the central effects (delirium, coma) of anticholinergic poisoning.

7.2 Neostigmine

- **Chemical class:** Reversible carbamate anticholinesterase; **synthetic**.
- **Structure (described in text):** A benzene ring carrying two substituents: a **dimethylcarbamate group** (–O–CO–N(CH_3)$_2$, the warhead) and, at the meta position, a **quaternary ammonium group** (–N^+(CH_3)$_3$, as the bromide salt). The permanent positive charge means neostigmine **cannot enter the brain** — its action is limited to the body (peripheral).
- **Therapeutic uses:** (1) **Myasthenia gravis** — the mainstay treatment in India; strengthens weak muscles by raising acetylcholine at the muscle junction. (2) Reverses the effect of muscle-relaxant drugs after surgery (anaesthesia reversal). (3) Urinary retention and paralytic ileus (stimulates bladder and gut).

7.3 Pyridostigmine

- **Chemical class:** Reversible carbamate anticholinesterase; synthetic; the "gentler, longer cousin" of neostigmine.
- **Structure (described in text):** Very close to neostigmine, but the benzene ring is replaced by a **pyridine ring** (a six-membered ring containing one nitrogen). It carries the same **dimethylcarbamate warhead** and a **quaternary $N^+(CH_3)$** group (bromide salt), so it also stays out of the brain.
- **Therapeutic uses:** (1) **Myasthenia gravis** — preferred for long-term daily use because it acts longer and causes fewer gut side effects than neostigmine. (2) Given to soldiers as pretreatment protection against nerve-gas (organophosphate) poisoning — a classic exam point.

7.4 Edrophonium chloride

- **Chemical class:** Reversible anticholinesterase — but **NOT a carbamate**. It blocks the enzyme by short, weak ionic/hydrogen bonding (no covalent hat).
- **Structure (described in text):** A simple benzene ring with two groups: a **phenolic –OH** (the part that hydrogen-bonds to the enzyme's active site) and a **quaternary ammonium ethyl group** (–CH_2–CH_2–N^+(CH_3)$_3$, chloride salt). Because the binding is weak, the block lasts only **minutes**.
- **Therapeutic uses:** (1) **Diagnosis of myasthenia gravis** — the "Tensilon test": an injection briefly restores muscle strength in a myasthenic patient, confirming the diagnosis. (2) Distinguishing myasthenic crisis (needs more drug) from cholinergic crisis (drug overdose) — an exam favourite.

7.5 Tacrine hydrochloride

- **Chemical class:** Reversible anticholinesterase (non-carbamate); an **acridine** derivative.
- **Structure (described in text):** A flat three-ring **acridine** system (three fused six-membered rings with one ring nitrogen) carrying an **amino (–NH_2) group** — chemically 1,2,3,4-tetrahydro-5-aminoacridine, as the hydrochloride salt. It binds to the enzyme's active site reversibly without a carbamate warhead.
- **Therapeutic uses:** (1) Historically the first drug approved for **Alzheimer's disease** (raises brain acetylcholine to improve memory) — now rarely used because of liver toxicity. (2) Exam point: prototype that led to safer Alzheimer's drugs (donepezil, rivastigmine).

7.6 Ambenonium chloride

- **Chemical class:** Reversible non-carbamate anticholinesterase.
- **Structure (described in text):** A **bis-quaternary** molecule — two quaternary ammonium heads (N^+(CH_3)$_3$) connected through a central aromatic linker (a benzene ring with amide/imine connections). The two positive charges let it grip the enzyme at two points, giving a longer reversible block than edrophonium. Chloride salt.
- **Therapeutic uses:** (1) **Myasthenia gravis** — an alternative when neostigmine/pyridostigmine are not tolerated; longer acting. (2) Occasionally for postoperative gut/bladder stimulation.

8. Irreversible Organophosphates

Simple intro: These are phosphorus-containing compounds that **phosphorylate** the enzyme's serine –OH. The block is practically permanent — the body must manufacture new enzyme (days to weeks). Two are medicines (used in the eye, where a tiny local dose is safe); two are **insecticides** (parathion, malathion) and are important as **poisons**, not medicines.

8.1 Isofluorphate (DFP — diisopropyl fluorophosphate)

- **Chemical class:** Irreversible organophosphate anticholinesterase.
- **Structure (described in text):** A central **phosphorus atom** double-bonded to oxygen (P=O), carrying a **fluorine atom** (the leaving group that departs when the phosphate bonds to the enzyme) and two **isopropoxy groups** (–O–$CH(CH_3)_2$). Small, oily, volatile liquid.
- **Therapeutic uses:** (1) Eye drops/ointment for **chronic glaucoma** — a very long-acting pupil constrictor (one dose lasts days). (2) Historical: studied as a nerve gas prototype — exam point linking to chemical warfare.

8.2 Echothiophate iodide

- **Chemical class:** Irreversible organophosphate anticholinesterase; synthetic **quaternary** compound (water-soluble, unlike most organophosphates).
- **Structure (described in text):** A **diethoxy-phosphoryl group** ($(C_2H_5O)_2P=O$) attached through a sulfur/oxygen linker to an ethyl chain ending in a **quaternary ammonium head** ($N^+(CH_3)_3$, iodide salt). The positive charge concentrates it at the enzyme and keeps it out of the brain.
- **Therapeutic uses:** (1) Eye drops for **chronic open-angle glaucoma** — long-acting. (2) Used in accommodative **esotropia** (a type of squint in children) — an exam favourite.

8.3 Parathion

- **Chemical class:** Irreversible organophosphate; **insecticide, NOT a medicine**.
- **Structure (described in text):** A central phosphorus with **P=S** (thiophosphate — the sulfur version), two **ethoxy groups** (–O–C_2H_5), and a **p-nitrophenyl group** (a benzene ring with an –NO_2 group opposite the attachment point). In the body/liver it is converted ("activated") to **paraoxon** (P=O), which is the true potent enzyme poison.
- **Use and poisoning relevance:** Used as an agricultural **insecticide** (crop pest control). It is highly toxic to humans — absorbed through skin, lungs, and gut. **Poisoning is common in rural India** (accidental farm exposure and deliberate ingestion). Signs: pinpoint pupils, excess saliva/tears, vomiting, diarrhoea, slow heart, muscle twitching, breathing difficulty. Treatment: **atropine + pralidoxime** (see Section 9).

> **Name note:** The syllabus spells this "Parathione" — the correct name is **parathion**. Remember the correct spelling for exams.

8.4 Malathion

- **Chemical class:** Irreversible organophosphate; **insecticide, NOT a medicine** (but safer than parathion).
- **Structure (described in text):** A **dithiophosphate** core — phosphorus with P=S and two **methoxy groups** (–O–CH_3) — attached through sulfur to a **succinate ester side chain** (a –CH(CO_2Et)–CH_2–CO_2Et group). Human liver breaks this side chain down quickly (carboxylesterases), which is why malathion is **much less toxic to humans** than parathion — a favourite exam comparison.
- **Use and poisoning relevance:** Agricultural and household **insecticide**; also used in public-health mosquito control. Poisoning is possible in overdose but less severe than parathion; treatment is the same (**atropine + pralidoxime**).

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9. Cholinesterase Reactivator — Pralidoxime chloride

- **Chemical class: Oxime** cholinesterase reactivator (not an agonist, not an anticholinesterase — it *undoes* the organophosphate block).
- **Structure (described in text):** A **pyridinium ring** (a six-membered aromatic ring with a positively charged nitrogen, N^+–CH_3) carrying an **aldoxime group** (–CH=N–OH) at the 2-position, as the chloride salt. The positive charge steers it to the enzyme's active site; the oxime –OH is the "claw" that grabs the phosphate.
- **Simple mechanism in 3 steps:**

1. **Aim:** The positively charged pyridinium ring is attracted to the blocked enzyme's active site (opposite charges attract), positioning the oxime right next to the phosphate "hat."
2. **Pull:** The oxime oxygen attacks the phosphorus atom and **pulls the phosphate group off** the serine –OH, forming an oxime–phosphate by-product.
3. **Free enzyme:** The serine –OH is free again → the enzyme can destroy acetylcholine normally → the poisoning signal fades. **Must be given early** — after "ageing" (hours), the phosphate bond hardens and pralidoxime cannot remove it.

> **Analogy:** Pralidoxime is like a strong magnet held next to a glued lid — it can yank the lid off only before the glue fully sets.

- **Therapeutic uses:** (1) **Organophosphate poisoning** — given WITH atropine: pralidoxime reactivates the enzyme (fixes muscle weakness/paralysis), while atropine blocks the muscarinic flood (fixes saliva, slow heart, pinpoint pupils). (2) Nerve-gas casualty treatment (military).

India context: Organophosphate pesticide poisoning is one of the commonest poisoning emergencies in rural Indian hospitals. Every emergency department stocks **atropine + pralidoxime** together — remember the pair: *"atropine dries, pralidoxime revives."*

Key takeaway: Pralidoxime does NOT work for carbamate poisoning (not needed — carbamates wear off by themselves) and does NOT work after ageing.

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10. Infographic Concept Box — "The Cholinergic Family Tree"

(Sketchable one-page visual for revision: draw a tree with three big branches.)

```
                  CHOLINERGIC DRUGS
                 (parasympathomimetics)
                         |
      +------------------+------------------+
      |                  |                  |
 DIRECT-ACTING     INDIRECT-ACTING     REACTIVATOR
 (switch receptor   (save ACh by        (undo the block)
  ON themselves)     blocking its
                     destroyer)
      |                  |                  |
Choline esters:    Reversible:         Pralidoxime
- Acetylcholine    - Carbamates:          (oxime claw
- Carbachol          physostigmine,        pulls phosphate
- Bethanechol        neostigmine,          off the enzyme)
- Methacholine       pyridostigmine
Alkaloid:          - Others:
- Pilocarpine        edrophonium,
(imidazole +         tacrine,
 lactone)            ambenonium
                   Irreversible:
                   - isofluorphate,
                     echothiophate
                     (eye medicines)
                   - parathion,
                     malathion
                     (insecticides!
                      poisons)
```

Colour code suggestion: Green = direct agonists, Yellow = reversible blockers, Red = irreversible poisons, Blue = rescue (pralidoxime).

11. Pharmacy Relevance

1. **Dispensing:** Pilocarpine and carbachol eye drops must be counselled — warn about blurred vision and brow ache (pupil constriction), and that night driving may be difficult.
2. **Myasthenia gravis:** Neostigmine/pyridostigmine doses are titrated to muscle strength — too little = weakness, too much = cholinergic crisis (weakness + saliva + cramps). Pharmacists must know the difference.
3. **Emergency stock:** Any hospital pharmacy in an agricultural district must stock **atropine injection + pralidoxime** for organophosphate poisoning — check expiry dates; this saves lives.
4. **Drug interactions:** Cholinergic drugs oppose anticholinergic drugs (e.g., atropine) — never combine casually; anaesthetists use neostigmine deliberately to reverse muscle relaxants.
5. **Patient counselling (bethanechol):** Take on an empty stomach (food reduces absorption) and expect increased salivation and urge to urinate — reassure the patient these are the drug working.

12. Key Points

1. Parasympathetic = rest-and-digest; acetylcholine is its messenger.
2. Muscarinic receptors = organs (heart, gut, glands, eye); nicotinic = muscles and nerve ganglia.
3. Direct-acting: choline esters (ACh, carbachol, bethanechol, methacholine) + pilocarpine (alkaloid).
4. Carbachol = carbamate → stable to cholinesterase. Bethanechol = beta-methyl → muscarinic selective. Methacholine = beta-methyl + acetyl ester → selective but short.
5. Indirect-acting = anticholinesterases: carbamates (reversible, hours) vs organophosphates (irreversible, days–weeks).
6. Physostigmine (tertiary amine) enters the brain — antidote for atropine poisoning; neostigmine (quaternary) does not — used in myasthenia gravis.
7. Edrophonium = ultra-short diagnostic (Tensilon test); tacrine = first Alzheimer's drug (liver toxic); ambenonium = bis-quaternary, long reversible.
8. Isofluorphate & echothiophate = irreversible but used in the eye for glaucoma; parathion & malathion = insecticides/poisons (syllabus typo "Parathione" = parathion).
9. Malathion is safer than parathion because human liver detoxifies its succinate side chain.
10. Pralidoxime (oxime) reactivates phosphorylated enzyme — 3 steps: aim, pull, free enzyme — only before ageing; always paired with atropine.

13. Common Confusions

Confused pair	Clear difference
Reversible vs irreversible anticholinesterases	Reversible (carbamates) wear off in hours — enzyme recovers by itself. Irreversible (organophosphates) need days–weeks and new enzyme; only pralidoxime (early) helps.
Carbachol vs bethanechol	Carbachol = carbamate only (acts on muscarinic + nicotinic, stable). Bethanechol = carbamate + beta-methyl (muscarinic-selective, stable). "Beta-methyl = be-thanechol's badge of selectivity."
Physostigmine vs neostigmine	Physostigmine = tertiary amine → enters brain → atropine-poisoning antidote. Neostigmine = quaternary → stays in body → myasthenia gravis.
Direct vs indirect acting	Direct = drug itself switches the receptor on (carbachol, pilocarpine). Indirect = drug saves natural ACh by blocking its destroyer (neostigmine, parathion).
Myasthenic crisis vs cholinergic crisis	Myasthenic = too little drug → weakness. Cholinergic = too much drug → weakness PLUS saliva, cramps, diarrhoea, pinpoint pupils. Edrophonium test tells them apart.
Pralidoxime vs atropine in OP poisoning	Atropine blocks muscarinic effects (dries secretions, speeds heart). Pralidoxime reactivates the enzyme (restores muscle strength). Both are given together.

14. Common Mistakes (Exam Hall Traps)

1. Writing "Parathione" — the correct spelling is **parathion**. The syllabus has a typo; examiners expect the correct drug name.
2. Calling parathion/malathion medicines — they are **insecticides**; their exam relevance is poisoning and its treatment.
3. Saying pralidoxime treats carbamate poisoning — it is for **organophosphate** poisoning only.
4. Forgetting that physostigmine crosses the blood–brain barrier while neostigmine does not — this single fact explains their different uses.
5. Mixing up the Tensilon test drug — it is **edrophonium** (ultra-short), not neostigmine.
6. Describing methacholine as long-acting — it keeps the acetyl ester, so cholinesterase still destroys it; it is **short-acting** and used diagnostically.
7. Omitting the oxime group when drawing/describing pralidoxime — the –CH=N–OH is the whole point of the drug.

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15. Mnemonics

- **Direct choline esters:** "**A**ll **C**lever **B**oys **M**emorise" — **A**cetylcholine, **C**arbachol, **B**ethanechol, **M**ethacholine.
- **Reversible carbamates:** "**P**hysio, **N**eo, **P**yridostigmine" — "**P**retty **N**urses **P**refer carbamates."
- **Irreversible organophosphates:** "**I** **E**at **P**oisonous **M**angoes" — **I**sofluorphate, **E**chothiophate, **P**arathion, **M**alathion.
- **OP poisoning treatment:** "**A**tropine **P**lus **P**ralidoxime" — "**A** **P**air **P**rotects."
- **Beta-methyl's job:** "**B**eta-methyl **B**rings **M**uscarinic selectivity" (Bethanechol, Methacholine).

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16. Exam Summary (One-Page Capsule)

- **Parasympathetic** = rest-and-digest; messenger = **acetylcholine**; destroyed by **cholinesterase**.
- **Muscarinic** (organs, blocked by atropine) vs **nicotinic** (muscle/ganglia, blocked by curare).
- **Direct:** ACh, carbachol (carbamate → stable), bethanechol (beta-methyl → muscarinic selective), methacholine (beta-methyl + acetyl → selective, short), pilocarpine (alkaloid, imidazole + lactone).
- **Reversible anticholinesterases:** physostigmine (tertiary, enters brain, atropine antidote), neostigmine (quaternary, myasthenia gravis), pyridostigmine (longer, myasthenia), edrophonium (minutes, Tensilon test), tacrine (first Alzheimer's drug), ambenonium (bis-quaternary).
- **Irreversible:** isofluorphate, echothiophate (glaucoma eye use), parathion, malathion (insecticides; poisoning).
- **Mechanism:** carbamylation (slow reversible, hours) vs phosphorylation (near-permanent, days–weeks) of serine –OH.
- **Pralidoxime:** oxime reactivator — aim, pull phosphate off, free enzyme; before ageing; always with atropine.
- **India:** neostigmine in myasthenia gravis; pilocarpine in glaucoma; OP pesticide poisoning → atropine + pralidoxime.

