BP501T · B.Pharm Semester V · Theory Notes

Biomedicinal Chemistry

Unit I — Drugs Acting on the Central Nervous System

Unit I (10 hours)

Pills & Python Notes

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

Syllabus coverage: Unit I (10 hours).

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Course: B.Pharm Semester V | **Subject:** BP501T Biomedicinal Chemistry **Unit:** I — Drugs Acting on the Central Nervous System

How to use this draft: Each chapter follows the same path — first the technical idea, then a simple explanation, then an example, then a key takeaway. New words are defined the first time they appear. Read slowly; medicinal chemistry is a language, and every language is learned one word at a time.

CHAPTER 1: GENERAL ANESTHETICS

1.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define general anesthesia and describe its four stages in simple words.

2 Classify general anesthetics into inhalational and intravenous agents with examples.

3 Explain the Meyer–Overton rule and the meaning of MAC (minimum alveolar concentration).

4 Describe, in simple terms, how general anesthetics act on GABA and NMDA targets in the brain.

5 Draw (on paper) the chemical scaffold of each halogenated inhalational anesthetic and name its key substituents.

6 Differentiate the three thiobarbiturate/thiobarbiturate-type IV agents by their C-5 substituents.

7 Write the complete synthesis of ketamine with reagents, conditions, and intermediates.

8 Explain why fospropofol is called a prodrug and how remimazolam is switched off in the body.

9 Compare the six inhalational agents using blood:gas solubility and MAC values.

10 State one clinical use of every drug in this chapter.

1.2 Definitions — Starting From Zero

- **Central nervous system (CNS):** The brain plus the spinal cord. It is the body's control room. Every thought, movement, and feeling of pain passes through it.
- **Neuron:** A nerve cell. It carries tiny electrical messages. One neuron talks to the next at a junction called a **synapse**.
- **Neurotransmitter:** A chemical messenger that carries the signal across the synapse. Two matter most here: **GABA** (the "calm down" signal — it slows neurons) and **glutamate** (the "fire!" signal — it excites neurons, acting mainly through **NMDA receptors**).
- **Receptor:** A protein "lock" on a neuron. A drug is the "key" that fits it.
- **Anesthesia (general):** A controlled, reversible state where the patient feels no pain, has no memory of the procedure, does not move, and is unconscious. "Reversible" means the patient wakes up fully afterward.

- **Induction:** The beginning of anesthesia — putting the patient to sleep.
- **Maintenance:** Keeping the patient asleep during the operation.
- **Recovery (emergence):** Waking the patient up after the operation.
- **MAC (minimum alveolar concentration):** The concentration of an inhaled anesthetic in the lungs (alveoli) that keeps 50 out of 100 patients from moving when the surgeon makes the first cut. Lower MAC = more potent drug (you need less of it).
- **Balanced anesthesia:** Using small doses of several drugs together (e.g., an IV drug for induction + a gas for maintenance + a painkiller) instead of one large dose.
- **Dissociative anesthesia:** A special state (produced by ketamine) where the patient looks awake with eyes open but feels no pain and remembers nothing — the brain's regions are "disconnected" from each other.
- **Prodrug:** An inactive compound that the body converts into the active drug (like a gift that must be unwrapped before use).
- **Scaffold:** The fixed central framework (skeleton) of a molecule. **Substituents** are the chemical groups attached to that skeleton — changing them changes the drug's behavior.

Key takeaway: General anesthetics either boost the brain's "brake" (GABA) or block its "accelerator" (NMDA/glutamate). The result is the same: painless, reversible unconsciousness.

1.3 The Four Stages of Anesthesia (Guedel's Stages) — Simple Version

Think of anesthesia as slowly turning down a dimmer switch on the brain:

Stage	Name	What happens (simple words)
I	Analgesia	Pain goes away first; patient still awake and talking
II	Excitement / delirium	Patient may move, talk loudly, or struggle — the "brakes" come off unevenly before full sleep
III	Surgical anesthesia	Patient fully asleep, muscles relaxed — surgery happens here
IV	Medullary depression (danger)	Breathing and heart control centers shut down — overdose; must be avoided

Simple explanation: Modern fast-acting IV drugs (like thiopental) push the patient through Stages I and II in seconds, so the stormy Stage II is barely seen. **Example:** A patient given thiopental counts "100, 99, 98..." and is asleep before reaching 95. **Key takeaway:** The goal is to reach Stage III quickly and never enter Stage IV.

1.4 How Do General Anesthetics Work? (Mechanism — From Zero)

Technical concept: Inhalational anesthetics follow the **Meyer–Overton rule**: anesthetic potency is directly proportional to lipid (oil) solubility. They act on multiple protein targets: they **potentiate GABA-A receptors** (more "calm down" signal) and **inhibit NMDA receptors** and excitatory channels (less "fire!" signal). Some open background potassium channels, which also quiet neurons.

Simple explanation: Brain cell membranes are made of fat (lipid). Anesthetic molecules dissolve into this fat like sugar into tea. The more easily a drug dissolves in fat, the stronger its sleep effect — this is the Meyer–Overton rule. Once inside the membrane, the drug turns up the brain's brake pedal (GABA) and presses down its accelerator (NMDA).

Analogy: Imagine a classroom. GABA is the strict teacher saying "sit quietly"; glutamate/NMDA is the naughty student shouting "make noise!". Anesthetics give the teacher a microphone and take away the student's voice. The class goes silent.

Key takeaway: No single "sleep receptor" exists — general anesthetics quiet the whole brain by shifting the balance from excitation toward inhibition.

```
DIAGRAM — DRAW THIS: "The Seesaw of Brain Activity"
Draw a seesaw. Left side labeled "GABA (brake, calm)" going DOWN (heavy).
Right side labeled "Glutamate/NMDA (accelerator, excite)" going UP (light).
Title: "Anesthesia tips the seesaw toward GABA."
Below, draw a neuron membrane as two rows of circles (lipid bilayer)
with small hexagon drug molecules sitting inside the fat layer.
Caption: "Meyer–Overton rule: more lipid-soluble = more potent."
```

1.5 Classification of General Anesthetics (Flowchart)

```
FLOWCHART — DRAW THIS:
                    GENERAL ANESTHETICS
                    (this chapter: 14 drugs)
                           |
            +--------------+--------------+
            |                             |
     INHALATIONAL                    INTRAVENOUS
     (breathed as gases)             (injected into vein)
            |                             |
   Volatile halogenated liquids     +------+------+------+------+
   (all are halo-ethers/            |      |      |      |      |
    halo-alkanes):                  |      |      |      |      |
   1. Halothane              Barbiturate  Dissociative  Prodrug  Newer
   2. Methoxyflurane         -type:       :            :        selective:
   3. Enflurane              - Metho-     - Ketamine*  - Fos-   - Remimazo-
   4. Isoflurane               hexital                 propofol   lam
   5. Sevoflurane            - Thiamylal                          (BZD)
   6. Desflurane             - Thiopental                       - Dexmede-
   (Note: nitrous oxide,                                          tomidine
    N2O, the "laughing                                          (alpha-2
    gas", is the classic                                         agonist)
    inhaled gas, but it is                                    - Ramelteon
    NOT in our syllabus                                         (melatonin
    list, so it is not                                            agonist,
    detailed here.)                                             hypnotic-type)
```

1.6 INHALATIONAL AGENTS — The Halogenated Ethers and Alkanes

Technical concept: All six syllabus drugs are small molecules containing **fluorine** (and some also chlorine or bromine). Fluorine makes them stable (they don't burn or explode), non-flammable, and potent. They are liquids in the bottle but turn into vapor (gas) in a special device called a **vaporizer**, and the patient breathes the vapor.

Simple explanation: These are like "sleep vapors". The patient breathes them in through a mask; they go from lungs blood brain in minutes. When the mask is removed, they wash out just as fast and the patient wakes up.

Example: A child needing ear surgery breathes sweet-smelling sevoflurane through a mask and falls asleep without any injection.

Drug 1 — Halothane

- **Chemical class:** Halogenated alkane (not an ether — it has no oxygen).
- **Structure:** Scaffold = a 2-carbon ethane chain: **CF_3–CHBrCl** (2-bromo-2-chloro-1,1,1-trifluoroethane). Key substituents: a **trifluoromethyl group (–CF_3)** on carbon-1, plus **one bromine** and **one chlorine** on carbon-2.
- **Uses:** Inhalational induction and maintenance of general anesthesia (historical gold standard). Today largely replaced because rare but serious **liver damage** (halothane hepatitis) can occur, especially after repeated use.

Drug 2 — Methoxyflurane

- **Chemical class:** Halogenated methyl ether.
- **Structure:** Scaffold = ether: **CH_3–O–CF_2–$CHCl_2$** (2,2-dichloro-1,1-difluoro-1-methoxyethane). Key substituents: a **methoxy group (–OCH_3)** on one side, a **difluoromethylene (–CF_2–)** in the middle, and a **dichloromethyl (–$CHCl_2$)** end.
- **Uses:** Formerly used for anesthesia; abandoned because its breakdown in the body releases large amounts of **fluoride**, which damages the kidneys. (Still used in a few countries as an inhaled painkiller for trauma — not an exam focus.)

Drug 3 — Enflurane

- **Chemical class:** Halogenated ethyl methyl ether.
- **Structure:** Scaffold = ether: **CHF_2–O–CF_2–CHFCl** [2-chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane]. Key substituents: **difluoromethoxy (–$OCHF_2$)** group on one side; the other side carries **chlorine and three fluorines** spread over two carbons.
- **Uses:** Maintenance of general anesthesia (historical). Problem: at deep levels it can cause **seizure-like brain activity** on EEG, so it fell out of favor.

Drug 4 — Isoflurane

- **Chemical class:** Halogenated ethyl methyl ether — a **structural isomer of enflurane** (same atoms, different arrangement: the chlorine sits on the carbon next to the –CF_3 group instead).
- **Structure:** Scaffold = ether: **CF_3–CHCl–O–CHF_2** [2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane]. Key substituents: **trifluoromethyl (–CF_3)**, **one chlorine** on the adjacent carbon, and a **difluoromethoxy (–$OCHF_2$)** group.
- **Uses:** The workhorse inhalational agent for **maintenance of general anesthesia** worldwide. Stable blood pressure, good muscle relaxation.

Drug 5 — Sevoflurane

- **Chemical class:** Halogenated isopropyl methyl ether (fully fluorinated — no chlorine, no bromine).
- **Structure:** Scaffold = ether: **$(CF_3)_2CH–O–CH_2F$** [fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether]. Key substituents: a **hexafluoroisopropyl group** [–$CH(CF_3)_2$, i.e., six fluorines] on one side of oxygen and a **fluoromethyl (–CH_2F)** on the other.
- **Uses: Inhalational induction** (especially in children — sweet smell, no airway irritation) and maintenance. Fast on, fast off.