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17. One-Minute Revision

Cholinergic = copy acetylcholine. Two ways: **direct** (carbachol, bethanechol, methacholine, pilocarpine switch the receptor on) or **indirect** (block cholinesterase so natural ACh piles up). Carbamates (physostigmine, neostigmine, pyridostigmine) block reversibly for hours; organophosphates (isofluorphate, echothiophate, parathion, malathion) block irreversibly for weeks. **Pralidoxime** (oxime) yanks the phosphate off — early only. Uses to remember: **pilocarpine–glaucoma**, **neostigmine–myasthenia gravis**, **edrophonium–Tensilon test**, **methacholine–asthma diagnosis**, **atropine + pralidoxime–OP poisoning**. Syllabus "Parathione" = **parathion**.

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18. Exam Questions

A. Multiple Choice Questions (10)

Q1. Which structural change makes carbachol stable to cholinesterase? (a) Beta-methyl group (b) Carbamate instead of ester (c) Quaternary nitrogen (d) Lactone ring

Q2. Bethanechol is muscarinic-selective mainly because of: (a) The carbamate group (b) The beta-methyl group (c) The pyridine ring (d) The oxime group

Q3. The Tensilon (edrophonium) test is used in the diagnosis of: (a) Glaucoma (b) Myasthenia gravis (c) Asthma (d) Alzheimer's disease

Q4. Which drug is a tertiary amine that crosses the blood–brain barrier and is used as an antidote in atropine poisoning? (a) Neostigmine (b) Physostigmine (c) Pyridostigmine (d) Ambenonium

Q5. Pralidoxime chloride reactivates cholinesterase by: (a) Blocking muscarinic receptors (b) Removing the phosphate group from the serine –OH via its oxime group (c) Adding a carbamate to the enzyme (d) Destroying acetylcholine faster

Q6. The syllabus name "Parathione" is a typo for: (a) Paraoxon (b) Parathion (c) Malathion (d) Echothiophate

Q7. Malathion is less toxic to humans than parathion because: (a) It is not an organophosphate (b) Human liver rapidly detoxifies its succinate ester side chain (c) It cannot be absorbed through skin (d) It is a carbamate

Q8. Methacholine is used clinically mainly for: (a) Treating glaucoma (b) Diagnosing bronchial hyperreactivity (methacholine challenge test) (c) Long-term myasthenia gravis therapy (d) Reversing anaesthesia

Q9. Which pair is given TOGETHER in organophosphate poisoning? (a) Neostigmine + edrophonium (b) Atropine + pralidoxime (c) Pilocarpine + carbachol (d) Tacrine + ambenonium

Q10. Tacrine is chemically: (a) A choline ester (b) An aminoacridine derivative (c) A bis-quaternary compound (d) An organophosphate

Answer key: 1-(b), 2-(b), 3-(b), 4-(b), 5-(b), 6-(b), 7-(b), 8-(b), 9-(b), 10-(b).

B. Viva Questions (5)

V1. What is the difference between carbamylation and phosphorylation of cholinesterase?
Carbamylation attaches a carbamate group to the enzyme's serine –OH; water removes it slowly over hours, so the block is reversible. Phosphorylation attaches a phosphate group; it is practically permanent (days–weeks, needs new enzyme) and can only be undone early by pralidoxime before "ageing."

V2. Why is neostigmine preferred over physostigmine in myasthenia gravis? Neostigmine is a quaternary ammonium compound, so it does not enter the brain and causes no central side effects; it acts peripherally at the muscle junction where it is needed. Physostigmine enters the brain and is reserved for central indications like atropine-poisoning antidote and glaucoma.

V3. How does the beta-methyl group change a choline ester? It physically shields the molecule from cholinesterase (greater stability) and makes the drug prefer muscarinic receptors over nicotinic ones — seen in bethanechol and methacholine.

V4. Why must pralidoxime be given early in organophosphate poisoning? Because of "ageing": after a few hours the enzyme–phosphate bond hardens (loses an alkyl group), after which even the oxime cannot pull the phosphate off. Late pralidoxime is useless.

V5. Name two irreversible organophosphates used as medicines and two used as insecticides, with one use each. Medicines: isofluorphate (chronic glaucoma eye ointment) and echothiophate (glaucoma; accommodative esotropia). Insecticides: parathion and malathion (agricultural pest control; poisoning risk).

C. Application-Based Questions (3)

Q1. A farmer from rural Maharashtra is brought to casualty with pinpoint pupils, heavy salivation, vomiting, slow pulse, and muscle twitching after spraying crops. What poisoning do you suspect, and what two drugs form the emergency treatment? Explain each drug's role in one line. *Guidance:* Organophosphate (e.g., parathion/malathion) poisoning. Atropine blocks the muscarinic flood (dries secretions, raises heart rate); pralidoxime reactivates the phosphorylated enzyme (restores muscle strength). Give pralidoxime early, before ageing.

Q2. A myasthenia gravis patient on neostigmine develops weakness along with abdominal cramps, diarrhoea, and excessive saliva. Is this myasthenic crisis or cholinergic crisis, and how would you confirm it? *Guidance:* Cholinergic crisis (overdose — weakness PLUS muscarinic signs). Confirm with the edrophonium (Tensilon) test: brief improvement suggests myasthenic crisis (needs more drug); no improvement or worsening suggests cholinergic crisis (needs less drug / atropine).

Q3. An elderly glaucoma patient cannot tolerate beta-blocker eye drops. The doctor considers pilocarpine. Explain in simple terms how pilocarpine lowers eye pressure, and name two counselling points for the patient. *Guidance:* Pilocarpine (muscarinic agonist) constricts the pupil and pulls open the eye's drainage channels, letting fluid drain and lowering pressure. Counsel: expect blurred vision and brow ache initially; night driving may be difficult — instil drops as directed and do not stop without asking the doctor.

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UNIT II — Drugs Acting on the Autonomic Nervous System

Chapter 6 — Anti-cholinergic (Parasympatholytic) Agents

Learning Objectives

After studying this chapter, you should be able to:

1. Define anti-cholinergic (parasympatholytic) agents in simple words and explain what they block in the body.
2. Classify the 19 drugs of this chapter into five chemical groups: (a) solanaceous alkaloids and semi-synthetics, (b) synthetic aminoalcohol esters, (c) aminoethers, (d) aminoalcohols, and (e) quaternary ammonium compounds.
3. Describe the structure of each drug as a scaffold (the basic ring skeleton) plus its key substituents (the side groups attached to it), and state its chemical class.
4. State 1–3 therapeutic uses of each of the 19 drugs.
5. Explain what "quaternary" means in simple language and list which drugs in this chapter are quaternary, with reasons why they act only on the body and not on the brain.
6. State the five SAR rules of cholinergic blockers with one drug example for each rule.
7. Answer exam questions on atropine vs scopolamine vs hyoscyamine, tertiary vs quaternary amines, and the India-context uses of dicyclomine, atropine and ipratropium.

Definitions

- **Acetylcholine (ACh)** — A chemical messenger (neurotransmitter) used by nerves to send signals. In the parasympathetic system it carries "rest-and-digest" messages such as: slow the heart, contract the gut, make saliva and tears, narrow the pupil.
- **Parasympathetic nervous system** — The branch of the automatic (autonomic) nervous system that works when we rest and digest food. Simple meaning: the body's "slow down and digest" mode.
- **Parasympatholytic** — A drug that *dissolves/loosens* (lytic = loosening) the effects of the parasympathetic system. It is another name for anti-cholinergic.
- **Anti-cholinergic** — A drug that blocks the action of acetylcholine. Simple meaning: it switches OFF the rest-and-digest signals.
- **Muscarinic receptor** — A receiving station (receptor) on cells of the heart, gut, glands, eye and bladder that responds to acetylcholine. Anti-cholinergics sit on these stations and block acetylcholine from acting.
- **Competitive blockade** — The drug and acetylcholine fight for the same seat on the receptor; whoever is present in larger amount wins. Simple meaning: a musical-chairs fight at the receptor.
- **Mydriatic** — A drug that dilates (widens) the pupil of the eye so the doctor can look inside the eye.
- **Cycloplegic** — A drug that temporarily paralyses the focusing muscle of the eye (the ciliary muscle), used during eye testing, especially in children.
- **Quaternary ammonium compound** — A molecule in which the nitrogen atom makes FOUR bonds and therefore carries a permanent positive (+) charge. It is explained fully in this chapter.

Terminology (Words You Must Know)

- **Alkaloid** — A naturally occurring nitrogen-containing compound made by plants (e.g., the nightshade family). Many have strong effects on nerves.
- **Solanaceous** — Belonging to the nightshade plant family (Solanaceae), e.g., *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), *Datura*. The source of atropine, hyoscyamine and scopolamine.
- **Racemic mixture** — A 50:50 mixture of the left-handed and right-handed forms of the same molecule. Atropine is the racemic form of hyoscyamine.
- **Ester** — A chemical link (–COO–) formed when an acid joins an alcohol with loss of water. Most drugs in this chapter are esters.
- **Aminoalcohol** — A molecule that has both an amine group (nitrogen part) and an alcohol group (–OH part). In this chapter it means the "alcohol half" of the ester drugs.
- **Tertiary amine** — A nitrogen with THREE bonds and no permanent charge; it is fat-loving enough to cross into the brain. Simple meaning: the "free" nitrogen that can enter the brain.
- **Quaternary nitrogen** — A nitrogen with FOUR bonds and a permanent positive charge; it is water-loving and CANNOT cross the blood–brain barrier well. Simple meaning: the "locked, charged" nitrogen that stays in the body.
- **Blood–brain barrier (BBB)** — A tight wall of cells around brain blood vessels that stops charged and water-soluble molecules from entering the brain.
- **Scaffold** — The basic ring skeleton of a molecule, like the frame of a building; substituents hang on it like furniture.
- **Substituent** — A side group attached to the scaffold (e.g., a phenyl ring, a methyl group, an –OH).
- **SAR (Structure–Activity Relationship)** — The rules connecting a drug's chemical structure to its biological activity: which parts of the structure are needed for the drug to work.
- **Tropane ring** — The bicyclic (two-ring) nitrogen skeleton found in atropine, scopolamine and benztropine: a six-membered ring fused with a five-membered ring sharing a bridgehead nitrogen.
- **Antispasmodic** — A drug that stops painful cramps/spasms of smooth muscle (gut, bladder).
- **Antisialagogue** — A drug that reduces saliva production (used before surgery so the airway stays dry).
- **Bronchodilator** — A drug that opens (widens) the airways of the lungs.
- **Extrapyramidal symptoms (EPS)** — Unwanted movement side effects of some psychiatric drugs (tremor, stiffness, restlessness) that anti-cholinergics can correct.

Explanations (Concept → Simple Explanation → Example → Takeaway)

1. What do anti-cholinergics do in the body?

- *Concept:* Acetylcholine binds muscarinic receptors and produces rest-and-digest effects: slow heart, gut contraction, saliva/tear/sweat secretion, pupil narrowing, bladder contraction, bronchial narrowing.
- *Simple explanation:* Imagine acetylcholine is a set of "slow down and digest" text messages sent to organs. Anti-cholinergics put the phone on silent — the messages are sent but never received.
- *Example:* Atropine blocks the "slow the heart" message, so the heart beats faster; it blocks the "make saliva" message, so the mouth goes dry.
- *Takeaway:* Anti-cholinergic = acetylcholine-blocker = parasympathetic-OFF switch.

2. How do they block? (Mechanism — competitive antagonism)

- *Concept:* The drug molecule has a shape similar to acetylcholine, so it sits on the muscarinic receptor but does NOT switch it on; it just occupies the seat.
- *Simple explanation:* A wrong key fits into the lock but cannot turn it — and while it sits there, the real key (acetylcholine) cannot get in. If a lot of acetylcholine arrives (as in poisoning), it can push the drug out — that is why the blockade is called *competitive*.
- *Example:* In organophosphate pesticide poisoning, huge amounts of acetylcholine flood the body; large doses of atropine are given to compete at the receptors and keep the patient alive.
- *Takeaway:* They are *blockers*, not destroyers — they occupy muscarinic receptors reversibly.

3. Why are there five chemical groups if they all do the same blocking job?

- *Concept:* The blocking "warhead" (basic nitrogen + ester + bulky acid part) can be built on different scaffolds; each scaffold changes where the drug goes and which organ it affects most.
- *Simple explanation:* Same engine, different car bodies. The tropane "car" goes to the eye and brain; the quaternary "car" cannot enter the brain so it works only in the gut or lungs.
- *Example:* Scopolamine (tertiary amine, crosses into brain) prevents motion sickness via the brain's vomiting centre; ipratropium (quaternary, stays out) opens only the lung airways when inhaled.
- *Takeaway:* Chemical group decides *where* the drug acts and *how long* it stays.

4. What does "quaternary" actually mean, and why does it matter?

- *Concept:* Nitrogen normally makes 3 bonds. If it is forced to make a 4th bond (e.g., by adding a methyl group), it gains a permanent positive charge: R_4N^+.
- *Simple explanation:* Think of nitrogen as a person with 3 hands. Give them a 4th object to hold and they become electrically charged — and a charged molecule is like a person wearing a heavy wet coat: it cannot slip through the oily walls of the gut or the blood–brain barrier.
- *Example:* Propantheline and glycopyrrolate are quaternary — they are poorly absorbed from the gut and do not cause brain side effects (no drowsiness, no confusion); they act peripherally on gut glands.
- *Takeaway:* Quaternary = permanent + charge = poor gut absorption + no brain entry = peripheral action only.

5. Why do some anti-cholinergics help Parkinson's disease?

- *Concept:* In Parkinson's disease the brain has too little dopamine and relatively too much acetylcholine activity, causing tremor and stiffness.
- *Simple explanation:* It is a see-saw: dopamine on one side, acetylcholine on the other. Parkinson's tips the see-saw toward acetylcholine; anti-cholinergics that CAN enter the brain (tertiary amines like benztropine, biperiden, procyclidine, orphenadrine, ethopropazine) push the see-saw back toward balance.
- *Example:* Benztropine is given to Parkinson's patients to reduce tremor and rigidity, and to patients on antipsychotic drugs to treat drug-induced stiffness.
- *Takeaway:* Only brain-penetrating (tertiary amine) anti-cholinergics help Parkinson's — quaternary ones are useless there.

Classifications

Master classification table (all 19 drugs):

Group	Chemical class	Drugs (7 + 5 + 2 + 3 + 2 = 19)
(a) Solanaceous alkaloids and semi-synthetics	Natural tropane alkaloids and their modified forms	Atropine, Hyoscyamine, Scopolamine, Homatropine, Ipratropium*, Tropicamide, Cyclopentolate
(b) Synthetic aminoalcohol esters	Man-made esters of an aminoalcohol with a bulky acid	Dicyclomine, *Methantheline*, Propantheline, *Clidinium*, Glycopyrrolate*
(c) Aminoethers	Ether (not ester) linkage, benzhydryl type	Benztropine, Orphenadrine
(d) Aminoalcohols	Free –OH with basic side chain (no ester)	Biperiden, Procyclidine, Ethopropazine
(e) Quaternary ammonium compounds	Permanent R_4N^+ charge, peripheral action	Tridihexethyl, *Isopropamide*

* = quaternary nitrogen (permanent positive charge). Full quaternary list: Ipratropium, Clidinium, Glycopyrrolate, Methantheline, Propantheline, Tridihexethyl, Isopropamide.

Classification by therapeutic area (same drugs, different view):

Therapeutic area	Drugs used
Eye (mydriatics/cycloplegics)	Atropine, Homatropine, Tropicamide, Cyclopentolate
Gut (antispasmodics, ulcer)	Hyoscyamine, Dicyclomine, Methantheline, Propantheline, Clidinium, Tridihexethyl, Isopropamide, Glycopyrrolate
Lungs (bronchodilator)	Ipratropium
Parkinson's / movement disorders	Benztropine, Orphenadrine, Biperiden, Procyclidine, Ethopropazine
Motion sickness / pre-anaesthetic	Scopolamine, Atropine, Glycopyrrolate

Mechanism in one flowchart (sketchable):

```
Acetylcholine released by parasympathetic nerve
        │
        ▼
Binds MUSCARINIC receptor (M1/M2/M3) → rest-and-digest effect
        │
        ▼  (anti-cholinergic drug arrives)
Drug sits on the SAME receptor but does NOT activate it
        │
        ▼
Acetylcholine is blocked (competitive blockade)
        │
        ▼
Effect REVERSED: heart speeds up, gut relaxes, saliva dries,
pupil dilates, airways open, bladder relaxes
```

Textual diagram — the atropine model (the template for SAR). Sketch this:

```
        BULKY ACID PART (tropic acid)          BASIC AMINOALCOHOL PART (tropine)
   phenyl ring – CH(CH2OH) – C(=O) – O – [tropane ring with N-CH3]
         |               |     |              |
   (iii) big aryl    (iv) -OH on     (i) ESTER        (ii) basic nitrogen
         group boosts   alpha carbon  linkage is      at fixed distance
         activity       boosts potency  essential      from the ester
```

Infographic concept box — "The Five-Finger Rule of Anti-cholinergics" (design idea for the final PDF: a hand with five labelled fingers): Thumb = ESTER LINK (holds the two halves together); Index finger = BASIC NITROGEN (points at the receptor); Middle finger = BULKY ARYL RING (the big group that grips); Ring finger = ALPHA –OH (the potency booster); Little finger = CHARGE DECIDES ADDRESS (tertiary → brain; quaternary → body only). Palm text: "Block acetylcholine → dry, fast heart, wide pupil, relaxed gut."

Drug Profiles — Group (a): Solanaceous Alkaloids and Semi-synthetics

These come from nightshade plants or are made by small changes to those plant alkaloids. All share the **tropane** scaffold unless stated: picture a six-membered ring (like a chair) fused to a five-membered ring, sharing one nitrogen atom at the bridgehead — a rigid, cage-like base. The –OH at position 3 of tropine forms the ester.

1. Atropine

- *Chemical class:* Solanaceous tropane alkaloid; the **racemic** (50:50 left + right) form of hyoscyamine. Simple meaning: the plant makes mostly the left-handed form; the isolated medicine is an equal mixture of both hands.
- *Structure (textual):* Tropine (3α-hydroxy-tropane) esterified at the 3-position with **tropic acid** = 3-hydroxy-2-phenylpropanoic acid (a phenyl ring attached to a –CH(CH_2OH)–COOH unit). The tropane nitrogen carries a methyl group (tertiary amine → can enter the brain).
- *Therapeutic uses:* (1) Eye drops as mydriatic/cycloplegic for eye examination and uveitis (long-acting — effect lasts days); (2) Antidote in **organophosphate (pesticide) poisoning** — blocks the flood of acetylcholine; (3) Pre-anaesthetic to dry saliva/bronchial secretions; emergency treatment of slow heart rate (bradycardia).

2. Hyoscyamine

- *Chemical class:* Solanaceous tropane alkaloid; the **laevorotatory (–) enantiomer** — the active left-handed half of atropine. (Atropine = (±)-hyoscyamine.)
- *Structure (textual):* Identical to atropine except it is the single (–) isomer: (–)-tropine ester of (–)-tropic acid; tropane nitrogen with a methyl group (tertiary amine).
- *Therapeutic uses:* (1) Gastrointestinal antispasmodic — relieves intestinal cramps and colic; (2) Irritable bowel syndrome (IBS) and bladder spasm; (3) Used in combination tablets for urinary and biliary colic.

3. Scopolamine (Hyoscine)

- *Chemical class:* Solanaceous tropane alkaloid; the 6,7-**epoxide** of hyoscyamine.
- *Structure (textual):* Same tropine–tropic-acid ester as atropine, PLUS an oxygen bridge (epoxide) connecting carbons 6 and 7 of the tropane ring — picture a tiny oxygen "staple" across the top of the cage. Tertiary amine → strong brain entry.
- *Therapeutic uses:* (1) **Motion sickness** — transdermal patch behind the ear, acts on the brain's vomiting centre; (2) Pre-anaesthetic — produces sedation and amnesia, dries secretions; (3) Anti-emetic in vertigo.

4. Homatropine

- *Chemical class:* Semi-synthetic tropane alkaloid (made from tropine + mandelic acid in the laboratory).
- *Structure (textual):* Tropine esterified with **mandelic acid** (phenyl–CH(OH)–COOH) instead of tropic acid — one carbon shorter, phenyl directly on the alpha carbon bearing the –OH. Tertiary amine.
- *Therapeutic uses:* (1) Shorter-acting mydriatic for eye examination (effect lasts hours, not days like atropine); (2) Treatment of uveitis/iritis (dilates pupil, rests the inflamed iris).

5. Ipratropium (Ipratropium bromide)

- *Chemical class:* Semi-synthetic **quaternary** tropane alkaloid, derived from atropine by adding an isopropyl group to the nitrogen.
- *Structure (textual):* The atropine skeleton (tropine + tropic acid ester) in which the tropane nitrogen now carries BOTH a methyl and an isopropyl group — four bonds total, permanent positive charge, with bromide as the counter-ion. Because it is quaternary it cannot cross into the brain or be well absorbed from the gut.
- *Therapeutic uses:* (1) **Bronchodilator inhaler/nebuliser for asthma and COPD** — opens airways locally in the lungs; (2) Combined with salbutamol (Duolin-type inhalers) for acute breathlessness.
- *Note:* The full synthesis of Ipratropium is given in Chapter 8 (Synthesis Handbook); it is NOT repeated here.

6. Tropicamide

- *Chemical class:* Synthetic tropic-acid **amide** (note: amide, not ester — an interesting exception to the ester rule).
- *Structure (textual):* Tropic acid (phenyl–CH(CH_2OH)–COOH) joined via an **amide** link (–CONH–) to an N-ethyl-N-(4-pyridylmethyl) amine — picture the tropic-acid half identical to atropine's acid half, but the alcohol half replaced by a small amine carrying an ethyl group and a pyridine (nitrogen-containing aromatic) ring.
- *Therapeutic uses:* (1) Very short-acting mydriatic for routine eye examination (effect wears off in ~6 hours — patient can go home the same day); (2) Fundus (back-of-eye) examination.

7. Cyclopentolate

- *Chemical class:* Synthetic aminoalcohol ester (tropane-free mydriatic).
- *Structure (textual):* Ester of 2-(dimethylamino)ethanol (a tiny aminoalcohol: –O–CH_2CH_2–N(CH_3)$_2$) with 1-hydroxy-1-phenyl-cyclopentane-acetic acid — picture a **five-membered cyclopentane ring** carrying both a phenyl group and an –OH on the same carbon, joined through –CH_2–COO– to the aminoalcohol. The cyclopentane replaces atropine's open-chain acid part.
- *Therapeutic uses:* (1) Mydriatic + **cycloplegic** for eye testing in children (paralyses focusing so the true refractive error can be measured); (2) Pre-operative dilation before eye surgery.

Drug Profiles — Group (b): Synthetic Aminoalcohol Esters

Man-made esters that copy atropine's two-half design (bulky acid + basic aminoalcohol) on non-tropane scaffolds. Mostly gut-selective antispasmodics.

8. Dicyclomine (Dicycloverine)

- *Chemical class:* Synthetic aminoalcohol ester; a **bicyclohexyl** carboxylic ester.
- *Structure (textual):* 2-(Diethylamino)ethyl ester of 1-cyclohexyl-cyclohexane-1-carboxylic acid — picture TWO cyclohexane rings joined at one carbon (like two wheels on one axle); that junction carbon carries the –COO– link to a –CH_2CH_2–N(ethyl)$_2$ aminoalcohol. Tertiary amine (crosses into brain mildly, but used for gut).
- *Therapeutic uses:* (1) **Abdominal cramps and IBS** — relaxes intestinal smooth muscle; (2) Infantile colic (in some countries, with caution); (3) In India combined with mefenamic acid (Meftal-Spas) for menstrual and abdominal cramps — see India context.
- *Note:* The full synthesis of Dicyclomine is given in Chapter 8 (Synthesis Handbook); it is NOT repeated here.

9. Methantheline (Methantheline bromide)

- *Chemical class:* Synthetic **quaternary** aminoalcohol ester of **xanthene-9-carboxylic acid**.
- *Structure (textual):* Xanthene (two benzene rings joined by an oxygen bridge and a central carbon — a flat tricyclic "butterfly") with a –COOH at the centre carbon (position 9), esterified with 2-(diethylmethylammonio)ethanol — the nitrogen is quaternary (two ethyls + one methyl + the chain = 4 bonds, permanent + charge).
- *Therapeutic uses:* (1) Peptic ulcer — reduces gastric acid secretion and gut spasm; (2) Hyperhidrosis (excessive sweating) — blocks sweat glands; (3) GI hypermotility.

10. Propantheline (Propantheline bromide)

- *Chemical class:* Synthetic **quaternary** aminoalcohol ester of xanthene-9-carboxylic acid (the diisopropyl cousin of methantheline).
- *Structure (textual):* Same xanthene-9-carboxylate acid half as methantheline, esterified with 2-(diisopropylmethylammonio)ethanol — the aminoalcohol now carries two bulkier **isopropyl** groups plus a methyl on the quaternary nitrogen (permanent + charge).
- *Therapeutic uses:* (1) Peptic ulcer disease — antisecretory + antispasmodic; (2) Irritable bowel and urinary bladder spasm; (3) Excessive sweating (hyperhidrosis).

11. Clidinium (Clidinium bromide)

- *Chemical class:* Synthetic **quaternary** aminoalcohol ester; a **quinuclidinyl benzilate**.
- *Structure (textual):* **Quinuclidine** — a rigid cage of three fused rings sharing one nitrogen (1-azabicyclo[2.2.2]octane) — with an –OH at position 3 esterified with **benzilic acid** (diphenylglycolic acid: two phenyl rings + one –OH on the same carbon next to –COOH). The cage nitrogen is methylated → quaternary (permanent + charge).
- *Therapeutic uses:* (1) IBS and peptic ulcer — gut antispasmodic; (2) Combined with chlordiazepoxide (Librax-type combinations) for gut spasm with anxiety; (3) Diverticulitis-related cramps.

12. Glycopyrrolate (Glycopyrronium bromide)

- *Chemical class:* Synthetic **quaternary** aminoalcohol ester; a **pyrrolidinium** ester of cyclopentylmandelic acid.
- *Structure (textual):* A five-membered **pyrrolidine** ring (nitrogen-containing) carrying an –O–CO– link at position 3 to **cyclopentylmandelic acid** (a cyclopentane ring + phenyl ring + –OH all on the carbon next to –COOH). The ring nitrogen has two methyl groups → quaternary (permanent + charge).
- *Therapeutic uses:* (1) **Pre-anaesthetic antisialagogue** — dries saliva without brain effects (quaternary, so no sedation); (2) Peptic ulcer; (3) Inhaled for COPD maintenance; also used for drooling and hyperhidrosis.

Drug Profiles — Group (c): Aminoethers

These replace the ester link (–COO–) with an **ether** link (–O–). The benzhydryl (diphenylmethyl) group provides the bulk that the acid part normally gives.

13. Benztropine (Benztropine mesylate)

- *Chemical class:* Aminoether; 3-(diphenylmethoxy)-tropane.
- *Structure (textual):* The familiar **tropane** cage, but at position 3 the –OH is joined via an **ether** oxygen to a **benzhydryl** group — one carbon carrying TWO phenyl rings (diphenylmethyl, like two balloons on one string). The tropane nitrogen keeps its methyl (tertiary amine → enters the brain). Supplied as the mesylate (methanesulfonate) salt.
- *Therapeutic uses:* (1) **Parkinson's disease** — reduces tremor and rigidity (brain action); (2) Drug-induced extrapyramidal symptoms (stiffness/tremor caused by antipsychotic drugs); (3) Has added antihistaminic activity.

14. Orphenadrine

- *Chemical class:* Aminoether; dimethylaminoethyl benzhydryl ether with an ortho-methyl.
- *Structure (textual):* A 2-(dimethylamino)ethyl chain (–CH_2CH_2–$N(CH_3)_2$, tertiary amine) joined via an ether oxygen to a benzhydryl carbon carrying two phenyl rings, ONE of which has a **methyl group at the ortho (2-) position**. No tropane ring — a simple open-chain ether.
- *Therapeutic uses:* (1) **Parkinson's disease** (brain-penetrating anticholinergic); (2) Painful muscle spasm and musculoskeletal pain (combined with paracetamol in some countries); (3) Drug-induced movement disorders.

Drug Profiles — Group (d): Aminoalcohols

These keep a **free –OH** on the bulky carbon (no ester, no ether) with a basic side chain — the simplest mimics of the atropine two-half design.

15. Biperiden

- *Chemical class:* Aminoalcohol (tertiary amine, brain-penetrating).
- *Structure (textual):* One central carbon carries FOUR things: an –OH, a **phenyl** ring, a **norbornenyl** group (a bridged bicyclic ring — bicyclo[2.2.1]hept-5-ene, picture a folded envelope shape), and a 3-carbon chain ending in a **piperidine** ring (six-membered nitrogen ring). Tertiary amine → crosses the blood–brain barrier.
- *Therapeutic uses:* (1) **Parkinson's disease** — controls tremor and rigidity; (2) Drug-induced extrapyramidal symptoms; (3) Sometimes used in acute dystonia (sudden muscle spasm from antipsychotics).
- *Name note:* The syllabus prints "Biperidine" — this is a **spelling typo** for **biperiden**, the antiparkinsonian drug described here.

16. Procyclidine

- *Chemical class:* Aminoalcohol (tertiary amine, brain-penetrating).
- *Structure (textual):* Same skeleton as biperiden, but the norbornenyl "envelope" is replaced by a simple **cyclohexyl** (six-membered saturated) ring, and the piperidine is replaced by a smaller five-membered **pyrrolidine** ring: central carbon with –OH + phenyl + cyclohexyl + 3-carbon chain ending in pyrrolidine.
- *Therapeutic uses:* (1) **Parkinson's disease**; (2) Drug-induced parkinsonism and extrapyramidal symptoms; (3) Acute dystonic reactions.

17. Ethopropazine (Profethamine)

- *Chemical class:* Aminoalcohol-type anticholinergic built on a **phenothiazine** tricycle (the same tricycle as antipsychotic drugs, but here acting as anticholinergic + antihistaminic).
- *Structure (textual):* **Phenothiazine** — three fused rings (two benzene rings joined by sulfur and nitrogen bridges, like a folded butterfly) — with a side chain on the ring nitrogen: –CH_2–$CH(CH_3)$–CH_2–$N(ethyl)_2$? More precisely, a 2-(diethylamino)propyl chain (tertiary amine). The phenothiazine gives bulk; the basic side chain gives the nitrogen.
- *Therapeutic uses:* (1) **Parkinson's disease**; (2) Drug-induced extrapyramidal symptoms; (3) Has useful antihistaminic/sedative side properties.

Drug Profiles — Group (e): Quaternary Ammonium Compounds

Nitrogen with four bonds and a permanent positive charge. Poorly absorbed from the gut, cannot enter the brain — **peripheral action only** (gut, glands, bladder). Given in higher oral doses or by injection.

18. Tridihexethyl (Tridihexethyl chloride)

- *Chemical class:* Quaternary ammonium anticholinergic (open-chain).
- *Structure (textual):* A 3-carbon chain: carbon-3 carries an –OH, a **cyclohexyl** ring and a **phenyl** ring (the bulky half); carbon-1 carries the quaternary nitrogen with **three ethyl groups** plus the chain (–N^+(ethyl)$_3$). Permanent positive charge; chloride counter-ion.
- *Therapeutic uses:* (1) Peptic ulcer — reduces acid and spasm; (2) GI hypermotility and spastic colon; (3) Sometimes for urinary urgency.

19. Isopropamide (Isopropamide iodide)

- *Chemical class:* Quaternary ammonium anticholinergic with a **carbamoyl** (amide) group on the bulky half.
- *Structure (textual):* A 3-carbon chain: carbon-3 carries a **carbamoyl** (–$CONH_2$) group and TWO phenyl rings (diphenyl); carbon-1 carries the quaternary nitrogen with two **isopropyl** groups + one methyl (–N^+(methyl)(isopropyl)$_2$). Permanent positive charge; iodide counter-ion.
- *Therapeutic uses:* (1) Peptic ulcer disease; (2) GI spasm and hypermotility; (3) Adjunct in gastritis with cramping.

Quick quaternary roll-call (exam favourite): Ipratropium, Methantheline, Propantheline, Clidinium, Glycopyrrolate, Tridihexethyl, Isopropamide — *"I Met Proud Clara, Graceful Tina In-pune"* (first letters I-M-P-C-G-T-I). All are peripheral-only: no brain effects, poor oral absorption.