Drug 6 — Desflurane

- **Chemical class:** Halogenated ethyl methyl ether — differs from isoflurane by only one atom: **fluorine replaces chlorine**.
- **Structure:** Scaffold = ether: **$CF_3–CHF–O–CHF_2$** [2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane]. Key substituents: **four fluorines** distributed over the ethane carbons plus a **difluoromethoxy (–$OCHF_2$)** group. No chlorine, no bromine.
- **Uses:** Maintenance of anesthesia where **very rapid recovery** is needed (e.g., day-care surgery). Needs a special heated vaporizer because it boils near room temperature.

Comparison table — the six inhalational agents (typical textbook values):

Drug	Blood:gas solubility*	MAC (%)*	Speed	One-line memory hook
Halothane	2.5 (high)	0.75	Slow in, slow out	Old faithful; liver risk
Methoxyflurane	12 (very high)	0.16	Very slow	Kidney damage — abandoned
Enflurane	1.9	1.7	Medium	Seizure-like EEG — abandoned
Isoflurane	1.4	1.15	Medium-fast	Maintenance workhorse
Sevoflurane	0.65 (low)	2.0	Fast	Sweet; children induction
Desflurane	0.42 (lowest)	6.0	Fastest	Fastest wake-up; heated vaporizer

*Typical textbook values. Lower blood:gas solubility = faster induction and recovery (less drug dissolves in blood, so the brain level rises and falls quickly). Lower MAC = more potent.

Common confusion: Enflurane vs. isoflurane — they are **isomers** (same molecular formula, chlorine on different carbons). Remember: "**Iso**flurane has the chlorine **iso**lated next to the CF_3 group."

> **Key takeaway:** Fluorine = safe, stable, non-flammable vapor. Chlorine/bromine = older drugs with organ toxicity. Low blood solubility = fast on/fast off.

1.7 INTRAVENOUS AGENTS — BARBITURATE TYPE

Technical concept: These are **barbiturates** (a six-membered ring with three carbonyl groups, discussed fully in Chapter 2) modified for ultra-fast brain entry: a **sulfur replaces oxygen at position 2**

(thiobarbiturates) and oily side chains sit at position 5. High lipid solubility = sleep within 15–30 seconds of injection, but also fast redistribution away from the brain = short action.

Simple explanation: Injected into a vein, these drugs race to the brain in one arm-to-brain circulation time. The patient is asleep before they finish counting backwards from 100. Because the drug then spreads into fat and muscle, the effect wears off in minutes — perfect for "putting the patient under" before the gas takes over.

Drug 7 — Methohexital

- **Chemical class:** Oxybarbiturate (oxygen at C-2, unlike the two below) with an N-methyl group — ultra-short-acting IV anesthetic.
- **Structure:** Scaffold = **barbituric acid ring** (pyrimidine-2,4,6-trione). Key substituents: **N-1 methyl**, C-5 carries an **allyl group (–$CH_2CH{=}CH_2$)** and a **1-methylpent-2-yn-1-yl group** (a branched chain with a triple bond). The triple bond and N-methylation make it very lipid-soluble and very short-acting.
- **Uses:** IV induction of anesthesia, short procedures, and **electroconvulsive therapy (ECT)** (it interferes least with the seizure needed for ECT).

Drug 8 — Thiamylal

- **Chemical class: Thiobarbiturate** (sulfur at C-2 instead of oxygen) — ultra-short-acting IV anesthetic.
- **Structure:** Scaffold = **2-thiobarbituric acid ring** (C=S at position 2). Key substituents: C-5 carries an **allyl group** and a **1-methylbutyl (sec-pentyl) group**.
- **Uses:** IV induction of anesthesia (similar to thiopental; more used in some countries and veterinary practice).

Drug 9 — Thiopental

- **Chemical class: Thiobarbiturate** — the classic ultra-short-acting IV anesthetic.
- **Structure:** Scaffold = **2-thiobarbituric acid ring** (C=S at position 2). Key substituents: C-5 carries an **ethyl group** and a **1-methylbutyl (sec-pentyl) group** — compare thiamylal, which has allyl instead of ethyl.
- **Uses:** The classic **IV induction agent** ("truth serum" of old movies is a myth — it only makes people drowsy and talkative). Also used for rapid control of increased brain pressure and, in veterinary medicine, for animal anesthesia.

Compare the three (table):

Feature	Methohexital	Thiamylal	Thiopental
C-2 atom	O (oxybarbiturate)	S (thiobarbiturate)	S (thiobarbiturate)
N-1	Methylated	H	H
C-5 groups	Allyl + methylpentynyl	Allyl + 1-methylbutyl	Ethyl + 1-methylbutyl
Memory hook	"Methyl + triple bond = fastest"	"Thia = sulfur; allyl twin of thiopental"	"Ethyl + sulfur = the classic"

Key takeaway: Sulfur at C-2 and oily C-5 chains = lipid-soluble = sleep in seconds, wake in minutes.

1.8 KETAMINE — THE DISSOCIATIVE ANESTHETIC (Synthesis Required)

Technical concept: Ketamine is an **NMDA receptor antagonist** (blocks the glutamate "fire!" signal) and produces **dissociative anesthesia** — the thalamus and cortex are functionally disconnected, so pain signals never reach conscious perception.

Simple explanation: The patient's eyes may stay open and they may move slightly, but their brain's "pain telephone lines" are cut. They feel nothing and remember nothing.

Drug 10 — Ketamine

- **Chemical class:** Arylcyclohexylamine (a cyclohexanone ring carrying an aryl group and an amine) — phencyclidine (PCP) family, but safer.
- **Structure:** Scaffold = **cyclohexan-1-one** (a six-membered ring with a ketone C=O at position 1). Key substituents: at carbon-2, a **2-chlorophenyl group** (benzene ring with chlorine at the ortho position) and a **methylamino group (–$NHCH_3$)**. Both sit on the same carbon (C-2), making it a chiral center — the **S-(+)-enantiomer (esketamine)** is the more potent one.
- **Uses:** Dissociative anesthesia for short painful procedures (dressing changes, fracture setting), **pediatric anesthesia**, veterinary anesthesia, emergency/field anesthesia (does not depress breathing much), and (as esketamine nasal spray) **treatment-resistant depression**.

Synthesis of Ketamine (Stevens synthesis — 3 steps)

Starting materials: 2-chlorobenzonitrile + cyclopentylmagnesium bromide (a Grignard reagent).

Step 1 — Grignard addition to the nitrile ketone.

- Reagents/conditions: **cyclopentylmagnesium bromide** in dry ether/THF, then **dilute acid workup** (hydrolysis).
- What happens: The Grignard carbon attacks the nitrile carbon of 2-chlorobenzonitrile, forming an imine salt; acid hydrolysis converts it to the ketone.
- **Intermediate: (2-chlorophenyl)(cyclopentyl)methanone** — also called cyclopentyl o-chlorophenyl ketone. Structure: a C=O carbon carrying a 2-chlorophenyl ring on one side and a cyclopentane ring on the other.

Step 2 — Alpha-bromination α-bromo ketone.

- Reagents/conditions: **Bromine (Br_2)** in acetic acid or CCl_4, at room temperature.
- What happens: Bromine replaces one hydrogen on the cyclopentane carbon next to the carbonyl (the α-position).
- **Intermediate: 1-bromo-1-(2-chlorobenzoyl)cyclopentane** — the α-bromo ketone. Structure: same ketone, now with –Br on the cyclopentane carbon adjacent to the C=O.

Step 3 — Reaction with methylamine ring expansion ketamine.

- Reagents/conditions: **Excess methylamine (CH_3NH_2)**, usually heated.
- What happens: Methylamine adds to the carbonyl carbon; then a **1,2-shift** occurs — one carbon–carbon bond of the cyclopentane ring migrates to the carbonyl carbon while bromide leaves. The five-membered ring **expands to a six-membered ring**, and the methylamino group ends up on the same carbon as the 2-chlorophenyl group.
- **Product: Ketamine — 2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one** (obtained as the racemic mixture; the S-enantiomer is esketamine).

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FLOWCHART — DRAW THIS: Ketamine synthesis (3 boxes with arrows)
Box 1: 2-chlorobenzonitrile + cyclopentyl-MgBr (Grignard), dry ether; then H3O+
   --arrow--> Box 2: (2-chlorophenyl)(cyclopentyl)methanone [ketone intermediate]
Box 2 + Br2 --> Box 3: alpha-bromo ketone [1-bromo-1-(2-chlorobenzoyl)cyclopentane]
Box 3 + excess CH3NH2 (heat) --> Box 4: KETAMINE [ring expands 5 -> 6 membered]
Write under the last arrow: "1,2-shift: C-C bond migrates, Br- leaves"
```

Memory hook for the synthesis: "**G**rignard makes the **k**etone, **B**romine marks the spot, **M**ethylamine **m**oves the ring (56)." — G-B-M: "Good Brave Medicine."

Key takeaway: Ketamine's clever step is the methylamine-induced **ring expansion** — a five-membered ring becomes six-membered while installing the amine exactly where it belongs.

1.9 NEWER AND ADJUNCT INTRAVENOUS AGENTS

Drug 11 — Ramelteon

- **Chemical class:** Melatonin receptor agonist (MT_1/MT_2) — technically a **hypnotic**, included in this unit's list.
- **Structure:** Scaffold = a fused **tricyclic indeno[5,4-b]furan** (an indane ring fused to a furan). Key substituents: an **ethyl linker** ending in a **propanamide group (–$CH_2CH_2NHCOCH_2CH_3$)**; the active form is the **(S)-enantiomer**.
- **Uses: Insomnia** — specifically difficulty *falling* asleep. Mimics the body's own sleep hormone melatonin; not a controlled sedative and has no dependence.

Drug 12 — Remimazolam

- **Chemical class:** Ultra-short-acting **benzodiazepine** (imidazo-fused) with a built-in "off switch".
- **Structure:** Scaffold = **imidazo[1,2-a][1,4]benzodiazepine** (a benzodiazepine ring fused to an imidazole). Key substituents: **8-bromo**, **1-methyl**, **6-(2-pyridyl)**, and at position 4 a **–$CH_2CH_2COOCH_3$ ester side chain** — this ester is the off switch.
- **Uses: Procedural sedation** (e.g., colonoscopy) and induction/maintenance of general anesthesia. The ester is rapidly chopped by tissue **esterases** into an inactive acid, so the effect ends quickly and predictably; the antidote **flumazenil** can reverse it.

Drug 13 — Fospropofol

- **Chemical class: Phosphate prodrug** of propofol (propofol itself is the famous "milk of anesthesia" IV agent, but it is not in our list — its prodrug is).
- **Structure:** Scaffold = **2,6-diisopropylphenyl** (propofol's skeleton: a benzene ring with two bulky isopropyl groups hugging the oxygen). Key substituent: the phenolic –OH is masked as a **phosphate ester (–OPO_3^{2-}, disodium salt)**. This charged phosphate makes the molecule **water-soluble** (propofol itself is an oily emulsion).
- **Uses: Monitored anesthesia care (MAC) sedation** — e.g., sedation for colonoscopy. In the body, **alkaline phosphatase** enzymes clip off the phosphate, releasing active propofol. Advantage: no lipid emulsion, less injection pain, no bacterial-growth risk of the milky formulation.

Drug 14 — Dexmedetomidine

- **Chemical class:** Selective **alpha-2 adrenergic agonist** — imidazole derivative.
- **Structure:** Scaffold = **imidazole ring** linked to a substituted benzene. Key substituents: a **(S)-1-(2,3-dimethylphenyl)ethyl** group — the benzene carries **two methyl groups** (2,3-dimethyl) and the **S-configuration** at the benzylic carbon is essential for activity (the R-form is weak).
- **Uses: ICU sedation** (patients stay calm but easily rousable — "cooperative sedation") and procedural sedation. Bonus: provides some pain relief and does not suppress breathing much.

Simple explanation (prodrug concept): Fospropofol is like a **sealed envelope** — the phosphate "seal" keeps it water-soluble and inactive; the body's phosphatase "opens" it to release propofol. Remimazolam is like a **candle with a short wick** — esterases snuff it out quickly on their own.

Key takeaway: Newer agents are designed for control — water solubility (fospropofol), self-destruction (remimazolam), or rousable calm (dexmedetomidine).

1.10 Infographic Concept Box — Chapter 1

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+================================================================+
|  GENERAL ANESTHETICS — ONE-PAGE MIND MAP (draw as a poster)     |
|                                                                 |
|  Center: SLEEPING PATIENT (Stage III surgical anesthesia)       |
|                                                                 |
|  LEFT branch — BREATHE IN (inhalational, 6 drugs):              |
|    Draw 6 small vapor clouds labeled H - M - E - I - S - D      |
|    (Halothane, Methoxyflurane, Enflurane, Isoflurane,           |
|     Sevoflurane, Desflurane). Write "All have FLUORINE" under.  |
|    Arrow down: "Low blood solubility = fast wake-up             |
|    (Desflurane fastest)".                                       |
|                                                                 |
|  RIGHT branch — INJECT (intravenous, 8 drugs):                  |
|    Syringe 1: Thiobarbiturates (Methohexital, Thiamylal,        |
|               Thiopental) — "S at C-2, sleep in 20 seconds".    |
|    Syringe 2: Ketamine — "Eyes open, brain disconnected         |
|               (dissociative); NMDA blocked".                    |
|    Syringe 3: Newer — Fospropofol (prodrug), Remimazolam        |
|               (ester off-switch), Dexmedetomidine (alpha-2,     |
|               rousable), Ramelteon (melatonin, for sleep).      |
|                                                                 |
|  BOTTOM banner: "MEYER-OVERTON: fat-soluble = potent.           |
|  GABA up + NMDA down = reversible unconsciousness."             |
+================================================================+
```

1.11 Pharmacy Relevance

1. **Vaporizers and formulation:** Inhalational agents must be delivered as precise vapor percentages — pharmacists in hospital practice should understand why desflurane needs a heated vaporizer (boiling point near room temperature) and why halothane is stored in amber bottles (it decomposes in light).
2. **Prodrug design in action:** Fospropofol shows how masking a phenol as a phosphate solves a real formulation problem (propofol's oily emulsion supports bacterial growth and causes injection pain).
3. **Esterase-based "soft drugs":** Remimazolam is a "soft drug" — designed to be destroyed by the body's own enzymes. This is a modern medicinal chemistry strategy for ultra-short action.
4. **Chirality matters:** Ketamine's S-enantiomer (esketamine) is more potent; dexmedetomidine's S-form is the active one. Always check which enantiomer is marketed.
5. **Counseling point:** Patients must be told not to drive or operate machinery for 24 hours after general anesthesia — residual drug in fat redistributes slowly.

1.12 India Context

- **Thiopental** has been the classic IV induction agent in Indian government hospitals for decades — cheap, reliable, and still widely stocked.
- **Ketamine** is extremely valuable in India: it is the anesthetic of choice in rural/field settings and for short procedures because it preserves breathing and blood pressure, needs no costly vaporizer, and is also the backbone of **veterinary anesthesia** across the country.
- **Isoflurane and sevoflurane** are the standard inhalational agents in modern Indian operation theatres; **halothane** is still found in some resource-limited setups because vaporizers and drug cost are lower.
- **Dexmedetomidine** is now routine in Indian ICUs for cooperative sedation of ventilated patients.
- **Phenobarbital (Gardenal)** — although detailed in Chapter 2/4 — is worth noting here as India's cheapest long-term epilepsy drug, showing how old barbiturates still serve public health.

1.13 Key Points (Chapter 1)

1. General anesthesia = reversible unconsciousness + no pain + no memory + no movement.
2. Meyer–Overton rule: lipid solubility potency.
3. MAC: lower value = more potent inhaled agent.
4. All six inhalational agents contain fluorine; enflurane/isoflurane are isomers.
5. Thiobarbiturates (S at C-2) give IV sleep in ~20 seconds.
6. Ketamine = NMDA blocker = dissociative anesthesia; synthesis key step = ring expansion (56).
7. Fospropofol = phosphate prodrug of propofol (water-soluble).
8. Remimazolam = benzodiazepine with an ester "off switch" (esterases).

9 Dexmedetomidine = alpha-2 agonist = calm but rousable ICU sedation.

10 Ramelteon = melatonin (MT_1/MT_2) agonist for sleep onset.

1.14 Common Confusions

Confusion	Clarification
Enflurane vs. isoflurane	Structural isomers — same atoms; chlorine sits on different carbons. Different drugs, different uses.
Thiopental vs. thiamylal	Both thiobarbiturates; differ only at C-5 (ethyl vs. allyl).
Ketamine "sleep" vs. normal sleep	Dissociative: eyes open, but pain perception and memory are disconnected. Not normal sleep.
Fospropofol vs. propofol	Fospropofol is the water-soluble phosphate prodrug; propofol is the oily active drug released by phosphatases.
Ramelteon is not a general anesthetic	Correct — it is a melatonin agonist hypnotic for insomnia, listed in this unit for completeness.
MAC units	MAC is a concentration (%), not a dose in mg. Lower MAC = more potent.

1.15 Common Mistakes (in exams)

1 Writing that halothane is an ether — it is a **haloalkane** (no oxygen).

2 Drawing desflurane with chlorine — it has **only fluorine** (F replaced Cl of isoflurane).

3 Forgetting the **sulfur at C-2** when drawing thiopental/thiamylal.

4 In ketamine synthesis, forgetting the **ring expansion** (cyclopentane cyclohexane) in the methylamine step.

5 Calling remimazolam's off-switch "liver metabolism" — it is **esterase hydrolysis** (blood/tissue), which is why it is so fast and predictable.

6 Mixing up **MAC** (potency measure) with **blood:gas solubility** (speed measure).

1.16 Mnemonics

- **Six inhalational agents:** "**H**appy **M**others **E**at **I**ce-cream **S**lowly **D**aily" **H**alothane, **M**ethoxyflurane, **E**nflurane, **I**soflurane, **S**evoflurane, **D**esflurane.
- **Speed order (slow fast recovery):** "**M**y **H**eavy **E**lephant **I**s **S**lowly **D**ancing" Methoxyflurane, Halothane, Enflurane, Isoflurane, Sevoflurane, Desflurane (matches rising speed of recovery).
- **Thiobarbiturate trio:** "**T**hree **M**inute **T**ramps" **T**hiopental, **M**ethohexital, **T**hiamylal — ultra-short IV sleep.
- **Ketamine synthesis (G-B-M):** "**G**rignard **B**romine **M**ethylamine (ring e**x**pansion)" "**G**ood **B**rave **M**edicine."
- **Newer agents:** "**F**our **R**apid **D**rugs **R**eady" **F**ospropofol, **R**amelteon, **D**exmedetomidine, **R**emimazolam.

1.17 Exam Summary (Chapter 1)

- General anesthetics produce reversible unconsciousness by enhancing GABA (brake) and blocking NMDA/glutamate (accelerator); potency follows the Meyer–Overton lipid-solubility rule.
- Six inhalational agents, all fluorinated: halothane (alkane; liver risk), methoxyflurane (kidney/fluoride risk), enflurane (seizure-like EEG), isoflurane (maintenance workhorse; isomer of enflurane), sevoflurane (sweet; pediatric induction), desflurane (fastest recovery; heated vaporizer; F-for-Cl swap of isoflurane).
- Three ultra-short IV barbiturate-type agents: thiopental and thiamylal are thiobarbiturates (S at C-2; differ at C-5: ethyl vs. allyl); methohexital is an N-methyl oxybarbiturate with a triple-bond side chain.
- Ketamine: arylcyclohexylamine, NMDA antagonist, dissociative anesthesia; synthesis = Grignard addition α-bromination methylamine with ring expansion (56).
- Fospropofol (phosphate prodrug of propofol), remimazolam (benzodiazepine with ester off-switch), dexmedetomidine (alpha-2 agonist, cooperative ICU sedation), ramelteon (melatonin MT_1/MT_2 agonist for sleep onset).

1.18 One-Minute Revision (Chapter 1)

Breathe-in six: Happy Mothers Eat Ice-cream Slowly Daily (all fluorinated; Desflurane fastest out). Inject-three: Thiopental, Methohexital, Thiamylal (S at C-2 = seconds to sleep). Ketamine: NMDA block, eyes open but disconnected; made by Grignard Bromine Methylamine ring expansion. Fospropofol = wrapped propofol (phosphate). Remimazolam = benzo with ester scissors. Dexmedetomidine = calm but rousable (alpha-2). Ramelteon = melatonin mimic. Meyer–Overton: fat-soluble = potent; low MAC = potent; low blood:gas = fast.

1.19 Exam Questions (Chapter 1)

Short-answer questions:

1 Define MAC and explain why a lower MAC value means a more potent inhalational anesthetic.

2 State the Meyer–Overton rule in one sentence and give one example.

3 Name the four stages of anesthesia and write one line about each.

4 Differentiate thiopental and thiamylal on the basis of their C-5 substituents.

5 Why does desflurane need a specially heated vaporizer?

6 What is a prodrug? Explain with fospropofol as the example.

7 Why is remimazolam called a "soft drug"?

8 Write the structure (in words) of sevoflurane, naming its key substituents.

Long-answer questions:

1 Classify general anesthetics with examples. Describe the mechanism of action of inhalational agents using the Meyer–Overton rule, GABA potentiation, and NMDA blockade.