SAR of Cholinergic Blockers (detailed — explicitly in syllabus)

The SAR is built on the **atropine model**: bulky acid half + ester link + basic aminoalcohol half. Numbered rules with one drug example each:

Rule No.	SAR rule	Simple meaning	Drug example
(i)	An **ester linkage** between the acid part and the basic aminoalcohol part is essential for full activity	The –COO– bridge holds the two working halves at the right angle; breaking it breaks the fit	Atropine (tropine–tropic-acid ester). *Exception to note:* Tropicamide is an **amide**, not an ester — it still dilates the pupil but is shorter-acting and weaker systemically, proving the ester is preferred
(ii)	A **basic nitrogen** (tertiary amine or quaternary ammonium) must sit at a **fixed distance** from the ester group	The nitrogen is the "anchor" that binds the receptor's negative pocket; move it closer/farther and the anchor misses	Cyclopentolate — its dimethylaminoethyl chain keeps the N at the same 2-carbon distance from the ester as tropine does
(iii)	A **bulky aryl/ring group** on the acid (acyl) side increases activity	A big flat group (phenyl, xanthene, benzhydryl) grips the receptor like a wide hand grips a ball	Propantheline — the huge tricyclic **xanthene** acid half gives strong gut blocking
(iv)	An **–OH on the alpha carbon** of the acid (as in tropic acid) boosts potency	The –OH forms an extra hydrogen bond with the receptor — a bonus grip	Atropine/Scopolamine (tropic acid has α–OH) are far more potent than analogues made with plain phenylacetic acid (no –OH)
(v)	**Quaternary nitrogen → peripheral action only** (cannot cross BBB or gut wall well); **tertiary amine → can enter the brain**	Charge decides the address: charged stays in the body; uncharged can visit the brain	Quaternary: Glycopyrrolate (dries saliva before surgery with NO sedation) vs Tertiary: Benztropine/Biperiden/Procyclidine (enter brain → treat Parkinson's tremor)

SAR takeaway in one line: *Two halves (bulky acid + basic amine) joined by an ester at the right distance, with an alpha –OH for extra power — and the nitrogen's charge decides whether the drug works in the brain or only in the body.*

Worked Examples

Example 1 — Classify and predict: A new molecule is "tropine esterified with benzilic acid, nitrogen methylated twice."

- Step 1: tropine + ester + acid with two phenyls + quaternary N → it is a synthetic aminoalcohol ester, quaternary → peripheral-only gut antispasmodic (this is exactly the design of clidinium).
- Key takeaway: read the structure like a sentence — scaffold + link + acid bulk + nitrogen charge tells you class and address.

Example 2 — Tertiary or quaternary? Glycopyrrolate vs Benztropine for a Parkinson's patient.

- Glycopyrrolate's pyrrolidine nitrogen has two methyls + ring bonds = quaternary → cannot enter brain → useless for Parkinson's. Benztropine's tropane nitrogen has one methyl = tertiary → enters brain → correct choice.
- Key takeaway: when the question says "Parkinson's," look for the tertiary amine.

Example 3 — Eye-drop choice: A doctor wants pupil dilation that wears off the same evening.

- Atropine lasts days (too long); homatropine lasts hours; tropicamide wears off fastest (~6 h) → choose tropicamide.
- Key takeaway: same blocking action, different duration — match duration to the clinical need.

Analogies

- **The locked gate:** The muscarinic receptor is a gate opened by the acetylcholine key. Anti-cholinergics are broken keys jammed in the lock — the gate stays shut.
- **The see-saw (Parkinson's):** Dopamine and acetylcholine sit on opposite ends of a see-saw in the brain. Parkinson's removes dopamine, so the acetylcholine side crashes down (tremor, stiffness). Brain-penetrating anti-cholinergics lift the heavy side back up.
- **The charged coat (quaternary):** A quaternary nitrogen is a person wearing a heavy, electrically-charged raincoat trying to walk through an oily curtain (gut wall, blood–brain barrier) — they get stuck outside. That is why quaternary drugs work only in the body.
- **The 50:50 hands (racemic):** Atropine is like a pair of gloves — one left, one right — sold together; hyoscyamine is just the left glove, the one that actually fits the hand (receptor) best.

Pharmacy Relevance

- As a pharmacist you will **dispense dicyclomine combinations** (Meftal-Spas) daily for cramps — counsel that dry mouth, blurred vision and urinary difficulty are expected anticholinergic effects, not allergy.
- You must recognise **anticholinergic side effects** in elderly patients on multiple such drugs (confusion, constipation, urinary retention, dry mouth) — a common cause of falls and delirium.
- In **organophosphate poisoning** (a medical emergency in agricultural areas), atropine injection is life-saving — know that it is given in large, repeated doses to compete with the acetylcholine flood.
- **Inhaler technique counselling** for ipratropium (and Duolin-type combinations): the drug works only where it lands — correct inhalation decides success.
- Never substitute a **quaternary** drug (e.g., glycopyrrolate) when a **brain action** is needed (e.g., Parkinson's) — same "anticholinergic" label, completely different address.

India Context

- **Dicyclomine (Meftal-Spas: mefenamic acid + dicyclomine)** is one of India's most widely used medicines for abdominal cramps, menstrual pain and colicky pain — available in almost every pharmacy.
- **Atropine injection** is stocked in rural hospitals as the antidote for **organophosphate pesticide poisoning**, a frequent emergency in farming states; it is also a routine pre-anaesthetic in Indian operation theatres.
- **Ipratropium** (often as salbutamol + ipratropium, e.g., Duolin rotacaps/nebulisation) is a mainstay for **asthma and COPD** in Indian chest clinics, especially where smoking-related COPD is common.
- **Tropicamide eye drops** are used in nearly every Indian eye camp and refraction clinic for pupil dilation before eye check-ups.
- **Biperiden and procyclidine** (brand names like Disipal-type and Kemadrin-type products) are prescribed in Indian psychiatry/neurology for antipsychotic-induced stiffness and Parkinson's tremor.

Key Points

1. Anti-cholinergics = parasympatholytics = competitive blockers of muscarinic receptors → they switch OFF rest-and-digest signals.
2. Five chemical groups: (a) solanaceous alkaloids/semi-synthetics (7 drugs), (b) synthetic aminoalcohol esters (5), (c) aminoethers (2), (d) aminoalcohols (3), (e) quaternary ammonium compounds (2) — total 19.
3. Atropine = racemic hyoscyamine (50:50 mixture); hyoscyamine = the active (–) form; scopolamine = hyoscyamine + 6,7-epoxide.
4. Quaternary = nitrogen with 4 bonds, permanent + charge → poor gut absorption, cannot cross BBB → peripheral action only. The 7 quaternary drugs: ipratropium, methantheline, propantheline, clidinium, glycopyrrolate, tridihexethyl, isopropamide.
5. SAR: ester link essential; basic N at fixed distance; bulky aryl on acid side boosts activity; alpha –OH boosts potency; quaternary = peripheral, tertiary = brain entry.
6. Eye drugs: atropine (long), homatropine (medium), tropicamide (short), cyclopentolate (cycloplegic for children).
7. Gut drugs: hyoscyamine, dicyclomine, methantheline, propantheline, clidinium, tridihexethyl, isopropamide, glycopyrrolate.
8. Lung drug: ipratropium (inhaled quaternary bronchodilator).
9. Parkinson's drugs (all tertiary, brain-penetrating): benztropine, orphenadrine, biperiden, procyclidine, ethopropazine.
10. "Biperidine" in the syllabus is a typo — the drug is **biperiden**.

Common Confusions

- **Atropine vs Hyoscyamine vs Scopolamine:** Atropine is the racemic mixture (both hands); hyoscyamine is the pure active (–) form (one hand); scopolamine is hyoscyamine PLUS an epoxide oxygen bridge (the "stapled" cage) — strongest brain effects, best for motion sickness.
- **Tertiary vs Quaternary:** Tertiary amine (3 bonds, no charge) CAN enter the brain → Parkinson's drugs, scopolamine patch. Quaternary (4 bonds, permanent + charge) CANNOT → gut/lung drugs, no drowsiness. If an exam asks "which has CNS effects," pick the tertiary one.
- **Mydriatic vs Cycloplegic:** Mydriatic only widens the pupil; cycloplegic ALSO paralyses focusing. Cyclopentolate is both; tropicamide is mainly mydriatic.
- **Tropicamide breaks the ester rule:** It is an amide, not an ester — remember it as the deliberate exception when stating SAR rule (i).
- **Benztropine vs Biperiden vs Procyclidine:** All three are tertiary-amine Parkinson's drugs; benztropine is the tropane-based aminoETHER, biperiden/procylidine are open-chain aminoALCOHOLS (biperiden has norbornenyl + piperidine; procyclidine has cyclohexyl + pyrrolidine).
- **Ipratropium is quaternary but inhaled:** Its poor absorption is an advantage — sprayed into the lungs it acts locally with almost no body-wide effects.

Common Mistakes

1. Writing "Biperidine" — the correct spelling is **biperiden** (syllabus typo; examiners accept biperiden).
2. Calling all 19 drugs "alkaloids" — only group (a) are alkaloids; the rest are synthetic.
3. Saying quaternary drugs "do not work orally" — they work, but are poorly absorbed, so higher doses or injections/inhalation are used.
4. Forgetting that scopolamine's epoxide is what gives it strong central (motion-sickness) action — do not describe it as "just like atropine."
5. Mixing up homatropine's acid (mandelic acid) with atropine's acid (tropic acid) — homatropine is one carbon shorter.
6. Giving syntheses in this chapter — ipratropium and dicyclomine syntheses belong to Chapter 8 (Synthesis Handbook) only.

Mnemonics

- **Group (a) — 7 alkaloids:** *"At Happy School, Honest Indians Teach Cycling"* — Atropine, Hyoscyamine, Scopolamine, Homatropine, Ipratropium, Tropicamide, Cyclopentolate.
- **Group (b) — 5 esters:** *"Delhi Metro Passengers Catch Garmi"* — Dicyclomine, Methantheline, Propantheline, Clidinium, Glycopyrrolate.
- **Groups (c)+(d) — brain drugs:** *"Ben Or Bought Pro Eth"* — Benztropine, Orphenadrine (ethers); Biperiden, Procyclidine, Ethopropazine (alcohols) — all five enter the brain for Parkinson's.
- **Quaternary seven:** *"I Met Proud Clara, Graceful Tina In-pune"* — Ipratropium, Methantheline, Propantheline, Clidinium, Glycopyrrolate, Tridihexethyl, Isopropamide.
- **SAR five rules:** *"Every Big Nose Has Quite (a charge)"* — Ester, Bulky aryl, Nitrogen at fixed distance, Hydroxyl (alpha), Quaternary-vs-tertiary charge rule.

Exam Summary

- **Definition:** Anti-cholinergics (parasympatholytics) competitively block muscarinic receptors, switching off acetylcholine's rest-and-digest effects.
- **Master classification (5 groups, 19 drugs):** (a) Solanaceous alkaloids/semi-synthetics — atropine, hyoscyamine, scopolamine, homatropine, ipratropium*, tropicamide, cyclopentolate; (b) synthetic aminoalcohol esters — dicyclomine*, methantheline*, propantheline*, clidinium*, glycopyrrolate*; (c) aminoethers — benztropine, orphenadrine; (d) aminoalcohols — biperiden, procyclidine, ethopropazine; (e) quaternary ammonium compounds — tridihexethyl*, isopropamide* (* = quaternary).
- **Atropine = (±)-hyoscyamine** (racemic); scopolamine = 6,7-epoxide of hyoscyamine (best for motion sickness); homatropine = tropine mandelate (shorter-acting mydriatic).
- **Quaternary rule:** R_4N^+ permanent charge → poor oral absorption, no BBB crossing → peripheral action only (7 drugs listed above).
- **SAR (5 rules):** (i) ester link essential; (ii) basic N at fixed distance from ester; (iii) bulky aryl on acid side ↑ activity; (iv) alpha –OH ↑ potency; (v) quaternary → peripheral, tertiary → CNS.
- **Therapeutic map:** Eye — atropine, homatropine, tropicamide, cyclopentolate; Gut — hyoscyamine, dicyclomine, methantheline, propantheline, clidinium, tridihexethyl, isopropamide, glycopyrrolate; Lungs — ipratropium; Parkinson's — benztropine, orphenadrine, biperiden, procyclidine, ethopropazine; Motion sickness/pre-anaesthetic — scopolamine, atropine, glycopyrrolate.
- **India:** dicyclomine (Meftal-Spas) for cramps; atropine for organophosphate poisoning; ipratropium inhalers for asthma/COPD.

One-Minute Revision

Block acetylcholine at muscarinic receptors → dry mouth, fast heart, wide pupil, relaxed gut, open airways. 19 drugs in 5 groups: 7 plant alkaloids (At Happy School, Honest Indians Teach Cycling), 5 synthetic esters (Delhi Metro Passengers Catch Garmi), 2 ethers + 3 alcohols = 5 brain drugs for Parkinson's (Ben Or Bought Pro Eth), 2 pure quats. Quaternary = 4-bonded charged nitrogen = stays in body, never brain (I Met Proud Clara, Graceful Tina In-pune — 7 drugs). SAR: Ester–Bulky–Nitrogen-distance–Hydroxyl–Charge (Every Big Nose Has Quite a charge). Atropine = racemic hyoscyamine; scopolamine = epoxide = motion sickness; "Biperidine" = typo for biperiden. Ipratropium & dicyclomine syntheses → Chapter 8.

Exam Questions

A. Multiple Choice Questions (10)

1. Which of the following best describes the action of anti-cholinergic drugs? (a) They increase acetylcholine release (b) They competitively block muscarinic receptors (c) They destroy acetylcholine (d) They stimulate nicotinic receptors
2. Atropine is: (a) (–)-hyoscyamine (b) (+)-hyoscyamine (c) Racemic (±)-hyoscyamine (d) An epoxide of hyoscyamine
3. Scopolamine differs from atropine structurally by the presence of: (a) A quaternary nitrogen (b) A 6,7-epoxide bridge (c) A xanthene ring (d) A pyridine ring
4. Which drug is a quaternary tropane alkaloid used as an inhaled bronchodilator? (a) Tropicamide (b) Ipratropium (c) Homatropine (d) Cyclopentolate
5. The acid part of homatropine is: (a) Tropic acid (b) Mandelic acid (c) Benzilic acid (d) Xanthene-9-carboxylic acid
6. Which of the following is NOT a quaternary ammonium compound? (a) Propantheline (b) Glycopyrrolate (c) Benztropine (d) Tridihexethyl
7. According to SAR rule (iv), potency is boosted by: (a) Removing the ester link (b) An –OH on the alpha carbon of the acid (c) Making the nitrogen tertiary (d) Removing the phenyl ring
8. Which anti-cholinergic is preferred as a pre-anaesthetic antisialagogue because it does NOT cause sedation? (a) Scopolamine (b) Atropine (c) Glycopyrrolate (d) Orphenadrine
9. Benztropine, biperiden and procyclidine are used in Parkinson's disease because they: (a) Are quaternary and act peripherally (b) Are tertiary amines that enter the brain (c) Are esters of xanthene acid (d) Dilate the pupil
10. The correct name of the drug printed as "Biperidine" in the syllabus is: (a) Biperidine (b) Biperiden (c) Biphenyl (d) Biperidol

Answer key: 1-(b), 2-(c), 3-(b), 4-(b), 5-(b), 6-(c), 7-(b), 8-(c), 9-(b), 10-(b).

B. Viva Questions (5)

1. *Q: What is a quaternary ammonium compound, in one line?* A: A nitrogen with four bonds carrying a permanent positive charge, which therefore cannot cross the gut wall or blood–brain barrier well and acts only peripherally.
2. *Q: Why is atropine called racemic hyoscyamine?* A: Because it is a 50:50 mixture of the (–) and (+) forms of hyoscyamine; the (–) form is the more active one.
3. *Q: Name the five SAR rules of cholinergic blockers.* A: (i) Ester link essential; (ii) basic nitrogen at fixed distance from ester; (iii) bulky aryl on acid side increases activity; (iv) alpha –OH on the acid boosts potency; (v) quaternary = peripheral only, tertiary = CNS entry.
4. *Q: Which anti-cholinergic is used for motion sickness and why?* A: Scopolamine (transdermal patch) — its epoxide structure and tertiary amine let it enter the brain and block the vomiting centre.
5. *Q: Why can't glycopyrrolate be used for Parkinson's disease?* A: It is quaternary (permanent positive charge), so it cannot cross the blood–brain barrier to reach the brain; only tertiary-amine drugs like benztropine or biperiden work there.