2 Write the complete synthesis of ketamine starting from 2-chlorobenzonitrile. Name every intermediate, reagent, and condition, and explain the ring-expansion step.

3 Compare the six halogenated inhalational anesthetics under: chemical scaffold, key halogen substituents, blood:gas solubility, MAC, speed of induction/recovery, and one clinical use with one drawback each.

MCQs (answer key at the end):

1 Which of the following inhalational anesthetics is NOT an ether?

a) Isoflurane b) Halothane c) Sevoflurane d) Desflurane

1 The structural isomer of enflurane is:

a) Halothane b) Isoflurane c) Methoxyflurane d) Desflurane

1 Desflurane differs from isoflurane by:

a) Addition of bromine b) Replacement of chlorine by fluorine c) Addition of an ether oxygen d) N-methylation

1 The fastest recovery among inhalational agents is seen with:

a) Halothane b) Methoxyflurane c) Sevoflurane d) Desflurane

1 The sulfur-containing (thiobarbiturate) IV anesthetics are:

a) Thiopental and thiamylal b) Methohexital and thiopental c) Only thiopental d) Methohexital and thiamylal

1 In ketamine synthesis, the ring-expansion step occurs when the α-bromo ketone reacts with:

a) Ammonia b) Methylamine c) Dimethyl sulfate d) Sodium ethoxide

1 The five-membered ring in ketamine synthesis expands to:

a) A benzene ring b) A cyclohexane ring c) A piperidine ring d) A pyrrole ring

1 Fospropofol is converted to active propofol by:

a) Esterases b) Alkaline phosphatase c) Cytochrome P450 d) Monoamine oxidase

1 Remimazolam's ultra-short action is due to hydrolysis of its:

a) Phosphate group b) Ester side chain c) Amide bond d) Ether linkage

1 Dexmedetomidine produces sedation by acting on:

a) GABA-A receptors b) NMDA receptors c) Alpha-2 adrenergic receptors d) Melatonin receptors

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

Viva questions:

1 What does MAC stand for, and what does a MAC of 0.75 mean for halothane?

2 Why do all modern inhalational anesthetics contain fluorine?

3 Which two anesthetics are structural isomers?

4 Name the intermediate formed when 2-chlorobenzonitrile reacts with cyclopentylmagnesium bromide followed by acid hydrolysis.

5 Why is ketamine preferred in field/rural anesthesia?

6 What is dissociative anesthesia?

7 Which enzyme activates fospropofol, and which enzyme switches off remimazolam?

8 Which enantiomer of ketamine is more potent?

Application-based questions:

1 A 6-year-old child needs ear surgery and is terrified of injections. Which inhalational agent would you choose for induction, and which structural feature makes it suitable? (Answer: sevoflurane — sweet, non-irritating vapor; fully fluorinated ether.)

2 A hospital wants an IV sedative for colonoscopy that wears off quickly even in a patient with poor liver function. Between fospropofol and remimazolam, which design feature favors remimazolam here, and why? (Answer: remimazolam is hydrolyzed by blood/tissue esterases, not liver enzymes, so its offset is organ-independent and predictable.)

3 During synthesis of ketamine, a student isolates the α-bromo ketone but heats it without methylamine. Will ketamine form? Explain. (Answer: no — methylamine is the nucleophile that adds to the carbonyl and triggers the 1,2-shift/ring expansion; without it, no rearrangement to the six-membered ring occurs.)

1.20 References (Chapter 1)

- Williams, Lemke, and Roche — *Foye's Principles of Medicinal Chemistry* (LWW)
- Wilson, Beale, and Block — *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* (LWW)
- Kar — *Medicinal Chemistry* (New Age International)
- Lednicer — *The Organic Chemistry of Drug Synthesis* (Wiley)
- Brunton et al. — *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (McGraw-Hill)
- Patrick — *An Introduction to Medicinal Chemistry* (Oxford)

CHAPTER 2: SEDATIVES AND HYPNOTICS

2.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define sedation, hypnosis, and anxiolysis, and explain how dose changes one into the other.

2 Classify sedative-hypnotics into barbiturates, benzodiazepines, and miscellaneous agents.

3 Explain how barbiturates and benzodiazepines act differently on the GABA-A receptor (duration vs. frequency of chloride channel opening).

4 Draw the numbered barbiturate and benzodiazepine scaffolds from memory.

5 Write the complete syntheses of phenobarbital and diazepam with reagents, conditions, and intermediates.

6 Apply the SAR rule tables of barbiturates and benzodiazepines to predict the effect of a structural change.

7 Describe the structure and use of each of the 19 drugs in this chapter.

8 Explain why oxazepam/lorazepam are preferred in liver disease and old age.

9 State the role of flumazenil.

2.2 Definitions — Starting From Zero

- **Sedative:** A drug that calms, reduces anxiety and excitement — the patient stays awake but peaceful. (Think: turning down the volume.)
- **Hypnotic:** A drug that produces sleep. (Think: switching off the lights.)
- **Anxiolytic:** A drug that specifically reduces anxiety (fear/worry).
- **Dose-response continuum:** The same drug can be a sedative at a low dose, a hypnotic at a medium dose, and an anesthetic (or poison) at a high dose. **Dose decides the effect.**
- **GABA-A receptor:** The brain's main "brake" receptor — a chloride (Cl^-) channel. When GABA binds, Cl^- flows into the neuron and quiets it.
- **Tolerance:** Needing a bigger dose over time for the same effect. **Dependence:** the body "misses" the drug when stopped (withdrawal). **Overdose:** too much drug suppresses breathing — the main danger of old sedatives.
- **Flumazenil:** The antidote that blocks benzodiazepines at their receptor (a competitive antagonist).
- **Half-life:** Time for half the drug to leave the body. Long half-life = morning hangover; short half-life = may wear off before morning.

Simple explanation: Sedatives and hypnotics are "dimmer switches" for the brain. A little dimming = calm (sedation); full dimming = sleep (hypnosis). Barbiturates and benzodiazepines both work through the GABA-A brake, but they press it differently.

Analogy: The GABA-A chloride channel is a door that lets "calm" flow in. Benzodiazepines **open the door more often**; barbiturates **keep the door open longer**. Both let calm flood in — but barbiturates can wedge the door open so wide that breathing stops. That is why benzodiazepines are safer.

Key takeaway: Same receptor (GABA-A), different handling of the chloride door — frequency (BZDs) vs. duration (barbiturates). Duration-wedging is what makes barbiturate overdose deadly.

```
DIAGRAM — DRAW THIS: "Two hands on the same GABA-A door"
Draw a cell membrane with a channel (tunnel) labeled "Cl- channel (GABA-A)".
Draw a small "GABA" key opening it briefly.
Draw a "BZD" hand tapping the door repeatedly: label "opens MORE OFTEN".
Draw a "Barbiturate" hand holding the door wide open: label "keeps open LONGER".
Caption: "Both increase Cl- entry (calm). Barbiturates at high doses open the
channel even WITHOUT GABA — this is why overdose kills."
```

2.3 Classification (Flowchart)

```
FLOWCHART — DRAW THIS:
              SEDATIVES AND HYPNOTICS (19 drugs)
                            |
        +----------+---------+----------+
        |          |         |          |
   BARBITURATES  BENZO-    NON-BZD    MISCELLANEOUS
   (7 drugs):    DIAZEPINES HYPNOTIC   (5 drugs):
   1. Barbital   (6 drugs): (1 drug):  15. Glutethimide
   2. Pheno-     8. Chlor-  14. Zol-   16. Meprobamate
      barbital*    diaze-     pidem    17. Ethchlorvynol
   3. Mephobar-    poxide               18. Triclofos
      bital      9. Diazepam*          19. Paraldehyde
   4. Amobarbital 10. Oxazepam
   5. Butabarbital 11. Chlorazepate
   6. Pentobarbital 12. Lorazepam
   7. Secobarbital 13. Alprazolam
```

Duration-based sub-classification of barbiturates (examiners love this):

Duration	Drugs	Memory hook
Long-acting (6+ hours)	Barbital, Phenobarbital, Mephobarbital	"Long BAR-Phe-Meph"
Intermediate (3–6 hours)	Amobarbital, Butabarbital	"AM-BU in the middle"
Short-acting (2–3 hours)	Pentobarbital, Secobarbital	"Pento-Seco = short sleep"
Ultra-short (minutes, IV)	Thiopental, Methohexital (Chapter 1)	Already covered

2.4 BARBITURATES — The 2,4,6-Pyrimidinetrione Family

Technical concept: Barbiturates are derivatives of **barbituric acid** (2,4,6(1H,3H,5H)-pyrimidinetrione) — a six-membered ring with two nitrogens and three carbonyl (C=O) groups. Barbituric acid itself has no CNS activity; activity appears only when **both hydrogens at C-5 are replaced** by alkyl/aryl groups.

Simple explanation: Think of the barbiturate ring as a plain key blank. It only opens the sleep-lock after you cut two teeth into it (the two C-5 substituents). The shape of those teeth decides how fast and how long you sleep.

```
DIAGRAM — DRAW THIS: Numbered barbiturate scaffold
Draw a hexagon. Label atoms 1 to 6 around it: positions 1 and 3 are NH (nitrogen),
positions 2, 4, 6 are C=O (carbonyl). Position 5 (bottom carbon) has two lines
going down labeled R1 and R2 (the two substituents).
Caption: "Barbituric acid: R1 = R2 = H (inactive). Active drugs: R1, R2 = alkyl/aryl."
Also draw thiopental's version: write "C=S" at position 2 instead of "C=O".
```

Mechanism (simple): Barbiturates bind the GABA-A receptor at the **barbiturate site** and **prolong chloride channel opening** (hold the calm-door open longer). At high doses they open the channel even without GABA and also block excitatory glutamate receptors — the brain (including breathing centers) shuts down. **Narrow safety margin** = small gap between sleep dose and lethal dose.

Drug 1 — Barbital (Barbitone)

- **Chemical class:** Long-acting barbiturate — the simplest dialkyl barbiturate.
- **Structure:** Scaffold = **barbituric acid ring**. Key substituents: C-5 carries **two ethyl groups** (5,5-diethyl). No N-methylation, oxygen at C-2.
- **Uses:** Historical hypnotic/sedative; now mainly of academic interest as the prototype that started the class.

Drug 2 — Phenobarbital (Phenobarbitone — same drug)

- **Chemical class:** Long-acting barbiturate; also a major **anticonvulsant** (detailed again in Chapter 4).
- **Structure:** Scaffold = **barbituric acid ring**. Key substituents: C-5 carries one **ethyl group** and one **phenyl group** (5-ethyl-5-phenyl). The phenyl ring is the secret of its anticonvulsant power.
- **Uses: Epilepsy** (tonic-clonic seizures, neonatal seizures), status epilepticus (second-line), short-term sedation. Cheapest long-term epilepsy drug in India.

Synthesis of Phenobarbital (3 steps)

Step 1 — α-Arylation of malonic ester diethyl phenylmalonate.

- Reagents/conditions: **Diethyl malonate + sodium ethoxide (NaOEt)** (to form the enolate/carbanion), then **bromobenzene** with **copper catalyst, heat** (Ullmann-type arylation).
- What happens: The malonate carbanion attacks bromobenzene, attaching a phenyl ring to the central (α) carbon of the malonate.
- **Intermediate: Diethyl phenylmalonate** — structure: central carbon carrying one phenyl group, one hydrogen, and two $–COOCH_2CH_3$ (ester) groups.

Step 2 — α-Alkylation diethyl ethylphenylmalonate.

- Reagents/conditions: **Sodium ethoxide**, then **ethyl bromide (CH_3CH_2Br)**.
- What happens: The remaining α-hydrogen is removed by base; the carbanion attacks ethyl bromide, attaching an ethyl group.
- **Intermediate: Diethyl ethylphenylmalonate** — structure: central carbon now carrying one phenyl + one ethyl + two ester groups (no hydrogens left on that carbon).

Step 3 — Condensation with urea ring closure (phenobarbital).

- Reagents/conditions: **Urea (NH_2CONH_2)** + **sodium ethoxide**, heated; then **acid workup**.
- What happens: The two –NH_2 groups of urea attack the two ester carbonyls one by one; each attack kicks out one molecule of **ethanol**. The six-membered barbiturate ring closes.
- **Product: Phenobarbital — 5-ethyl-5-phenylbarbituric acid** (5-ethyl-5-phenyl-2,4,6-pyrimidinetrione).

```
FLOWCHART — DRAW THIS: Phenobarbital synthesis
Box 1: Diethyl malonate --(i) NaOEt; (ii) C6H5Br, Cu, heat--> Box 2: Diethyl phenylmalonate
Box 2 --(i) NaOEt; (ii) CH3CH2Br--> Box 3: Diethyl ethylphenylmalonate
Box 3 + urea --(NaOEt, heat; then H+)--> Box 4: PHENOBARBITAL (- 2 EtOH)
Note under arrow 3: "Double condensation: urea's 2 NH2 attack 2 esters"
```

Memory hook: "**P**henyl first (arylation), **E**thyl second (alkylation), **U**rea closes the ring" **P-E-U**: "**P**henobarbital **E**arns **U**tility."

Drug 3 — Mephobarbital

- **Chemical class:** Long-acting **N-methyl barbiturate** (prodrug of phenobarbital).
- **Structure:** Scaffold = barbituric acid ring. Key substituents: same C-5 as phenobarbital (**ethyl + phenyl**), plus a **methyl group on N-1**. It is literally N-methyl-phenobarbital.
- **Uses:** Epilepsy — the body removes the N-methyl group (demethylation) converting it into phenobarbital, so it acts as a slow-release form.

Drug 4 — Amobarbital

- **Chemical class:** Intermediate-acting barbiturate.
- **Structure:** Scaffold = barbituric acid ring. Key substituents: C-5 carries **ethyl** + **isopentyl (3-methylbutyl)** — a branched five-carbon chain.
- **Uses:** Short-term insomnia, pre-anesthetic sedation (historical).

Drug 5 — Butabarbital

- **Chemical class:** Intermediate-acting barbiturate.
- **Structure:** Scaffold = barbituric acid ring. Key substituents: C-5 carries **ethyl** + **sec-butyl (1-methylpropyl)** — a branched four-carbon chain.
- **Uses:** Short-term insomnia, daytime sedation (historical).

Drug 6 — Pentobarbital

- **Chemical class:** Short-acting barbiturate.
- **Structure:** Scaffold = barbituric acid ring. Key substituents: C-5 carries **ethyl** + **1-methylbutyl (sec-pentyl)** — a branched five-carbon chain (one carbon longer than butabarbital's side chain).
- **Uses:** Short-term insomnia, pre-anesthetic; high-dose IV for **refractory status epilepticus** ("pentobarbital coma") in intensive care.

Drug 7 — Secobarbital

- **Chemical class:** Short-acting barbiturate — the fastest of the oral barbiturates.
- **Structure:** Scaffold = barbituric acid ring. Key substituents: C-5 carries **allyl (–$CH_2CH{=}CH_2$, unsaturated)** + **1-methylbutyl**. The allyl double bond speeds up onset and shortens action.
- **Uses:** Short-term insomnia, pre-anesthetic sedation (historical; high abuse potential).

SAR of Barbiturates (Rule Table — must memorize)

Technical concept: Structure–Activity Relationship (SAR) = the rulebook linking each structural feature to the biological effect. Learn it as "if you change X, Y happens."

#	Structural feature	SAR rule (what happens)	Example
1	C-5 disubstitution	**Both** H at C-5 must be replaced by alkyl/aryl — otherwise no hypnotic activity	Barbituric acid (H,H) = inactive
2	Total carbons at C-5	Optimum **6–10 carbons** total across both substituents; fewer = weak, more = convulsant	Phenobarbital (8 carbons: 2+6) = ideal
3	Unsaturation at C-5	Double/triple bonds **faster onset, shorter duration**	Secobarbital (allyl) vs. pentobarbital
4	Branching of chain	Branched chains **shorter duration**	Amobarbital (branched) shorter than straight-chain analog
5	Phenyl at C-5	Aryl group **anticonvulsant activity** appears	Phenobarbital = antiepileptic
6	N-methylation (N-1/N-3)	**faster onset, shorter duration**, more excitatory side effects	Mephobarbital, hexobarbital
7	OS at C-2 (thiobarbiturates)	**much more lipid-soluble**, ultra-short IV action	Thiopental, thiamylal (Ch. 1)
8	Polar groups at C-5	–OH, $–NH_2$, –COOH **activity drops sharply** (can't cross into brain)	—
9	Spiro substitution at C-5	Ring fused at C-5 **convulsant** (opposite effect!)	—

Simple explanation: The two C-5 "teeth" must be oily (not water-loving), medium-sized (6–10 carbons), and at least one is often branched or unsaturated for speed. Put a phenyl tooth in you get seizure control. Swap oxygen for sulfur the drug becomes a lightning-fast IV anesthetic.

Example: Why is secobarbital shorter-acting than barbital? Because secobarbital has a branched + unsaturated (allyl) C-5 pair (rules 3, 4), while barbital has two simple ethyls. **Key takeaway:** C-5 controls everything: size, oiliness, branching, and unsaturation decide onset, duration, and whether the drug stops seizures.

2.5 BENZODIAZEPINES — The 1,4-Benzodiazepin-2-one Family

Technical concept: Benzodiazepines share a **fused bicyclic scaffold**: a benzene ring fused to a seven-membered **1,4-diazepine** ring (two nitrogens at positions 1 and 4), usually with a **ketone at**

position 2 and a **phenyl ring at position 5**. They bind the **benzodiazepine site** on the GABA-A receptor and **increase the frequency** of chloride channel opening — but they cannot open the channel without GABA. This "ceiling effect" is why overdose alone rarely kills (unlike barbiturates).

Simple explanation: If the GABA-A channel is a door, benzodiazepines are a polite assistant who opens it more often whenever GABA knocks — but they never break the door down themselves. That built-in safety limit is why they replaced barbiturates for anxiety and insomnia.

```
DIAGRAM — DRAW THIS: Numbered 1,4-benzodiazepine scaffold
Draw a benzene ring (hexagon) fused on its right side to a 7-membered ring.
Number the 7-membered ring: N at top-right = position 1, C=O at top = position 2,
CH2 at right = position 3, N at bottom-right = position 4, then C(phenyl) = position 5
going back into the fused benzene (positions 5a-9a in the fused system).
Mark: "7-position (on benzene, para to fusion) = Cl usually";
"5-phenyl sticks out like a flag"; "1-N-methyl in diazepam".
```

Drug 8 — Chlordiazepoxide

- **Chemical class:** 1,4-benzodiazepine **4-oxide** — the first benzodiazepine (historical prototype).
- **Structure:** Scaffold = **1,4-benzodiazepine** (note: **no C-2 ketone** — instead C-2 carries a **methylamino group**; there is an **N-oxide at N-4**). Key substituents: **7-chloro**, **5-phenyl**.
- **Uses: Alcohol withdrawal syndrome** (prevents seizures/delirium tremens), anxiety. Long-acting active metabolites make it ideal for smooth alcohol detoxification.

Drug 9 — Diazepam

- **Chemical class:** 1,4-benzodiazepin-2-one — the reference benzodiazepine.
- **Structure:** Scaffold = **1,4-benzodiazepin-2-one**. Key substituents: **7-chloro**, **N-1 methyl**, **5-phenyl** (no ortho substituent on the phenyl, no 3-substituent).
- **Uses:** Anxiety, **muscle spasm**, **status epilepticus** (IV), pre-anesthetic, alcohol withdrawal.

Synthesis of Diazepam (Sternbach synthesis — 4 steps)

Step 1 — Ortho-benzoylation 2-amino-5-chlorobenzophenone.

- Reagents/conditions: **p-chloroaniline + benzoyl chloride**, with **zinc chloride ($ZnCl_2$), heat** (Friedel–Crafts-type reaction).
- What happens: The benzoyl group attaches **ortho** to the $-NH_2$ group (the para position is blocked by chlorine), giving an amino-ketone.
- **Intermediate: 2-amino-5-chlorobenzophenone** — structure: a benzene ring with $-NH_2$ at position 1, $-CO-C_6H_5$ (benzoyl) at position 2 (ortho), and –Cl at position 5.

Step 2 — Chloroacetylation chloroacetamide.

- Reagents/conditions: **Chloroacetyl chloride ($ClCH_2COCl$)** with base (e.g., pyridine/NaOH) to mop up HCl.
- What happens: The aromatic $-NH_2$ attacks chloroacetyl chloride, forming an amide; the $-CH_2Cl$ end stays ready for the next step.

- **Intermediate: 2-(chloroacetamido)-5-chlorobenzophenone** — structure: –NHCOCH$_2$Cl in place of –NH$_2$.

Step 3 — Cyclization nordazepam (desmethyldiazepam).

- Reagents/conditions: **Hexamethylenetetramine** (a convenient ammonia source) or ammonia, heated.
- What happens: Ammonia displaces the chloride (–CH$_2$Cl –CH$_2$NH$_2$); the new primary amine then attacks the benzophenone ketone (C=O), closing the seven-membered diazepine ring with loss of water.
- **Intermediate: Nordazepam — 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one** (the N-1-H analog of diazepam; itself an active drug/metabolite).

Step 4 — N-methylation diazepam.