C. Application-Based Questions (3)

1. *A farmer is brought unconscious after spraying pesticides, with pinpoint pupils, heavy salivation and slow heartbeat. Which drug from this chapter is the emergency antidote, and what is the logic of using large repeated doses?* (Atropine — organophosphate poisoning floods the body with acetylcholine; because blockade is competitive, large atropine doses are needed to out-compete acetylcholine at muscarinic receptors.)
2. *An eye doctor needs to examine the retina of a schoolchild and also measure the true refractive power of the eye. Which two drugs from this chapter would you suggest, and why these two?* (Tropicamide for quick short-acting pupil dilation for the retinal exam; cyclopentolate as the cycloplegic that paralyses focusing so the true refractive error can be measured in children.)
3. *A 70-year-old Parkinson's patient on antipsychotic therapy develops tremor and rigidity. The doctor considers glycopyrrolate vs biperiden. Which is correct and why? What counselling would you give as the pharmacist?* (Biperiden — tertiary amine, enters the brain; glycopyrrolate is quaternary and cannot. Counsel about dry mouth, blurred vision, constipation, urinary difficulty, and caution in the elderly about confusion.)

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Chapter 7: Local Anesthetic Agents

Subject: BP402T – Medicinal Chemistry **Unit:** II (Drugs Acting on the Autonomic Nervous System — Local Anesthetics)

7.1 Learning Objectives

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

1. Define what a local anesthetic is and how it is different from a general anesthetic.
2. Draw and explain the general three-part structure (pharmacophore) of local anesthetics.
3. Classify all 19 listed local anesthetic drugs into their chemical families.
4. Describe the chemical structure and therapeutic uses of each of the 19 drugs.
5. Explain the structure–activity relationship (SAR) rules that make a local anesthetic potent, long-acting, and safe.
6. Describe the mechanism of action (sodium-channel blockade) in four simple steps.
7. Correctly distinguish ester-type from amide-type local anesthetics, and avoid common exam confusions (lignocaine/lidocaine, procaine/procainamide).

7.2 Introduction — What Do Local Anesthetics Do?

A **local anesthetic** is a drug that makes a **small area of the body numb** so that surgery, stitching, or dental work can be done without pain, while the patient stays awake.

- **Technical concept:** A local anesthetic blocks **sodium channels** in nerve fibers. (A sodium channel is a tiny gate in the nerve cell wall that lets sodium ions flow in; that flow is what carries the pain signal to the brain.)
- **Simple explanation:** Pain travels to the brain as a small electrical message along a nerve. Local anesthetics lock the doors (sodium channels) that let this message start. No message, no pain.
- **Example:** When a dentist pulls a tooth, they inject lignocaine (the most famous local anesthetic) near the tooth. The mouth area goes numb for about an hour, but the patient is fully awake.
- **Key takeaway:** Local anesthetics work **locally** (in one small area), not all over the body. That is the difference from **general anesthetics**, which make the whole body unconscious.

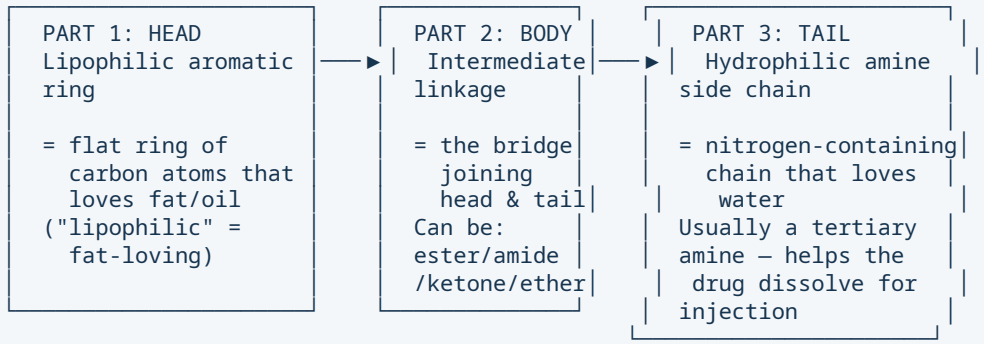
Cocaine — The Natural Prototype

- **Technical concept:** Cocaine was the first local anesthetic ever used. It comes naturally from the leaves of the coca plant (*Erythroxylum coca*).
- **Simple explanation:** Cocaine is the "original model" of this whole drug family. All the other local anesthetics were designed to copy cocaine's pain-killing power but to avoid its two big problems: it is **addictive** (makes people depend on it) and it **constricts blood vessels** in the nose.
- **Example:** In 1884, eye surgeon Karl Koller used cocaine on patients' eyes for eye surgery — the first surgical use of a local anesthetic.
- **Key takeaway:** Cocaine is the prototype (the natural starting model). Every drug in this chapter is a synthetic (man-made) improvement on cocaine's structure.

7.3 The General Pharmacophore — Three Parts Every Local Anesthetic Needs

Definition: A **pharmacophore** is the minimum set of structural parts a drug needs so it can do its job. Every local anesthetic has the same three-part skeleton.

Simple explanation: Think of a local anesthetic like a small tadpole with three sections:



Word meanings (before we go further):

- **Lipophilic** = "fat-loving"; mixes easily with the oily nerve membrane.
- **Hydrophilic** = "water-loving"; dissolves easily in watery body fluids.
- **Aromatic ring** = a flat six-carbon ring (like benzene); the "head".
- **Intermediate linkage** = the connecting bridge between head and tail; its type (ester or amide) decides which family the drug belongs to.
- **Amine** = a group containing a nitrogen atom; at body pH it carries a positive charge and binds inside the sodium channel.

Key takeaway: Lipophilic head – linker – hydrophilic amine tail. All three parts are needed; changing any one of them changes how the drug works. This is the foundation of the SAR section (7.5).

7.4 Terminology Word Bank

Term	Simple Meaning
Local anesthetic	Drug that numbs one small body area; patient stays awake
Prototype	The first/original model drug of a family (here: cocaine)
Pharmacophore	The essential parts of a molecule that give it activity
Lipophilic	Fat-loving; mixes with oily membranes
Hydrophilic	Water-loving; dissolves in body fluids
Ester linkage	Bridge made by joining an acid + alcohol (–COO–); broken easily by enzymes
Amide linkage	Bridge made by joining an acid + amine (–CONH–); stronger, broken slowly
Tertiary amine	Nitrogen joined to three carbon groups; can form water-soluble salts
Esterase	Enzyme in blood plasma that cuts ester bonds
pKa	A number showing how easily a drug picks up a proton (charge) at body pH
Topical	Applied on the surface (skin, mouth, eye)
Infiltration	Injected into the tissue around the surgical area
Spinal anesthesia	Injected into the fluid around the spinal cord
Onset	Time until the drug starts working
Duration	How long the numbness lasts
Potency	How strong the drug is (less drug needed = more potent)

7.5 Chemical Classification — Master Table

Technical concept: Local anesthetics are classified by the **intermediate linkage** (the middle bridge). Ester linkages give one family; amide linkages give another; two drugs don't fit either family.

Class	Linkage	Drugs (12 + 4 + 1 + 2 = 19)
(a) Benzoic acid / PABA esters	Ester (–COO–)	Cocaine, Benzocaine, Procaine, Butacaine, Propoxycaine, Tetracaine, Benoxinate, Butamben, Hexylcaine, Meprylcaine, Cyclomethycaine, Piperocaine
(b) Acetanilide / xylidide amides	Amide (–CONH–)	Lignocaine (lidocaine), Mepivacaine, Prilocaine, Etidocaine
(c) Quinoline amide	Amide on quinoline ring	Dibucaine (cinchocaine)
(d) Others (miscellaneous)	Ether / ketone linkages	Phenacaine (holocaine), Diperodon

Simple explanation:

- The **12 ester drugs** all have the ester bridge. Their heads come from benzoic acid or PABA (para-aminobenzoic acid — a benzene ring with an $–NH_2$ group).
- The **4 amide drugs** have the stronger amide bridge; their heads are the acetanilide/xylidide type (a benzene ring joined to nitrogen).
- **Dibucaine** is an amide too, but its ring is a quinoline (a two-ring system), so it gets its own group.
- **Phenacaine** uses an ether bridge and **Diperodon** uses a ketone bridge — they don't fit groups (a)–(c), so they sit in "Others".

⚠️ **NOTE: Lignocaine = Lidocaine.** These are two names for the SAME drug. "Lignocaine" is the name used in India and in older British books; "lidocaine" is the name used in America. Don't treat them as different drugs!

Key takeaway: Learn the class by the bridge: ester (12 drugs) → broken fast → short action, allergy risk; amide (4 + 1 drugs) → resists breaking → longer action. Quinoline amide and the two "others" are single-case groups.

7.6 Individual Drugs — Structure and Uses

How to read each drug card: Chemical class → structure in words (scaffold + the key substituents, i.e. the important extra groups) → therapeutic uses.

7.6.1 Cocaine

- **Chemical class:** Benzoic acid ester (natural prototype).
- **Structure:** A complex natural molecule built around a **tropane ring system** (a fused double-ring cage of carbon and nitrogen). On it: a **benzoyl ester group** (–OCO–phenyl) at one position and a **methyl ester** ($–COOCH_3$) at another. The benzoyl ester is the "benzoic acid ester" part of the pharmacophore.
- **Therapeutic uses:** (1) Topical anesthesia of the nose and throat (it also narrows blood vessels, reducing bleeding during nose surgery); (2) rarely, eye anesthesia. *Now almost never used because of addiction risk.*

7.6.2 Hexylcaine

- **Chemical class:** Benzoic acid ester.
- **Structure:** A benzoic-acid ester scaffold where the alcohol part is a **1-cyclohexylaminopropan-2-ol** chain — i.e., the side chain carries a **cyclohexyl ring** (a six-carbon ring) attached to a secondary amine, plus an **n-hexyl ester chain**. Hence the name "hexylcaine".
- **Therapeutic uses:** (1) Infiltration anesthesia for minor surgery; (2) nerve blocks. *Fast onset, short duration.*

7.6.3 Meprylcaine (also spelled meprylcaine)

- **Chemical class:** Benzoic acid ester.
- **Structure:** Benzoic-acid ester with an amine side chain that is a **piperidine ring** (a six-membered nitrogen ring) carrying a **methyl group** on the nitrogen — i.e., an N-methyl piperidyl alcohol ester of benzoic acid.
- **Therapeutic uses:** (1) Infiltration anesthesia; (2) spinal anesthesia. *Used historically; largely replaced by newer agents.*

7.6.4 Cyclomethycaine

- **Chemical class:** Benzoic acid ester.
- **Structure:** A benzoic-acid ester scaffold with a **p-methoxy group** ($–OCH_3$ at the para position) on the aromatic ring, and an ester alcohol part containing a **cyclohexyl ring** with a **methylamino side chain** (a $–NHCH_3$ group).
- **Therapeutic uses:** (1) Topical anesthesia of skin and mucous membranes; (2) local infiltration. *Very low toxicity.*

7.6.5 Piperocaine

- **Chemical class:** Benzoic acid ester.
- **Structure:** Benzoic-acid ester whose alcohol side chain is **3-(1-piperidyl)propan-1-ol** — a three-carbon chain ending in a **piperidine ring**. Simple benzoic ester + piperidine tail.
- **Therapeutic uses:** (1) Spinal anesthesia (its main use); (2) infiltration anesthesia; (3) topical use. *Notable for good spinal action with short recovery.*

7.6.6 Benzocaine

- **Chemical class:** PABA ester (para-aminobenzoic acid ester).
- **Structure:** The simplest member — just **ethyl p-aminobenzoate**: a benzene ring with an **$-NH_2$ (primary amino) group** at the para position and an **ethyl ester** ($-COOCH_2CH_3$). There is **no amine side chain**; the primary $-NH_2$ plays both roles.
- **Therapeutic uses:** (1) Topical anesthesia of skin, mouth ulcers, teething pain, sunburn; (2) throat lozenges for sore throat (very common in India); (3) ear drops with other agents. *Surface use only — it cannot be injected.*

7.6.7 Butamben (Butyl aminobenzoate)

- **Chemical class:** PABA ester.
- **Structure: n-Butyl p-aminobenzoate**: same PABA head as benzocaine but with a longer **n-butyl ester** ($-COOCH_2CH_2CH_2CH_3$) instead of ethyl. The extra carbons make it more fat-loving.
- **Therapeutic uses:** (1) Topical anesthesia of skin and wounds; (2) added to some burn and hemorrhoid creams. *Longer topical action than benzocaine.*

7.6.8 Procaine

- **Chemical class:** PABA ester.
- **Structure:** The classic ester: a **p-aminobenzoic acid head** (benzene ring + para $-NH_2$) joined by an ester bridge to a **diethylaminoethyl side chain** ($-CH_2CH_2N(CH_2CH_3)_2$). This is the textbook "three-part" molecule: lipophilic head – ester – tertiary amine tail.
- **Therapeutic uses:** (1) Infiltration anesthesia for minor surgery; (2) nerve blocks; (3) spinal anesthesia (older practice). *Short action; broken quickly by plasma esterases. Can cause allergy (PABA sensitivity).*

> 📝 **Note box:** Procaine* synthesis in full is given in **Chapter 8 (Synthesis Handbook)**. No synthesis is given here.

7.6.9 Butacaine

- **Chemical class:** PABA ester.
- **Structure:** A PABA ester head with a **p-aminobenzoyl** group joined to a **dibutylamino-propanol side chain**: the amine tail carries **two n-butyl groups**, making it more lipophilic (fat-loving) than procaine.
- **Therapeutic uses:** (1) Topical anesthesia, especially of mucous membranes; (2) ophthalmic (eye) anesthesia — it was an early surface eye anesthetic. *More potent than procaine but more toxic.*

7.6.10 Propoxycaine

- **Chemical class:** PABA ester.
- **Structure:** A PABA ester head with a **2-propoxy group** ($-OCH_2CH_2CH_3$ at the ortho position of the ring) — this is where the name "propoxy" comes from — joined by an ester bridge to a **diethylaminoethyl** side chain (like procaine).
- **Therapeutic uses:** (1) Infiltration anesthesia in dental work (often combined with procaine); (2) topical anesthesia. *Faster and stronger than procaine alone.*

7.6.11 Tetracaine (Amethocaine)

- **Chemical class:** PABA ester.
- **Structure:** A PABA ester head with a **p-butylamino group** (–$NHCH_2CH_2CH_2CH_3$ at the para position) instead of plain –NH_2, joined by an ester bridge to a **dimethylaminoethyl** side chain. The butyl group greatly increases fat-loving character → high potency, long action.
- **Therapeutic uses:** (1) Spinal anesthesia (very important use); (2) topical/ophthalmic anesthesia; (3) nerve blocks. *Long-acting but more toxic than procaine.*

7.6.12 Benoxinate (Oxybuprocaine)

- **Chemical class:** PABA ester.
- **Structure:** A PABA-type ester head carrying a **p-butoxy group** (–O–butyl at the para position), joined by an ester bridge to a **diethylaminoethyl** side chain. Very close to tetracaine but with an oxygen (butoxy) instead of nitrogen (butylamino).
- **Therapeutic uses:** (1) Ophthalmic (eye) surface anesthesia — eye drops before eye examination or minor eye surgery; (2) nose and throat topical anesthesia. *Fast onset, short duration.*

7.6.13 Lignocaine (Lidocaine)

- **Chemical class:** Acetanilide/xylidide **amide**.
- **Structure:** The model amide: a **2,6-dimethylphenyl (2,6-xylidine) head** — a benzene ring with **two ortho methyl groups** (–CH_3 at both positions next to the nitrogen) — joined by an **amide bridge** (–NHCO–) to a **diethylaminoacetyl side chain** (–$COCH_2N(CH_2CH_3)_2$). The two ortho methyl groups shield the amide from attack → resists hydrolysis.
- **Therapeutic uses:** (1) Dental anesthesia (the standard injection at dental clinics across India); (2) infiltration and nerve blocks in minor surgery; (3) topical gels/jellies; (4) also used as an **antiarrhythmic** (heart rhythm drug). *The most widely used local anesthetic in the world.*

⚠️ **NOTE:** Lignocaine = lidocaine. Same drug, two names. India and Britain say "lignocaine"; America says "lidocaine."