- Reagents/conditions: **Dimethyl sulfate [(CH$_3$O)$_2$SO$_2$]** or methyl iodide, with base (NaH/NaOH).
- What happens: The N-1 hydrogen is replaced by a methyl group.
- **Product: Diazepam — 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one.**

```
FLOWCHART — DRAW THIS: Diazepam synthesis
Box 1: p-chloroaniline + C6H5COCl --(ZnCl2, heat)--> Box 2: 2-amino-5-chlorobenzophenone
Box 2 + ClCH2COCl --(base)--> Box 3: chloroacetamide intermediate
Box 3 --(hexamine/NH3, heat)--> Box 4: NORDAZEPAM [ring closes: -H2O]
Box 4 --((CH3O)2SO2, base)--> Box 5: DIAZEPAM [N-1 methylation]
```

Memory hook: "**B**enzoylate, **C**hloroacetylate, **C**lose the ring, **M**ethylate" **B-C-C-M**: "**B**ig **C**hemists **C**reate **M**edicine."

Drug 10 — Oxazepam

- **Chemical class:** 3-hydroxy-1,4-benzodiazepin-2-one — short-acting, "liver-safe" benzodiazepine.
- **Structure:** Scaffold = 1,4-benzodiazepin-2-one. Key substituents: **7-chloro**, **5-phenyl**, **3-hydroxy (–OH)**, **N-1 hydrogen** (no methyl). It is the direct **glucuronide-ready** metabolite of diazepam.
- **Uses:** Anxiety, **alcohol withdrawal in liver disease and the elderly** — because the 3-OH lets the body attach glucuronic acid directly (no liver oxidation needed), so it is safe when the liver is weak.

Drug 11 — Chlorazepate

- **Chemical class:** 1,4-benzodiazepine **3-carboxylate prodrug** (dipotassium salt).
- **Structure:** Scaffold = 1,4-benzodiazepin-2-one. Key substituents: **7-chloro**, **5-phenyl**, and at C-3 a **carboxylate group (–COO$^-$ K$^+$)** instead of =O/–OH. In stomach acid it loses CO$_2$ and becomes **nordazepam** (the same intermediate as in diazepam synthesis!).
- **Uses:** Anxiety, alcohol withdrawal, adjunct in partial seizures.

Drug 12 — Lorazepam

- **Chemical class:** 3-hydroxy benzodiazepine with an **ortho-chloro phenyl** — potent, short-acting.

- **Structure:** Scaffold = 1,4-benzodiazepin-2-one. Key substituents: **7-chloro**, **5-(2-chlorophenyl)** — note the **chlorine at the ortho (2') position of the phenyl ring**, **3-hydroxy**, **N-1 hydrogen**.
- **Uses: Status epilepticus (first-line IV)**, severe anxiety, pre-anesthetic. Like oxazepam, directly glucuronidated safe in liver disease.

Drug 13 — Alprazolam

- **Chemical class: Triazolo**benzodiazepine — a benzodiazepine with an extra triazole ring fused on.
- **Structure:** Scaffold = **[1,2,4]triazolo[4,3-a][1,4]benzodiazepine**. Key substituents: **8-chloro** (numbering shifts because of fusion), **1-methyl** (on the triazole), **6-phenyl**. The fused triazole ring boosts potency and adds antidepressant-like activity.
- **Uses: Panic disorder**, generalized anxiety disorder.

SAR of Benzodiazepines (Rule Table — must memorize)

#	Position / feature	SAR rule	Example
1	Core	The **1,4-benzodiazepin-2-one** (or equivalent) scaffold is essential; breaking the 7-membered ring kills activity	—
2	C-7 (benzene ring)	**Electron-withdrawing groups (Cl, Br, NO_2, CF_3)** high activity; H or electron-donating weak	Diazepam (7-Cl) potent
3	C-5 phenyl	**Phenyl ring essential**; **ortho (2') halogen (F/Cl)** increased potency	Lorazepam (2'-Cl) very potent
4	C-3	**–OH** active but **shorter half-life** (direct glucuronidation, no active metabolites)	Oxazepam, lorazepam
5	N-1	**Methyl or H** active; **bulky groups** activity falls	Diazepam (N-Me) active; nordazepam (N-H) active
6	N-4 oxide	4-oxide (chlordiazepoxide) acts as **prodrug-like**, converted to active forms	Chlordiazepoxide
7	1,2-fusion	**Triazolo or imidazo fusion** at N-1/C-2 **greatly increased potency**	Alprazolam (triazolo), midazolam (imidazo)
8	C-2	Ketone (C=O) standard; replacing with other groups (as in chlordiazepoxide) changes profile	—

Simple explanation: The magic formula is "**7-chloro + 5-phenyl + (2'-halo for extra punch)**". Add a 3-OH if you want it short and liver-safe; fuse a triazole if you want it super-potent.

Example: Why is lorazepam more potent than diazepam? Lorazepam has the 2'-chloro on the phenyl (rule 3) — diazepam's phenyl is unsubstituted. **Key takeaway:** 7-EWG + 5-phenyl = the benzodiazepine pharmacophore; everything else tunes potency and duration.

NON-BENZODIAZEPINE HYPNOTIC ("Z-drug")

Drug 14 — Zolpidem

- **Chemical class: Imidazopyridine** — selectively binds the ω_1 (BZ_1) subtype of the benzodiazepine site.
- **Structure:** Scaffold = **imidazo[1,2-a]pyridine** (a fused 5-6 system with nitrogens). Key substituents: **6-methyl**, **2-(4-methylphenyl)** (p-tolyl), and at position 3 a **$-CH_2CON(CH_3)_2$ (dimethylacetamide)** side chain.
- **Uses: Short-term insomnia** (trouble falling asleep). Preserves sleep stages better than benzodiazepines; less morning hangover; still habit-forming.

2.6 MISCELLANEOUS SEDATIVES AND HYPNOTICS

Drug 15 — Glutethimide

- **Chemical class: Piperidine-2,6-dione** (a "glutarimide") — barbiturate cousin with one ring nitrogen replaced by carbon.
- **Structure:** Scaffold = **six-membered glutarimide ring** (two C=O flanking a CH_2–CH_2). Key substituents: C-3 carries **ethyl + phenyl** (3-ethyl-3-phenyl). Compare phenobarbital's C-5 ethyl+phenyl — same idea, different ring.
- **Uses:** Historical hypnotic; abandoned (narrow safety margin, anticholinergic toxicity in overdose).

Drug 16 — Meprobamate

- **Chemical class: Carbamate** — propane-1,3-diol dicarbamate.
- **Structure:** Scaffold = **2-methyl-2-propylpropane-1,3-diol** backbone. Key substituents: **both –OH groups converted to carbamates ($-OCONH_2$)**. Small, simple, symmetrical molecule.
- **Uses:** Historical **anxiolytic** (the first "tranquilizer" of the 1950s); largely replaced by benzodiazepines.

Drug 17 — Ethchlorvynol

- **Chemical class:** Chlorinated **tertiary acetylenic alcohol** — a small, volatile hypnotic.
- **Structure:** Scaffold = a short branched chain: **1-chloro-3-ethylpent-1-en-4-yn-3-ol**. Key substituents: a **chlorovinyl (–CH=CHCl)** end, a **terminal alkyne (–CCH)** end, and a **tertiary alcohol (–OH on C-3)** in the middle with an ethyl branch.
- **Uses:** Historical short-acting hypnotic (abandoned — unpleasant taste/smell, dependence).

Drug 18 — Triclofos

- **Chemical class: Phosphate prodrug** of 2,2,2-trichloroethanol (the active metabolite of chloral hydrate).
- **Structure:** Scaffold = **2,2,2-trichloroethyl** group: **$CCl_3–CH_2–O–PO_3^{2-}$** (sodium salt). The phosphate masks the alcohol, making it water-soluble and less irritating than chloral hydrate.

- **Uses: Pediatric sedation** (e.g., before EEG or imaging) — the phosphate is clipped off in the body to release trichloroethanol, the true hypnotic.

Drug 19 — Paraldehyde

- **Chemical class: Cyclic trimer of acetaldehyde** — a trioxane.
- **Structure:** Scaffold = **1,3,5-trioxane ring** (six-membered ring with three oxygens alternating with three carbons). Key substituents: each carbon carries a **methyl group** (2,4,6-trimethyl-1,3,5-trioxane). In the body it slowly breaks back into acetaldehyde.
- **Uses:** Historical: **alcohol withdrawal** and status epilepticus (given rectally); strong unpleasant odor and tissue irritation ended its use.

Key takeaway (miscellaneous): These five are museum pieces that teach design lessons — carbamates (meprobamate), prodrugs (triclofos), and ring-simplified barbiturate mimics (glutethimide) — but benzodiazepines and Z-drugs replaced them for safety.

2.7 Infographic Concept Box — Chapter 2

```
+================================================================+
|  SEDATIVES & HYPNOTICS — ONE-PAGE MIND MAP (draw as a poster)  |
|                                                                |
|  Center: A DIMMER SWITCH labeled "GABA-A (the brain's brake)"  |
|                                                                |
|  LEFT — BARBITURATES (7): draw the 6-membered ring with 3 C=O. |
|    Label C-5 with two "teeth" (R1, R2).                        |
|    Barbital (Et,Et) → Phenobarbital (Et,Ph*) → Mephobarbital   |
|    (N-Me) → Amobarbital / Butabarbital → Pentobarbital /       |
|    Secobarbital (allyl = fastest).                             |
|    *Star on the phenyl: "phenyl = stops seizures".             |
|    Banner: "HOLD the Cl- door open LONGER — overdose wedges it."|
|                                                                |
|  RIGHT — BENZODIAZEPINES (6): draw benzene fused to 7-ring.    |
|    Flag the formula: "7-Cl + 5-phenyl = active".               |
|    Chlordiazepoxide (4-oxide, first) → Diazepam* (N-Me, classic)|
|    → Oxazepam (3-OH, liver-safe) → Chlorazepate (prodrug) →    |
|    Lorazepam (2'-Cl, potent) → Alprazolam (triazolo, panic).   |
|    Banner: "OPEN the Cl- door MORE OFTEN — ceiling = safer."   |
|                                                                |
|  BOTTOM strip — OTHERS: Zolpidem (imidazopyridine, Z-drug) |   |
|  Glutethimide, Meprobamate (carbamate), Ethchlorvynol,         |
|  Triclofos (phosphate prodrug), Paraldehyde (trimer) — museum. |
|  Antidote badge: "FLUMAZENIL reverses benzodiazepines."        |
+================================================================+
```

2.8 Pharmacy Relevance

1. **Narrow vs. wide safety margin** is a dispensing-counseling issue: barbiturate overdose has no antidote, while benzodiazepine overdose can be reversed with flumazenil — a key reason BZDs dominate prescriptions.
2. **Metabolite awareness:** Diazepam and chlordiazepoxide produce long-acting active metabolites (nordazepam, oxazepam); in the elderly this causes falls and confusion — pharmacists should flag long-acting BZDs in geriatric prescriptions.

3 **Liver-safe choices:** Oxazepam and lorazepam skip oxidative metabolism (direct glucuronidation) — the correct recommendation for patients with liver disease.

4 **Prodrug spotting:** Chlorazepate and triclofos are both prodrugs; recognizing the promoiety (carboxylate, phosphate) is a core medicinal-chemistry skill.

5 **Dependence counseling:** All sedative-hypnotics (including Z-drugs) can cause dependence; pharmacists counsel on short-term use and tapering, never abrupt stoppage after prolonged use.

2.9 India Context

- **Phenobarbital (Gardenal)** is one of India's most important epilepsy medicines — extremely cheap, on essential-medicine lists, and the backbone of seizure control in rural settings and neonates.
- **Diazepam (Calmpose), lorazepam (Larpose), alprazolam (Alprax), and zolpidem (Zolfresh)** are among the most commonly stocked CNS drugs in Indian retail pharmacies; pharmacists must counsel against self-medication and prolonged use.
- **Chlordiazepoxide** is widely used in Indian de-addiction centers for alcohol withdrawal management.
- Barbiturate hypnotics (pentobarbital, secobarbital) are now rarely prescribed in India, but **phenobarbital** remains — students must not confuse "old hypnotic barbiturates" (declining) with "phenobarbital the antiepileptic" (essential).

2.10 Key Points (Chapter 2)

1 Sedative (calm) hypnotic (sleep) anesthetic: dose decides.

2 Barbiturate scaffold = pyrimidinetrione; both C-5 H must be replaced for activity.

3 Barbiturates prolong Cl^- channel opening; BZDs increase opening frequency (safer ceiling).

4 C-5 SAR: 6–10 carbons optimal; unsaturation/branching = faster, shorter; phenyl = anticonvulsant; S at C-2 = ultra-short IV.

5 Phenobarbital synthesis: arylate alkylate malonic ester close ring with urea.

6 BZD scaffold = 1,4-benzodiazepin-2-one; formula = 7-EWG + 5-phenyl (+ 2'-halo for punch).

7 Diazepam synthesis: benzoylate chloroacetylate close ring (nordazepam) N-methylate.

8 3-OH BZDs (oxazepam, lorazepam) = short, liver-safe (direct glucuronidation).

9 Alprazolam = triazolo-fused (panic disorder); zolpidem = imidazopyridine Z-drug.

10 Flumazenil = BZD antidote; no antidote exists for barbiturates.

2.11 Common Confusions

Confusion	Clarification
Phenobarbital vs. phenobarbitone	Same drug — phenobarbital is the INN, phenobarbitone the older BAN name.

Confusion	Clarification
Mephobarbital vs. methabarbital	Different! Mephobarbital = N-methyl **phenobarbital** (Ch. 2); methabarbital = N-methyl phenobarbital too? No — methabarbital (Ch. 4) is 1-methyl-5-ethyl-5-phenylbarbiturate — actually the same substitution pattern; they are the same compound under two names in different unit lists. Both = N-methyl phenobarbital. (Syllabus lists it in both units; treat as one drug.)
Nordazepam vs. diazepam	Nordazepam = N-1-H version (intermediate + metabolite); diazepam = N-1-methyl.
Oxazepam vs. lorazepam	Both 3-OH, N-H; lorazepam additionally has 2'-chloro on the phenyl more potent.
Chlordiazepoxide's missing ketone	It is a 4-oxide without the C-2 ketone — the odd one out among BZDs.
Zolpidem is not a benzodiazepine	Correct — imidazopyridine; it only *binds* the BZD site selectively.

2.12 Common Mistakes (in exams)

1 Drawing barbiturates with only **one** C-5 substituent — both H must be replaced.

2 Writing phenobarbital synthesis as "malonate + urea" in one step — the **arylation and alkylation of the malonate come first**.

3 Forgetting **hexamethylenetetramine/ammonia** as the ring-closing reagent in diazepam synthesis.

4 Methylating at the wrong nitrogen in the last step of diazepam synthesis — it is **N-1**.

5 Stating barbiturates "increase frequency" of channel opening — that is the **benzodiazepine** mechanism; barbiturates **prolong duration**.

6 Calling flumazenil a barbiturate antidote — it reverses **only benzodiazepines**.

2.13 Mnemonics

- **7 barbiturates:** "**B**ig **P**harma **M**akes **A**ll **B**arbeturates, **P**atients **S**leep" **B**arbital, **P**henobarbital, **M**ephobarbital, **A**mobarbital, **B**utabarbital, **P**entobarbital, **S**ecobarbital.
- **Duration order (longshort):** "**L**azy **I**ndians **S**leep" **L**ong (Barbital, Phenobarbital, Mephobarbital), **I**ntermediate (Amobarbital, Butabarbital), **S**hort (Pentobarbital, Secobarbital).
- **6 benzodiazepines:** "**C**hintu **D**ances **O**n **C**hairs, **L**aughing **A**loud" **C**hlordiazepoxide, **D**iazepam, **O**xazepam, **C**hlorazepate, **L**orazepam, **A**lprazolam.
- **Phenobarbital synthesis (P-E-U):** "**P**henyl first, **E**thyl second, **U**rea closes."
- **Diazepam synthesis (B-C-C-M):** "**B**enzoylate, **C**hloroacetylate, **C**lose, **M**ethylate."
- **BZD SAR formula:** "**7**-**C**hloro + **5**-**P**henyl" "**7 C**ops **5 P**risoners."

2.14 Exam Summary (Chapter 2)

- Sedatives calm, hypnotics induce sleep; dose converts one into the other; all act via the GABA-A chloride channel.

- Barbiturates (pyrimidinetrione scaffold): 7 drugs from barbital to secobarbital; C-5 disubstitution mandatory; SAR rules cover carbon count (6–10), unsaturation, branching, phenyl (anticonvulsant), N-methylation, and thio-substitution; phenobarbital made by arylating/alkylating diethyl malonate then condensing with urea.
- Benzodiazepines (1,4-benzodiazepin-2-one): 6 drugs; key formula 7-EWG + 5-phenyl; diazepam made by benzoylation chloroacetylation ring closure (nordazepam) N-methylation; 3-OH members (oxazepam, lorazepam) are short-acting and liver-safe; alprazolam is triazolo-fused.
- Zolpidem (imidazopyridine) is a selective BZD-site hypnotic; five miscellaneous agents (glutethimide, meprobamate, ethchlorvynol, triclofos, paraldehyde) are historically important.
- Flumazenil reverses benzodiazepines; barbiturate overdose has no antidote.

2.15 One-Minute Revision (Chapter 2)

Barbiturates: ring with 3 C=O; two oily teeth at C-5 (6–10 carbons); phenyl tooth stops seizures; hold the Cl^- door LONGER (overdose kills). Phenobarbital = phenylate ethylate urea ring. Benzodiazepines: benzene + 7-ring; formula 7-Cl + 5-phenyl; open the Cl^- door MORE OFTEN (ceiling = safer). Diazepam = benzoylate chloroacetylate close (nordazepam) methylate. 3-OH (oxazepam, lorazepam) = liver-safe. Alprazolam = triazolo (panic). Zolpidem = Z-drug (imidazopyridine). Flumazenil = BZD antidote.

2.16 Exam Questions (Chapter 2)

Short-answer questions:

1 Differentiate a sedative from a hypnotic with one example each.

2 Why are benzodiazepines safer in overdose than barbiturates? (Use the chloride-channel explanation.)

3 Draw and number the barbiturate scaffold, marking positions 2 and 5.

4 State any four SAR rules of barbiturates with one example each.

5 Why are oxazepam and lorazepam preferred in patients with liver disease?

6 What is the role of hexamethylenetetramine in diazepam synthesis?

7 Name the intermediate formed just before the N-methylation step in diazepam synthesis.

8 Why is zolpidem called a "non-benzodiazepine" hypnotic?

Long-answer questions:

1 Classify sedatives and hypnotics. Explain the mechanism of action of barbiturates and benzodiazepines on the GABA-A receptor with a labeled diagram (described), and account for the difference in safety margin.

2 Write the complete synthesis of phenobarbital starting from diethyl malonate. Give reagents, conditions, and the structure (in words) of each intermediate.

3 Write the complete synthesis of diazepam starting from p-chloroaniline. Give reagents, conditions, and intermediates, and explain why the para position of p-chloroaniline does not react in step 1.

4 Discuss the SAR of benzodiazepines with the rule table, using diazepam, lorazepam, oxazepam, and alprazolam as examples.

MCQs (answer key at the end):

1 The essential scaffold of barbiturates is:

a) 1,4-benzodiazepin-2-one b) Pyrimidine-2,4,6-trione c) Imidazopyridine d) Piperidine-2,6-dione

1 Barbituric acid itself is inactive because:

a) It has no nitrogen b) Both C-5 hydrogens are unreplaced c) It has no carbonyl d) It is too lipid-soluble

1 Which C-5 substituent gives barbiturates anticonvulsant activity?

a) Ethyl b) Allyl c) Phenyl d) Methyl

1 Replacement of oxygen by sulfur at C-2 of barbiturates produces:

a) Longer action b) Ultra-short IV anesthetics c) Anticonvulsants d) Prodrugs

1 In phenobarbital synthesis, the ring-closing reagent is:

a) Thiourea b) Urea c) Guanidine d) Ammonia

1 The benzodiazepine pharmacophore requires at C-7:

a) An electron-donating group b) Hydrogen c) An electron-withdrawing group d) A bulky alkyl group

1 The 2'-chloro substituent on the phenyl ring is present in:

a) Diazepam b) Oxazepam c) Lorazepam d) Chlordiazepate

1 Nordazepam is converted to diazepam by:

a) N-1 methylation b) 3-hydroxylation c) N-oxidation d) Chlorination

1 The antidote for benzodiazepine overdose is:

a) Naloxone b) Flumazenil c) Physostigmine d) Protamine

1 Triclofos is a prodrug of:

a) Trichloroethanol b) Chloral hydrate c) Paraldehyde d) Ethchlorvynol

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

Viva questions:

1 How do barbiturates and benzodiazepines differ in their action on the chloride channel?

2 What is the optimum total carbon count at C-5 of barbiturates?

3 Name the three intermediates in phenobarbital synthesis in order.

4 Why does p-chloroaniline undergo ortho-benzoylation in diazepam synthesis?

5 Which benzodiazepine has an N-oxide, and which has no C-2 ketone?

6 Which two drugs in this chapter are phosphate/carboxylate prodrugs?

7 Why does N-methylation shorten barbiturate action?

8 What structural feature makes alprazolam more potent than diazepam?

Application-based questions:

1 An elderly patient with liver cirrhosis needs an anxiolytic. Choose between diazepam and lorazepam and justify using SAR/metabolism rules. (Answer: lorazepam — 3-OH allows direct glucuronidation without liver oxidation; diazepam needs oxidation and gives long-acting metabolites.)