7.6.14 Mepivacaine

- **Chemical class:** Acetanilide/xylidide **amide**.
- **Structure:** Like lignocaine's 2,6-xylidine head and amide bridge, but the amine tail is a **piperidine ring** — specifically an **N-methyl piperidine-2-carboxamide** (the side chain is locked into a piperidine ring with a methyl on nitrogen).
- **Therapeutic uses:** (1) Dental anesthesia (good where vasoconstrictors like adrenaline must be avoided); (2) infiltration, nerve blocks, and epidural anesthesia in obstetrics. *Medium duration, low toxicity.*

7.6.15 Prilocaine

- **Chemical class:** Acetanilide/xylidide **amide**.
- **Structure:** A **2-methylphenyl (o-toluidine) head** (only **one** ortho methyl group) joined by an amide bridge to a **propylamino side chain** — the nitrogen is a **secondary amine** carrying an n-propyl group (–$NHCH_2CH_2CH_3$).
- **Therapeutic uses:** (1) Dental anesthesia (often mixed with lignocaine as EMLA-like combinations); (2) infiltration and nerve blocks. *Less toxic than lignocaine, similar potency. Caution: high doses can cause methemoglobinemia (a blood disorder) — an exam favorite.*

7.6.16 Etidocaine

- **Chemical class:** Acetanilide/xylidide **amide**.
- **Structure:** A **2,6-xylidine head** (like lignocaine) with an amide bridge to a **butyramide side chain**: the amide carbonyl carries an **ethyl group** and the amine is a **propyl-substituted** nitrogen (N-ethyl-N-propyl type tail). Heavier and more fat-loving than lignocaine.
- **Therapeutic uses:** (1) Long-acting nerve blocks; (2) epidural anesthesia for prolonged surgery; (3) infiltration where a long numb period is wanted. *Very long duration, high potency, more motor block.*

7.6.17 Phenacaine (Holocaine)

- **Chemical class: Others** — ether-type (diamine ether).
- **Structure:** Not an ester or amide. It is a **diethoxy-diphenetidine derivative**: two **p-ethoxyphenyl (phenetidine) rings** joined through an **ether bridge** (–O–) with amidine-type nitrogens — chemically, a bis-(p-ethoxyphenyl) guanidine-like structure. The intermediate linkage is an **ether**, not ester/amide.
- **Therapeutic uses:** (1) Ophthalmic (eye) surface anesthesia — its historical main use; (2) topical anesthesia. *One of the first synthetic local anesthetics; now largely obsolete.*

7.6.18 Diperodon

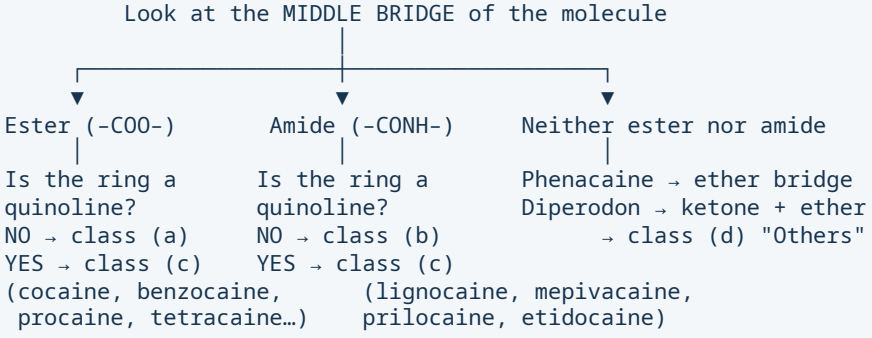
- **Chemical class: Others** — ketone/ether-type amino alcohol.
- **Structure:** A **phenyl ketone scaffold**: a **benzophenone-like core** (two phenyl rings joined by a **ketone C=O bridge**) carrying a **piperidino-ethoxy side chain** — an ether-linked chain ending in a **piperidine ring**. So the "linkage" is a **ketone + ether** combination, not ester/amide.
- **Therapeutic uses:** (1) Topical anesthesia of skin; (2) anti-itch (antipruritic) creams; (3) burn and wound preparations. *Surface use — mainly for itching and minor skin pain.*

7.6.19 Dibucaine (Cinchocaine)

- **Chemical class: Quinoline amide**.
- **Structure:** A **quinoline ring system** (a benzene ring fused to a pyridine ring — two rings joined) carrying a **butoxy group** (–O–butyl) at position 2 and an **amide bridge** at position 4 joined to a **diethylaminoethyl side chain**. The quinoline + butoxy makes it extremely fat-loving → the most potent local anesthetic here.
- **Therapeutic uses:** (1) Spinal anesthesia (long-acting); (2) topical anesthesia — creams and ointments for hemorrhoids, sunburn, and skin pain. *Most potent and most toxic; never used in high doses.*

> 📝 **Note box:** Dibucaine* synthesis in full is given in **Chapter 8 (Synthesis Handbook)**. No synthesis is given here.

7.7 Flowchart — How to Classify Any Local Anesthetic (Exam Trick)



Key takeaway: First check the bridge (ester vs amide), then check whether the ring is a quinoline (dibucaine). Two drugs have neither bridge — they go to "Others".

7.8 SAR of Local Anesthetics — The Six Rules (Syllabus Topic)

Definition: SAR = **Structure–Activity Relationship**: the rules connecting a drug's structure to how well it works.

Rule Table

#	Rule (technical)	Simple explanation	Drug example
(i)	The three-part pharmacophore (lipophilic aromatic ring – intermediate linker – hydrophilic amine) is **essential** for activity.	All three parts must be present. Remove the amine tail or the ring and the drug stops numbing.	**Procaine** shows the perfect three-part layout; **benzocaine** (missing the amine side chain) works only on the surface.
(ii)	**Ester vs amide linker** controls breakdown. Esters are hydrolyzed rapidly by plasma esterases → shorter action + possible PABA allergy. Amides resist hydrolysis → longer action, broken down in the liver.	An ester bridge is like a weak knot — blood enzymes cut it quickly, so the drug wears off fast and the leftover piece (PABA) can cause allergy. An amide bridge is a strong knot — it survives longer in blood and is broken slowly in the liver.	Esters: **procaine**, **tetracaine** (short action, allergy risk). Amides: **lignocaine**, **mepivacaine** (longer action, no PABA allergy).
(iii)	**Ortho methyl groups** on the aromatic ring (the 2,6-xylidine part) **hinder hydrolysis** and increase potency and duration.	Two methyl groups sitting right next to the bridge act like bodyguards — they physically block enzymes from reaching and cutting the bridge. Result: the drug lasts longer and works more strongly.	**Lignocaine** — its 2,6-dimethyl (ortho methyl) groups shield the amide bond, giving it longer action than an unshielded amide.
(iv)	**Increasing alkyl chain length** on the amine or on the ring increases **lipophilicity** → more potent and longer acting, but also **more toxic**.	Longer carbon chains make the drug "oilier", so it slips into nerves more easily (stronger, longer numbness). But oilier drugs also reach the heart and brain more easily — so they are more poisonous in overdose. A balance is needed.	**Tetracaine** (butyl chain on the ring) is far more potent and longer-acting than procaine but also more toxic. **Dibucaine** (butoxy on quinoline) is the most potent — and most toxic.
(v)	The amine must be **tertiary (or secondary)** so it can form **water-soluble salts** for injection; a primary amine with no side chain gives **surface use only**.	The nitrogen tail lets us make the drug into a salt (like lignocaine hydrochloride) that dissolves in water for injection. Without this tail, the drug can't be dissolved for injection — it can only sit on the skin or tongue.	**Lignocaine** (tertiary amine → injectable salt). **Benzocaine** (primary –NH_2, no side chain → surface use only, never injected).
(vi)	**pKa near physiological pH (7.4)** gives **fast onset**.	The drug must be partly uncharged to cross the nerve membrane, then charged to lock the channel. A pKa close to 7.4 gives the right balance, so numbness starts quickly.	**Lignocaine** (pKa ≈ 7.9, close to 7.4) has a fast onset; drugs with much higher pKa are slower to start.

Analogy — The Key and the Lock Shop

Think of each local anesthetic as a key being cut in a shop:

- **Rule (i):** The key needs all three cuts (head–bridge–tail) or it won't turn the lock.
- **Rule (ii):** An ester key is made of soft metal — it wears out (breaks) quickly. An amide key is hardened steel — it lasts.
- **Rule (iii):** The ortho methyl groups are like a protective cover over the key's weakest point.
- **Rule (iv):** Making the key oilier helps it slide in faster — but an over-oiled key slips into the wrong locks (heart, brain) too.
- **Rule (v):** Without the tail, the key has no handle — you can't push it into a syringe; you can only lay it on the surface.
- **Rule (vi):** The key must be the right size (pKa) to fit the lock quickly.

Worked Example — Why Is Tetracaine Stronger Than Procaine?

1. Both are PABA esters (same family, rule ii — both break down fast).
2. But tetracaine has a **butyl chain** on the ring while procaine has just $–NH_2$ (rule iv — longer chain = more lipophilic).
3. More lipophilic → enters nerves better → **more potent, longer-acting**.
4. Trade-off: also **more toxic** — so tetracaine is used in smaller, careful doses (e.g., spinal anesthesia).

Key takeaway: SAR is structure → property: bridge type decides duration/allergy; ortho methyls protect the bridge; longer chains boost potency and toxicity together; the amine tail decides injectable vs surface; pKa decides speed of onset.

7.9 Mechanism of Action — Sodium-Channel Blockade in 4 Steps

Definition: Local anesthetics work by blocking **voltage-gated sodium channels** — tiny gates in the nerve wall that open to let sodium ions rush in, starting the pain signal.

Step 1 — The drug reaches the nerve. The injected or applied drug travels to the nerve fiber. Because it is partly uncharged (lipophilic), it can slip through the oily nerve membrane.

Step 2 — It enters and re-charges inside. Inside the nerve cell, the drug picks up a proton (becomes positively charged). Now it is in the active, charged form that can block the channel.

Step 3 — It plugs the sodium channel from inside. The charged drug binds to a specific spot **inside** the sodium channel and plugs it, like a cork in a bottle. Sodium ions can no longer rush in.

Step 4 — The pain signal dies. With no sodium rushing in, the nerve cannot start or carry its electrical message. The pain signal never reaches the brain — the area feels numb. When the drug washes away, the channel unplugs and feeling returns.

> **Simple analogy:** The sodium channel is a door that must open for the "pain message" to leave the room. The anesthetic drug walks through the wall (uncharged form), puts on a big coat (becomes charged), and then stands in the doorway — nobody can pass until it leaves.

Key takeaway: Uncharged drug crosses membrane → becomes charged inside → plugs sodium channel → pain signal blocked → numbness; reversible when the drug leaves.

7.10 Infographic Concept Box (Sketchable)

Title: "LOCAL ANESTHETICS — ONE PAGE, WHOLE STORY" **Top strip:** Cocaine leaf 🌿 → "Natural prototype (1884) — addictive, so we made 18 synthetic copies" **Middle — the tadpole diagram:** [Fat-loving ring HEAD] — [ester/amide BRIDGE] — [water-loving amine TAIL] **Two roads split from the bridge:** 🟥 ESTER road (12 drugs: procaine, tetracaine…) — "cut fast by blood enzymes → short action, PABA allergy" · 🟦 AMIDE road (lignocaine, mepivacaine, prilocaine, etidocaine + dibucaine) — "strong bridge → long action, liver breakdown" **SAR ladder (bottom-up):** longer carbon chain ⬆ potency ⬆ toxicity | ortho methyls 🛡 protect the bridge | pKa ≈ 7.4 ⚡ fast onset **Memory anchors:** "–caine = numbing" · "Lignocaine = Lidocaine (same drug)" · "Benzocaine = surface only" · "Tetracaine = spinal star" · "Dibucaine = strongest, most toxic"

7.11 Pharmacy Relevance & India Context

- **Dental clinics across India:** Lignocaine (2% with adrenaline) is the standard injection every dentist uses before fillings, root canals, and extractions. A pharmacy student will dispense it daily.
- **Minor surgery and stitching:** Lignocaine infiltration is used in casualty departments and primary health centres for suturing cuts.
- **Throat lozenges:** Benzocaine lozenges for sore throat are sold over the counter in every Indian medical shop — a classic "surface only" example to remember.
- **Eye check-ups:** Benoxinate eye drops are used by ophthalmologists before eye examinations.
- **Spinal anesthesia:** Tetracaine and dibucaine are used for spinal blocks in lower-body surgeries in Indian hospitals.
- **Pharmacist's role:** Knowing ester vs amide matters in practice — a patient allergic to ester anesthetics (PABA allergy from procaine/tetracaine) can usually still receive an amide like lignocaine safely.

Key takeaway: This is not theory-only chemistry — these 19 drugs are on Indian pharmacy shelves and in every dental chair. The ester/amide split is a real clinical decision.

7.12 Common Confusions (Don't Mix These Up!)

Confusion	Truth
Ester vs amide local anesthetics	Check the middle bridge: –COO– = ester (short action, allergy risk); –CONH– = amide (long action). Procaine/tetracaine = esters; lignocaine/mepivacaine = amides.
Lignocaine vs lidocaine	Same drug, two names. India/UK: lignocaine. USA: lidocaine.
Procaine vs procainamide	Procaine = local anesthetic (ester). Procainamide = heart rhythm drug (amide) — different drug, different chapter, different use.
Cocaine vs "caine" drugs	Cocaine is the natural prototype; all others are synthetic and (except dibucaine's potency) safer. Cocaine itself is addictive and rarely used.
Benzocaine vs injectable anesthetics	Benzocaine has NO amine side chain → cannot be made into an injectable salt → surface use only.

7.13 Common Mistakes Students Make

1. **Calling dibucaine an ester** — it is a quinoline **amide** (class c), not an ester.
2. **Putting phenacaine and diperodon in the ester/amide classes** — they belong to "Others" (ether/ketone linkages).
3. **Forgetting that prilocaine's amine is secondary** — most others are tertiary; prilocaine carries a secondary amine with a propyl group.
4. **Mixing up benoxinate and tetracaine structures** — both have a butyl-length para group, but benoxinate has **butoxy** (–O–butyl) while tetracaine has **butylamino** (–NH–butyl).
5. **Writing "lidocaine" and "lignocaine" as two different drugs** in classification tables — it's one drug; list it once.
6. **Saying esters are longer-acting** — it's the opposite: esters break down faster (shorter action); amides last longer.

7.14 Mnemonics

- **Ester family memory:** "**C**ocaine **B**rought **P**rocaine **B**efore **T**etracaine" — **C**ocaine, **B**enzocaine, **P**rocaine/**P**ropoxycaine/**P**iperocaine, **B**utacaine/**B**utamben/**B**enoxinate, **T**etracaine (+ Hexylcaine, Meprylcaine, Cyclomethycaine) — all 12 are esters.
- **Amide four:** "**L**idocaine **M**akes **P**eople **E**asy" — **L**ignocaine, **M**epivacaine, **P**rilocaine, **E**tidocaine.
- **Bridge rule:** "**E**ster = **E**asy to break; **A**mide = **A**ble to last."
- **Lignocaine = Lidocaine:** "**L**ocal **L**ooks the same — one drug, two **L**abels."
- **Benzocaine = surface only:** "**B**enzocaine stays **B**arely on the surface — **B**asic amine missing."

7.15 Key Points (Exam Summary)

1. Local anesthetics numb a small area by **blocking sodium channels** in nerves; the patient stays awake.
2. **Cocaine** is the natural prototype from the coca plant; all others are synthetic improvements.
3. The pharmacophore: **lipophilic aromatic ring – intermediate linkage – hydrophilic amine**.
4. Classification by linkage: **(a)** benzoic/PABA esters — 12 drugs; **(b)** acetanilide/xylidide amides — lignocaine, mepivacaine, prilocaine, etidocaine; **(c)** quinoline amide — dibucaine; **(d)** others — phenacaine, diperodon.
5. **Lignocaine = lidocaine** (same drug).
6. SAR: three parts essential; **ester = short action + PABA allergy**, **amide = long action**; ortho methyls protect the bridge (lignocaine); longer chains = more potent but more toxic (tetracaine, dibucaine); tertiary amine needed for injectable salts (benzocaine = surface only); pKa near 7.4 = fast onset.
7. Mechanism in 4 steps: reach nerve → cross membrane uncharged → charge up inside → plug sodium channel → pain signal blocked (reversible).
8. Clinical stars: lignocaine (dental, most used), tetracaine (spinal), benzocaine (throat lozenges, surface only), benoxinate (eye drops), dibucaine (most potent, most toxic).

7.16 One-Minute Revision

- **What:** drugs that numb one small area by blocking nerve sodium channels.
- **Prototype:** cocaine (natural, addictive).
- **Skeleton:** fat-loving ring – bridge – water-loving amine.
- **12 esters** (cocaine, benzocaine, procaine, tetracaine, benoxinate…): short action, PABA allergy.
- **4 amides** (lignocaine = lidocaine, mepivacaine, prilocaine, etidocaine): long action.
- **Quinoline amide:** dibucaine (strongest, most toxic). **Others:** phenacaine, diperodon.
- **SAR in one line:** bridge decides duration; ortho methyls shield; longer chains = stronger + more toxic; amine tail allows injection; pKa ≈ 7.4 = fast.
- **Mechanism:** cross nerve wall → charge inside → plug channel → no pain signal.

7.17 Exam Questions

A. MCQs (10) — with Answer Key

Q1. Which of the following is the natural prototype of local anesthetics? (a) Procaine (b) Cocaine (c) Lignocaine (d) Tetracaine

Q2. The three-part pharmacophore of local anesthetics is: (a) ring – ketone – acid (b) lipophilic aromatic ring – intermediate linkage – hydrophilic amine (c) sugar – phosphate – base (d) steroid – lactone – amine

Q3. Which linkage is present in lignocaine? (a) Ester (b) Ether (c) Amide (d) Ketone

Q4. Ester-type local anesthetics are hydrolyzed rapidly by: (a) liver oxidases (b) plasma esterases (c) kidney peptidases (d) stomach acid

Q5. The ortho methyl groups in lignocaine's structure serve to: (a) increase water solubility (b) hinder hydrolysis of the amide bond and increase duration (c) reduce potency (d) cause allergy

Q6. Which local anesthetic can be used ONLY on the surface and never injected? (a) Procaine (b) Mepivacaine (c) Benzocaine (d) Etidocaine

Q7. Dibucaine belongs to which chemical class? (a) Benzoic acid ester (b) Acetanilide amide (c) Quinoline amide (d) Ether type

Q8. Which drug is most associated with spinal anesthesia among the following? (a) Benzocaine (b) Tetracaine (c) Diperodon (d) Phenacaine

Q9. Prilocaine differs from lignocaine in that its amine is: (a) tertiary (b) quaternary (c) secondary (d) primary aromatic

Q10. A patient allergic to procaine (PABA allergy) can usually safely receive: (a) tetracaine (b) benzocaine (c) lignocaine (d) butamben

Answer key: 1-(b), 2-(b), 3-(c), 4-(b), 5-(b), 6-(c), 7-(c), 8-(b), 9-(c), 10-(c)

B. Viva Questions (5) — with Short Answers

V1. What is a local anesthetic? A drug that produces numbness in a small area of the body by blocking sodium channels in nerves, while the patient remains awake.

V2. Name the three parts of the local anesthetic pharmacophore. Lipophilic aromatic ring, intermediate linkage (ester/amide/ketone/ether), hydrophilic amine side chain.

V3. Why do ester local anesthetics have a shorter duration than amides? Ester linkages are rapidly hydrolyzed by plasma esterases in the blood, so the drug is destroyed quickly; amide linkages resist these enzymes and are broken down slowly in the liver.

V4. Are lignocaine and lidocaine different drugs? No — they are the same drug with two names; "lignocaine" is used in India/UK and "lidocaine" in the USA.

V5. Why is benzocaine used only topically? It has a primary aromatic amine and no amine side chain, so it cannot form a water-soluble salt for injection; it works only on surfaces like skin and mucous membranes.

C. Application-Based Questions (3)

A1. A dentist wants an anesthetic for a 2-hour molar extraction in a patient with a known allergy to procaine. Which drug and class would you recommend, and why? *Expected answer:* Lignocaine (amide class) — amides don't produce PABA on breakdown, so they avoid the ester/PABA allergy; lignocaine is the standard dental anesthetic with suitable duration.

A2. Two drugs, procaine and tetracaine, are both PABA esters, yet tetracaine is much more potent and longer-acting. Explain using SAR. *Expected answer:* Tetracaine has a butyl chain on the aromatic ring (SAR rule iv) — longer alkyl chain increases lipophilicity, so it penetrates nerves better, giving higher potency and longer duration, with higher toxicity as the trade-off.

A3. A pharmacist receives a prescription for "lidocaine 2% injection" but the shelf label reads "lignocaine 2%". Should they dispense it? Justify. *Expected answer:* Yes — lignocaine and lidocaine are the same drug (two regional names); dispensing is correct after confirming strength and dosage form.

7.18 References

1. Lemke, Williams & Roche — *Foye's Principles of Medicinal Chemistry*.
2. Beale, Thomas & Duckett — *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*.
3. Abraham & Griffin — *Burger's Medicinal Chemistry and Drug Discovery*.
4. Patrick — *An Introduction to Medicinal Chemistry*.
5. Lednicer — *The Organic Chemistry of Drug Synthesis*.
6. Furniss et al. — *Vogel's Textbook of Practical Organic Chemistry*.
7. Brunton et al. — *Goodman and Gilman's The Pharmacological Basis of Therapeutics*.
8. Williams — *Foye's Principles of Medicinal Chemistry*.

End of Chapter 7: Local Anesthetic Agents

Chapter 8: Synthesis Handbook — Starred Drugs of Units I–II

Learning Objectives

After studying this chapter, you should be able to:

1. Write the complete synthesis of each of the 9 starred drugs with starting material, numbered steps, reagents, and named intermediates.
2. Draw a simple text reaction scheme (A → B → C) for every synthesis.
3. Name the key reaction used in each step (Henry reaction, SN2, epoxide ring opening, von Braun demethylation, Grignard + CO2, and so on).
4. Explain in one simple line WHY each step works (for example, why a leaving group is introduced before substitution).
5. Answer exam MCQs on reagents and intermediates, and viva questions on the star drugs.

Key Reactions Toolbox (one-line revision of the named reactions used here)

- **Henry reaction (nitroaldol):** An aldehyde + nitromethane in base join to give a carbon–carbon bond with a new –OH and –NO2 group; this is how we add two carbons to an aldehyde.
- **Alpha-bromination:** Bromine replaces one hydrogen on the carbon next to a ketone (–CO–CH3 becomes –CO–CH2Br); the Br becomes an excellent leaving group for the next step.
- **SN2 (bimolecular nucleophilic substitution):** A nucleophile (e.g., an amine) attacks a carbon holding a leaving group (e.g., Br) from the back side and pushes the leaving group out, all in one step.
- **Epoxide ring opening:** An amine attacks a strained 3-membered epoxide ring; the strain makes the ring eager to open, and the amine adds to one carbon.
- **Von Braun N-demethylation:** Cyanogen bromide (BrCN) cuts off an N-methyl group of a tertiary amine, giving an N-cyano intermediate (and methyl bromide).
- **Grignard + CO2:** A Grignard reagent (R–MgBr) adds to carbon dioxide and, after acidic workup, gives a carboxylic acid — this is how we add one carbon (–COOH) to a chain.
- **SOCl2 chlorination:** Thionyl chloride converts the –OH of a carboxylic acid into –Cl, making the acid chloride; –Cl is a much better leaving group than –OH, so esterification/amidation becomes easy.
- **Esterification / amidation:** Acid chloride + alcohol → ester; acid chloride + amine → amide; HCl is the side product, and SOCl2 was used first so the –OH leaves easily.
- **Nitro reduction:** A nitro group (–NO2) is reduced to an amine (–NH2) with tin/HCl or catalytic hydrogenation (H2/Pt or H2/Pd); the amine is the active form in many drugs.

1. Phenylephrine — Synthesis from m-Hydroxybenzaldehyde

Phenylephrine is an alpha-adrenergic agonist (a decongestant and vasoconstrictor) with the phenolic –OH in the meta position.

Text reaction scheme:

m-hydroxybenzaldehyde --(CH3NO2, base, Henry)--> nitroaldol --(H2/Pt or Zn/HCl, reduction)--> amino alcohol --(HCHO + HCOOH, N-methylation)--> phenylephrine

Step 1 — Henry (nitroaldol) reaction: m-Hydroxybenzaldehyde + nitromethane (CH_3NO_2) in base (e.g., KOH/ethanol) → **1-(3-hydroxyphenyl)-2-nitroethan-1-ol** (the nitroaldol). *Why it works:* The base removes one proton from nitromethane, making a carbon anion that attacks the aldehyde carbon; the two-carbon side chain is added and a new –OH forms.

Step 2 — Reduction of the nitro group: The nitroaldol + H_2 over Pt catalyst (or Zn/HCl) → **1-(3-hydroxyphenyl)-2-aminoethan-1-ol** (a primary amine alcohol). *Why it works:* The nitro group (–NO_2) is reduced all the way to –NH_2 while the –OH and phenolic ring stay untouched.

Step 3 — N-methylation (Eschweiler–Clarke): The amino alcohol + formaldehyde (HCHO) + formic acid (HCOOH), heated → **phenylephrine** [3-(1-hydroxy-2-(methylamino)ethyl)phenol]. *Why it works:* Formaldehyde first makes an imine with the primary amine, and formic acid gives hydrogen to reduce that imine — the net result is one methyl group added to nitrogen (secondary amine).

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2. Salbutamol — Synthesis from 3-(Hydroxymethyl)-4-hydroxyacetophenone

Salbutamol (albuterol) is a beta-2 selective adrenergic agonist used as a bronchodilator in asthma. Note: the starting ketone, 3-(hydroxymethyl)-4-hydroxyacetophenone, is itself prepared from methyl 5-acetylsalicylate.

Text reaction scheme:

3-(hydroxymethyl)-4-hydroxyacetophenone --(Br2, alpha-bromination)--> bromo ketone --(tert-butylamine, SN2)--> amino ketone --(NaBH4, reduction)--> salbutamol

Step 1 — Alpha-bromination: The acetophenone + bromine (Br_2) in acetic acid → **2-bromo-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethan-1-one** (alpha-bromo ketone). *Why it works:* The carbon next to the carbonyl is the most reactive for halogenation; Br replaces one methyl hydrogen so the next step has a good leaving group.

Step 2 — SN2 displacement with tert-butylamine: The bromo ketone + tert-butylamine (excess, warmed) → **2-(tert-butylamino)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethan-1-one** (amino ketone). *Why it works:* The amine nitrogen attacks the carbon holding Br and pushes Br out in one step (SN2); the bulky tert-butyl group is what gives salbutamol its beta-2 selectivity.

Step 3 — Reduction of the ketone: The amino ketone + sodium borohydride ($NaBH_4$, in methanol) → **salbutamol** [4-(2-(tert-butylamino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol]. *Why it works:* $NaBH_4$ delivers hydrogen to the ketone carbonyl, converting C=O into a secondary alcohol (–CH–OH) without touching the amine.

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3. Tolazoline — Cyclocondensation of Phenylacetonitrile with Ethylenediamine

Tolazoline is an alpha-adrenergic blocker used to treat peripheral vascular disorders. Its key ring is an imidazoline (a five-membered ring with two nitrogens and one double bond).

Text reaction scheme:

phenylacetonitrile --(ethylenediamine, heat; amidine intermediate)--> tolazoline + NH3

The chemistry in 2 simple sub-steps:

Sub-step 1 — Amidine formation: One nitrogen of ethylenediamine adds to the carbon of the nitrile group (–C≡N), giving an **amidine intermediate** (a carbon holding both –NH_2 and =NH). The nitrile carbon is electron-poor, so the amine attacks it. *Why it works:* Heating drives the nucleophilic addition of the amine to the triple bond of the nitrile.

Sub-step 2 — Intramolecular ring closure: The second nitrogen of ethylenediamine attacks the same carbon from within the molecule, the ring closes, and **ammonia (NH3) is eliminated** → **2-benzyl-4,5-dihydro-1H-imidazole** (tolazoline). *Why it works:* Ring closure is favoured because the second nitrogen is already close to the carbon (intramolecular attack is fast); loss of NH3 drives the reaction to completion.

4. Propranolol — Synthesis via the Glycidyl Ether Route

Propranolol is the prototype non-selective beta-blocker. Its classic route goes through an epoxide (glycidyl ether) intermediate.

Text reaction scheme:

1-naphthol --(NaOH, epichlorohydrin)--> glycidyl ether --(isopropylamine, ring opening)--> propranolol

Step 1 — Glycidyl ether formation: 1-Naphthol + sodium hydroxide (NaOH) + epichlorohydrin (warmed) → **1-(oxiran-2-ylmethoxy)naphthalene** (the glycidyl ether). *Why it works:* NaOH converts the naphthol –OH into a phenoxide ion (a strong nucleophile), which attacks epichlorohydrin and forms the epoxide ring — the aryloxy-propanol backbone is born here.

Step 2 — Epoxide ring opening with isopropylamine: The glycidyl ether + isopropylamine (excess, room temperature or warmed) → **propranolol** [1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol]. *Why it works:* The amine attacks the less-hindered carbon of the strained epoxide ring; the ring opens and a new –OH appears on the middle carbon, giving the characteristic –O–CH2–CH(OH)–CH2–NH– beta-blocker skeleton.

5. Carbachol — Choline Chloride Followed by Carbamoylation

Carbachol is a cholinergic agonist (carbamoyl ester of choline) used in glaucoma; unlike acetylcholine, its carbamate group resists cholinesterase hydrolysis.

Text reaction scheme:

trimethylamine --(2-chloroethanol)--> choline chloride --(urea, heat, carbamoylation)--> carbachol chloride

Step 1 — Formation of choline chloride: Trimethylamine + 2-chloroethanol (warmed) → **choline chloride** [(2-hydroxyethyl)trimethylammonium chloride]. *Why it works:* The tertiary amine nitrogen attacks the carbon holding chlorine (SN2), making a permanent quaternary ammonium salt with a free –OH at the other end.

Step 2 — Carbamoylation (urea route): Choline chloride + urea, heated strongly (urea melts and acts as the carbamoyl source, ammonia is driven off) → **carbachol chloride** [(2-carbamoyloxyethyl)trimethylammonium chloride]. *Why it works:* The –OH of choline attacks the carbonyl carbon of urea and one –NH2 leaves as ammonia; the product carries the –O–CO–NH2 (carbamoyl) group that resists cholinesterase.

Alternative (phosgene route, for reference): choline → chloroformate intermediate with phosgene, then ammonia replaces the chloride → same carbachol. The urea route is presented here as the main route.

6. Ipratropium Bromide — N-Demethylation of Atropine and Re-quaternization

Ipratropium bromide is an anticholinergic (muscarinic antagonist) bronchodilator. It is made by taking the natural product atropine, removing its N-methyl group, and putting on a bulkier isopropyl group.

Text reaction scheme:

atropine --(BrCN, von Braun)--> N-cyano-noratropine --(acid hydrolysis)--> noratropine --(isopropyl bromide, N-alkylation)--> ipratropium bromide

Step 1 — Von Braun N-demethylation: Atropine + cyanogen bromide (BrCN) → **N-cyano-noratropine** (+ methyl bromide, CH3Br). *Why it works:* BrCN cuts the N–CH3 bond of the tertiary amine; the methyl leaves as methyl bromide and the nitrogen is left holding a –C≡N group.

Step 2 — Acid hydrolysis of the N-cyano group: N-cyano-noratropine + dilute aqueous acid, heated → **noratropine** (secondary amine, the N-methyl removed). *Why it works:* Acid and water break the N–C≡N bond, releasing the cyano carbon and freeing the nitrogen as a secondary amine (–NH–).

Step 3 — N-alkylation with isopropyl bromide: Noratropine + isopropyl bromide → **ipratropium bromide** (quaternary ammonium salt). *Why it works:* The secondary amine nitrogen attacks isopropyl bromide twice (it is already tertiary after the first alkylation… actually the amine adds the isopropyl group to become quaternary); the bromide ion stays as the counter-ion of the salt — this is the drug as dispensed.

7. Dicyclomine — Grignard Route to a Bulky Ester

Dicyclomine is an antispasmodic (anticholinergic) with a very bulky dicyclohexyl group; it is dispensed as the hydrochloride salt.

Text reaction scheme:

cyclohexanone --(cyclohexylmagnesium bromide, Grignard)--> tertiary alcohol --(HCl)--> alkyl chloride --(Mg, then CO2, then H+)--> carboxylic acid --(SOCl2)--> acid chloride --(2-(diethylamino)ethanol)--> dicyclomine (·HCl salt)

Step 1 — Grignard addition: Cyclohexanone + cyclohexylmagnesium bromide (dry ether) → after workup, **1-cyclohexylcyclohexan-1-ol** (a tertiary alcohol with two cyclohexane rings). *Why it works:* The Grignard carbon attacks the ketone carbonyl carbon; a new C–C bond forms and two cyclohexane rings now share one carbon.

Step 2 — Conversion to the chloride: The tertiary alcohol + concentrated HCl → **1-chloro-1-cyclohexylcyclohexane**. *Why it works:* The –OH is a poor leaving group; HCl converts it to –Cl, which leaves easily in the next step.

Step 3 — Grignard reagent + CO2 (carboxylation): The alkyl chloride + magnesium (dry ether) → Grignard reagent; then CO2 is passed in, followed by acidic workup → **1-cyclohexylcyclohexane-1-carboxylic acid**. *Why it works:* Mg turns the chloride into a nucleophilic Grignard carbon, which attacks CO2; acid workup gives the free –COOH — this step adds exactly one carbon.

Step 4 — Acid chloride formation: The carboxylic acid + thionyl chloride (SOCl2) → the **acid chloride** (1-cyclohexylcyclohexane-1-carbonyl chloride). *Why it works:* SOCl2 converts the –OH of the acid into –Cl, a better leaving group, so the bulky alcohol can attack in the final step.

Step 5 — Esterification: The acid chloride + 2-(diethylamino)ethanol → **dicyclomine** [2-(diethylamino)ethyl 1-cyclohexylcyclohexane-1-carboxylate], isolated as the **hydrochloride salt**. *Why it works:* The alcohol oxygen attacks the acid chloride carbonyl, displacing Cl; the amine end picks up HCl during salt formation, making the drug water-soluble.

8. Procaine — Ester of p-Aminobenzoic Acid

Procaine is the classic local anaesthetic (ester type), made by esterifying p-aminobenzoic acid with 2-(diethylamino)ethanol. The nitro group is reduced only at the end.

Text reaction scheme:

p-nitrobenzoic acid --(SOCl2)--> p-nitrobenzoyl chloride --(2-(diethylamino)ethanol)--> p-nitro ester --(Sn/HCl or H2/Pt)--> procaine

Step 1 — Acid chloride formation: p-Nitrobenzoic acid (from oxidation of p-nitrotoluene) + SOCl2 → **p-nitrobenzoyl chloride**. *Why it works:* SOCl2 converts the –OH of the acid into –Cl, a better leaving group — the acid is now activated for esterification.

Step 2 — Esterification: p-Nitrobenzoyl chloride + 2-(diethylamino)ethanol → **2-(diethylamino)ethyl p-nitrobenzoate**. *Why it works:* The alcohol attacks the acid chloride carbonyl and Cl leaves; the nitro group is kept untouched because reducing it earlier would let the free amine interfere with the esterification.

Step 3 — Reduction of the nitro group: The p-nitro ester + Sn/HCl (or H2 over Pt) → **procaine** [2-(diethylamino)ethyl 4-aminobenzoate]. *Why it works:* The nitro group is reduced to the primary aromatic amine (–NH2), which is the pharmacophoric group of procaine; the ester survives because these reducing conditions target only the nitro group.

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9. Dibucaine — Quinoline-4-carboxamide with a 2-Butoxy Group

Dibucaine (cinchocaine) is a potent, long-acting local anaesthetic (amide type) built on a quinoline ring.

Text reaction scheme:

2-hydroxy-4-methylquinoline --(POCl3)--> 2-chloro-4-methylquinoline --(KMnO4 or SeO2)--> 2-chloroquinoline-4-carboxylic acid --(n-butanol / sodium n-butoxide)--> 2-butoxyquinoline-4-carboxylic acid --(SOCl2)--> acid chloride --(N,N-diethylethylenediamine)--> dibucaine

Step 1 — Chlorination of the 2-hydroxyquinoline: 2-Hydroxy-4-methylquinoline (2-hydroxylepidine) + phosphorus oxychloride (POCl3) → **2-chloro-4-methylquinoline** (2-chlorolepidine). *Why it works:* POCl3 converts the 2-hydroxy (which exists in the keto tautomer) into a 2-chloro group — aromatic chlorine that can later be replaced by butoxide.

Step 2 — Oxidation of the 4-methyl group: 2-Chlorolepidine + KMnO4 or SeO2 → **2-chloroquinoline-4-carboxylic acid**. *Why it works:* Strong oxidation converts the 4-methyl group (–CH3) all the way to the carboxylic acid (–COOH) while the ring and the 2-chloro group survive.

Step 3 — Nucleophilic aromatic substitution (2-butoxy introduction): The 2-chloro acid + n-butanol with sodium n-butoxide (or n-butanol + base, heated) → **2-butoxyquinoline-4-carboxylic acid**. *Why it works:* The 2-chloro of quinoline is activated for nucleophilic aromatic substitution (the ring nitrogen pulls electrons); butoxide replaces Cl, giving the 2-butoxy group that boosts anaesthetic potency.

Step 4 — Acid chloride formation: The 2-butoxy acid + SOCl2 → the **acid chloride**. *Why it works:* SOCl2 converts the –OH of the acid into –Cl, a better leaving group, so amidation in the final step is easy.

Step 5 — Amidation: The acid chloride + N,N-diethylethylenediamine → **dibucaine** [2-butoxy-N-(2-(diethylamino)ethyl)quinoline-4-carboxamide]. *Why it works:* The primary amine end of the diamine attacks the acid chloride carbonyl, forming the amide bond; the tertiary amine end stays free (it forms the salt in the final drug).

Key Points

- Phenylephrine is built by the Henry reaction (nitroaldol) on m-hydroxybenzaldehyde, then nitro reduction, then Eschweiler–Clarke N-methylation.
- Salbutamol needs alpha-bromination before the amine can be introduced by SN2; the ketone is reduced last with NaBH4.
- Tolazoline forms by cyclocondensation of phenylacetonitrile with ethylenediamine — amidine intermediate first, then ring closure with loss of NH3.
- Propranolol's classic route goes through the glycidyl ether (epoxide), which isopropylamine opens to give the beta-blocker skeleton.
- Carbachol = choline chloride + urea (carbamoylation); the carbamate group resists cholinesterase.
- Ipratropium bromide: von Braun N-demethylation of atropine (BrCN), hydrolysis to noratropine, then N-alkylation with isopropyl bromide.
- Dicyclomine uses two Grignard steps: first to build the dicyclohexyl tertiary alcohol, second with CO2 to add the –COOH carbon.
- Procaine: esterify FIRST with the nitro group still on, reduce the nitro to amine LAST (order matters).
- Dibucaine: POCl3 gives 2-chlorolepidine, oxidation gives the 4-acid, butoxide replaces the 2-chloro, then amide formation with N,N-diethylethylenediamine.
- SOCl2 appears in four syntheses (dicyclomine, procaine, dibucaine) — always for the same job: –OH → –Cl to make a better leaving group.
- Grignard reagents die in water or acid — every Grignard step uses dry ether and acidic workup only at the end.

Common Mistakes in Synthesis Questions

1. **Wrong order of steps (procaine):** Reducing the nitro group BEFORE esterification is the classic error — the free aromatic amine would react with the acid chloride and give the wrong product. Esterify first, reduce last.
2. **Forgetting the salt form:** Dicyclomine is isolated as the hydrochloride; ipratropium bromide and carbachol chloride are quaternary salts — always name the counter-ion (Br−, Cl−) in the final answer.
3. **Missing the leaving-group step:** In dicyclomine, students jump from the tertiary alcohol straight to the Grignard — the alcohol must first be converted to the chloride with HCl.
4. **Confusing the ipratropium steps:** N-demethylation (BrCN) comes BEFORE hydrolysis of the N-cyano group; hydrolysing first is impossible because the cyano intermediate does not exist yet.
5. **Forgetting what the tolazoline starting materials are:** The nitrile is phenylacetonitrile (benzyl cyanide), not benzoic acid; NH3 (not water) is the leaving by-product of ring closure.
6. **Alpha-bromination vs ring bromination (salbutamol):** Bromine goes on the side-chain methyl next to the ketone, not on the aromatic ring.
7. **Epoxide opening regiochemistry (propranolol):** Isopropylamine attacks the LESS hindered carbon of the epoxide — attacking the other carbon would give the wrong alcohol position.
8. **Reducing the wrong group:** In salbutamol, NaBH4 reduces the ketone, NOT the phenolic –OH or the –CH2OH; in dibucaine, oxidation targets the 4-methyl, not the ring.

Mnemonics

- **"Henry Helps Phenylephrine"** — the Henry reaction starts the phenylephrine synthesis.
- **"Bromine Before Butylamine"** — salbutamol: brominate first, then add the butylamine.
- **"Benzyl cyanide + diamine = imidazoline"** — tolazoline's two starting materials and ring.
- **"Naphthol, Epoxide, Isopropylamine = Propranolol"** — say the three, in order.
- **"Choline + Urea = Carbachol"** — the whole synthesis in four words.
- **"Atropine loses Methyl, gains isoPropyl"** — ipratropium: demethylate, then alkylate.
- **"Two Grignards for Dicyclomine"** — one to build the rings, one with CO2 for the acid.
- **"Nitro last, amine fast"** — procaine: reduce the nitro group in the LAST step.
- **"Chlorine in, butoxy out"** — dibucaine: 2-chloro is introduced by POCl3, then replaced by butoxy.

Exam Summary

Drug	Start	Key steps (in order)	Signature reagent
Phenylephrine	m-hydroxybenzaldehyde	Henry → nitro reduction → N-methylation	CH3NO2/base; HCHO/HCOOH
Salbutamol	3-(hydroxymethyl)-4-hydroxyacetophenone	α-bromination → SN2 → ketone reduction	Br2; tert-butylamine; NaBH4
Tolazoline	phenylacetonitrile + ethylenediamine	amidine → cyclocondensation (−NH3)	heat
Propranolol	1-naphthol	glycidyl ether → epoxide opening	epichlorohydrin; isopropylamine
Carbachol	trimethylamine	choline chloride → carbamoylation	2-chloroethanol; urea
Ipratropium Br	atropine	von Braun → hydrolysis → N-alkylation	BrCN; isopropyl bromide
Dicyclomine	cyclohexanone	Grignard → Cl → Grignard/CO2 → SOCl2 → ester	cyclohexylMgBr; SOCl2
Procaine	p-nitrobenzoic acid	SOCl2 → esterify → nitro reduction	SOCl2; Sn/HCl
Dibucaine	2-hydroxy-4-methylquinoline	POCl3 → oxidation → butoxy → SOCl2 → amidation	POCl3; KMnO4; N,N-diethylethylenediamine

One-Minute Revision

Phenylephrine: aldehyde + nitromethane (Henry) → reduce nitro → N-methylate. Salbutamol: brominate the ketone → SN2 with tert-butylamine → NaBH4 reduces ketone. Tolazoline: benzyl cyanide + ethylenediamine, heat, lose NH3. Propranolol: 1-naphthol + epichlorohydrin → glycidyl ether → open epoxide with isopropylamine. Carbachol: trimethylamine + 2-chloroethanol → choline chloride → urea, heat → carbamate. Ipratropium: atropine + BrCN (von Braun) → hydrolyse N-cyano → alkylate with isopropyl bromide. Dicyclomine: cyclohexanone + Grignard → HCl → Mg/CO2 → SOCl2 → ester with 2-(diethylamino)ethanol (HCl salt). Procaine: p-nitrobenzoic acid → SOCl2 → esterify → reduce nitro LAST. Dibucaine: POCl3 → oxidise 4-methyl → butoxide replaces 2-chloro → SOCl2 → amide with diamine.

Exam Questions

10 MCQs (with answer key — focused on reagents/intermediates)

1. In the synthesis of phenylephrine, the reagent used in the FIRST step (Henry reaction) is:
a) H2/Pt
b) Nitromethane in base
c) Formaldehyde + formic acid
d) Thionyl chloride
Answer: b

2. The intermediate formed after Step 1 of the salbutamol synthesis is:
a) The amino ketone
b) 2-Bromo-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethan-1-one
c) Salbutamol alcohol
d) The glycidyl ether
Answer: b

3. Tolazoline is formed by heating phenylacetonitrile with:
a) Isopropylamine
b) Ethylenediamine
c) tert-Butylamine
d) N,N-Diethylethylenediamine
Answer: b

4. In the propranolol synthesis, the epoxide intermediate (glycidyl ether) is opened with:
a) tert-Butylamine
b) Ammonia
c) Isopropylamine
d) Methylamine
Answer: c

5. The von Braun N-demethylation of atropine uses:
a) POCl3
b) Cyanogen bromide (BrCN)
c) KMnO4
d) Sodium borohydride
Answer: b

6. In the dicyclomine synthesis, the carboxylic acid is obtained from the Grignard reagent by reaction with:
a) Formaldehyde
b) Carbon dioxide, then acidic workup
c) Epichlorohydrin
d) Urea
Answer: b

7. In the procaine synthesis, the nitro group is reduced in the:
a) First step, before esterification
b) Last step, after esterification
c) Second step, with SOCl2
d) It is never reduced
Answer: b

8. The reagent used to convert 2-hydroxy-4-methylquinoline to 2-chlorolepidine is:
a) SOCl2
b) BrCN
c) POCl3
d) SeO2
Answer: c

9. Carbachol is prepared by carbamoylation of choline chloride with:
a) Phosgene only
b) Urea with heating
c) Isopropyl bromide
d) Nitromethane
Answer: b

10. The final amine used in the amidation step of dibucaine synthesis is:
a) tert-Butylamine
b) Isopropylamine
c) N,N-Diethylethylenediamine
d) Ethylenediamine
Answer: c

5 Viva Questions (with short answers)

1. Why is the nitro group reduced LAST in the procaine synthesis? Because a free aromatic amine would react with the acid chloride during esterification and give the wrong product; the nitro group acts as a protected form of the amine until the ester is built.

2. What is the role of SOCl2 in the dicyclomine, procaine, and dibucaine syntheses? It converts the –OH of a carboxylic acid into –Cl (acid chloride); chloride is a much better leaving group than hydroxide, so esterification/amidation proceeds easily.

3. How does the von Braun reaction help in making ipratropium bromide from atropine? Cyanogen bromide cuts off atropine's N-methyl group to give N-cyano-noratropine; after hydrolysis to noratropine, a bulkier isopropyl group is installed to give the quaternary ipratropium salt.

4. Why does the salbutamol synthesis brominate the ketone BEFORE adding tert-butylamine? Bromine creates a good leaving group on the side chain; the amine then displaces bromide by SN2. Without bromination, the amine has nothing to displace and no reaction occurs.

5. Why is carbachol resistant to cholinesterase while acetylcholine is not? Carbachol carries a carbamate (–O–CO–NH2) group instead of an acetate ester; cholinesterase hydrolyses the carbamate extremely slowly, so carbachol acts longer.

3 Application-Based Questions

1. A student proposes making procaine by first reducing p-nitrobenzoic acid to p-aminobenzoic acid and then esterifying. Predict the outcome and explain the correct sequence. *Guidance:* The free aromatic –NH2 of p-aminobenzoic acid would attack the acid chloride (or compete during esterification), giving amide side products instead of the clean ester. The correct sequence esterifies the nitro compound first (nitro is inert to SOCl2 and the alcohol) and reduces the nitro to the amine only in the final step.

2. In the tolazoline synthesis, why is ethylenediamine used in the reaction, and what small molecule is lost when the imidazoline ring closes? *Guidance:* Ethylenediamine supplies both nitrogens of the imidazoline ring — one forms the amidine intermediate, the second closes the ring intramolecularly. Ammonia (NH3) is eliminated during ring closure; its loss drives the cyclocondensation to completion.

3. A QC chemist finds that a batch labelled "ipratropium bromide" still contains noratropine. Which step failed, and what analytical check would confirm completion of that step? *Guidance:* The final N-alkylation with isopropyl bromide failed (or was incomplete) — noratropine is the secondary-amine intermediate of the step before. Completion is confirmed by the absence of the secondary amine (e.g., a negative secondary-amine test / chromatographic check) and the presence of the quaternary ammonium bromide salt.

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