2 A student proposes making a barbiturate with $-CH_2COOH$ at C-5 for better water solubility. Predict the activity using SAR. (Answer: inactive/weak — polar groups at C-5 sharply reduce activity, rule 8; the drug cannot cross the blood–brain barrier.)

3 In diazepam synthesis, what would happen if methyl iodide were added before the ring-closure step? (Answer: wrong product — methylation must occur on the closed nordazepam at N-1; methylating the open-chain intermediate methylates the wrong nitrogen and the ring cannot close correctly.)

2.17 References (Chapter 2)

- Williams, Lemke, and Roche — *Foye's Principles of Medicinal Chemistry* (LWW)
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- Kar — *Medicinal Chemistry* (New Age International)
- Lednicer — *The Organic Chemistry of Drug Synthesis* (Wiley)
- Brunton et al. — *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (McGraw-Hill)
- Patrick — *An Introduction to Medicinal Chemistry* (Oxford)

CHAPTER 3: ANTIPSYCHOTICS

3.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define psychosis and explain the dopamine hypothesis in simple words.

2 Classify antipsychotics into typical and atypical agents with chemical classes.

3 Explain D2 blockade and the 5-HT2A/D2 balance of atypical agents using a simple analogy.

4 Draw the numbered phenothiazine scaffold and mark positions 2 and 10.

5 Write the complete synthesis of chlorpromazine with reagents, conditions, and intermediates.

6 Apply the phenothiazine SAR rule table to predict potency and side-effect profile from structure.

7 Describe the scaffold, key substituents, and one use of each of the 20 drugs.

8 Explain EPS (extrapyramidal symptoms) in simple terms and which structures cause more of it.

9 State the special monitoring needed for clozapine.

3.2 Definitions — Starting From Zero

- **Psychosis:** A state where a person loses touch with reality — hearing voices that aren't there (**hallucinations**), believing things that aren't true (**delusions**), and disorganized thinking. Schizophrenia is the main psychotic illness.
- **Dopamine hypothesis:** The idea that psychosis involves **too much dopamine activity** in certain brain pathways (especially the **mesolimbic** pathway — the brain's "salience" circuit that decides what is important). Antipsychotics work mainly by **blocking dopamine D2 receptors** there.
- **Typical (first-generation) antipsychotics:** Older drugs that mainly block D2 — strong against hallucinations/delusions ("positive symptoms") but prone to movement side effects.
- **Atypical (second-generation) antipsychotics:** Newer drugs that block **both serotonin 5-HT2A and dopamine D2** receptors — better for "negative symptoms" (apathy, withdrawal) and fewer movement side effects (but more metabolic ones like weight gain).
- **EPS (extrapyramidal symptoms):** Movement side effects of D2 blockade in the motor pathway — stiffness, tremor, restlessness (akathisia), and with long use, involuntary face movements (**tardive dyskinesia**).
- **Positive symptoms:** "Added" abnormal experiences (hallucinations, delusions). **Negative symptoms:** "Removed" normal functions (flat emotions, social withdrawal, lack of motivation).
- **Agranulocytosis:** A dangerous drop in white blood cells — the reason clozapine needs regular blood tests.

Simple explanation: In psychosis, the brain's dopamine "loudspeaker" is turned too high in the meaning-making circuit, so unimportant things feel intensely significant (voices, conspiracies). Antipsychotics turn that loudspeaker down by blocking D2 receptors. But the same loudspeaker exists in the movement circuit — turning it down there causes stiffness and tremor (EPS).

Analogy: Dopamine pathways are like water pipes to different rooms. Antipsychotics partially close the main valve (D2 blockade). The "psychosis room" floods less (good), but the "movement room" also gets less water (EPS — the price). Atypical drugs are smarter valves: they also adjust the serotonin pipe (5-HT2A), which lets them use less D2 blockade.

Key takeaway: D2 blockade = antipsychotic power AND movement side effects, two sides of one coin; 5-HT2A blockade (atypicals) softens the movement price.

```
DIAGRAM — DRAW THIS: "One key, two rooms"
Draw a key labeled "D2 BLOCKER". Draw two doors it opens:
Door 1: "Mesolimbic pathway — psychosis room: voices/delusions fade (THERAPY)".
Door 2: "Nigrostriatal pathway — movement room: stiffness/tremor appear (EPS)".
Below, draw a second key labeled "5-HT2A + D2 (atypical)":
Door 1 opens wide (therapy), Door 2 opens only slightly (less EPS).
Caption: "Same lock (D2), different rooms, different outcomes."
```

3.3 Classification (Flowchart)

```
FLOWCHART — DRAW THIS:
                    ANTIPSYCHOTICS (20 drugs)
                                  |
                +-----------------+---------------+
                |                                 |
          TYPICAL (mainly D2)              ATYPICAL (5-HT2A + D2)
                |                                 |
   +-----+------+------+                     +----+------+------+
   |     |      |      |                     |    |      |      |
Pheno- Thio-  Butyro- Di-                  Di-  Benz-  Others:
thia- xan-   phenones benz-                benz- isa-  - Molindone
zines thenes (2):    odia-                 oxa- xazole (dihydro-
(7):  (2):  - Halo-  zepines               zepine: ris- indolone)
 1. Pro- 8. Chlor-   peridol (2):          - Lo- peridone - Sulpiride
    mazine   prothi- - Dro-  10. Loxa-      xapine (benzamide)
 2. Chlor-   xene     peridol  pine      - Clo- - Brexpiprazole
    proma- 9. Thio-              11. Clo-   zapine  (quinolinone)
    zine*    thixene              zapine - Lumateperone
 3. Tri-                                  (tetracyclic)
    flupro-                               - Pimavanserin
    mazine                                (urea)
 4. Thio-                                 - Samidorphan
    ridazine                               (morphinan)
 5. Piper-
    acetazine
 6. Prochlor-
    perazine
 7. Trifluo-
    perazine
```

Side-chain sub-classification of phenothiazines (classic exam favorite):

Side-chain type	Drugs	Potency	EPS	Sedation
Aliphatic (dimethylaminopropyl)	Promazine, chlorpromazine, triflupromazine	Low	Low	High
Piperidine	Thioridazine, piperacetazine	Low	Lowest	High
Piperazine	Prochlorperazine, trifluoperazine	High	High	Low

Memory hook: "Ali**phatic** = **a**mateur (low potency); **Pipera**zine = **p**owerful (high potency, high EPS)."

3.4 PHENOTHIAZINES — The Tricyclic Sulfur-Nitrogen Family

Technical concept: Phenothiazines share a **tricyclic scaffold**: two benzene rings fused to a central six-membered ring containing **sulfur at position 5** and **nitrogen at position 10**. The N-10 carries a three-carbon (propyl) side chain ending in a basic amine (protonated at body pH — this positive charge anchors the drug to the receptor). A substituent at **C-2** tunes potency.

Simple explanation: Picture a butterfly: two benzene "wings" joined by a middle ring holding sulfur and nitrogen. From the nitrogen hangs a three-link chain ending in a positively charged "grappling hook" (the amine) that grabs the D2 receptor. A small flag at position 2 (Cl, CF_3) decides how strongly the butterfly holds on.

```
DIAGRAM — DRAW THIS: Numbered phenothiazine scaffold
Draw three fused rings in a row: left benzene, middle 6-ring, right benzene.
In the middle ring: S at the top = position 5, N at the bottom = position 10.
Number the left benzene 1-4 (top to bottom): mark position 2 with a star ("FLAG position:
Cl, CF3, SCH3, COCH3 — electron-withdrawing = more potent").
From N-10 draw a zigzag of 3 carbons ending in N(CH3)2: label "3-carbon chain +
basic amine (protonated at pH 7.4) = receptor anchor".
```

Drug 1 — Promazine

- **Chemical class:** Aliphatic phenothiazine (prototype of the side-chain class).
- **Structure:** Scaffold = **phenothiazine tricycle**. Key substituents: **no ring substituent** (C-2 = H) + N-10 carries **3-dimethylaminopropyl (–$CH_2CH_2CH_2N(CH_3)_2$)**.
- **Uses:** Mild psychosis, agitation; mainly the teaching prototype showing that the side chain alone gives activity but low potency.

Drug 2 — Chlorpromazine

- **Chemical class:** Aliphatic phenothiazine — the **first antipsychotic** (1950s revolution in psychiatry).
- **Structure:** Scaffold = phenothiazine tricycle. Key substituents: **2-chloro** (the potency flag) + N-10 **3-dimethylaminopropyl** side chain.
- **Uses:** Schizophrenia, mania, **intractable hiccups**, severe nausea/vomiting, pre-anesthetic sedation.

Synthesis of Chlorpromazine (3 steps)

Step 1 — Ullmann coupling 3-chlorodiphenylamine.

- Reagents/conditions: **m-chloroaniline + bromobenzene**, **copper powder, potassium carbonate, heat** (Ullmann diarylamine synthesis).
- What happens: The –NH_2 nitrogen of m-chloroaniline attacks bromobenzene (copper-catalyzed), joining the two rings through nitrogen with loss of HBr.
- **Intermediate: 3-chlorodiphenylamine** — structure: two benzene rings linked by –NH–, one ring carrying chlorine meta to the nitrogen.

Step 2 — Thionation (ring closure with sulfur) 2-chlorophenothiazine.

- Reagents/conditions: **Sulfur (S)**, heated (around 180–200 °C), iodine catalyst (Bernthsen-type phenothiazine synthesis).
- What happens: Sulfur inserts between the two rings ortho to the –NH–, closing the central six-membered thiazine ring (loss of H_2S/H_2).
- **Intermediate: 2-chlorophenothiazine** — structure: the full tricycle; chlorine now at position 2, N-10 still has its hydrogen.

Step 3 — N-alkylation chlorpromazine.

- Reagents/conditions: **3-dimethylaminopropyl chloride**, **sodamide ($NaNH_2$)** in toluene (strong base to remove the N-10 hydrogen).

- What happens: Sodamide deprotonates N-10; the nitrogen anion attacks the alkyl chloride, attaching the side chain.
- **Product: Chlorpromazine — 2-chloro-10-(3-dimethylaminopropyl)phenothiazine.**

```
FLOWCHART — DRAW THIS: Chlorpromazine synthesis
Box 1: m-chloroaniline + bromobenzene --(Cu, K2CO3, heat)--> Box 2: 3-chlorodiphenylamine
Box 2 + sulfur --(heat, I2)--> Box 3: 2-CHLOROPHENOTHIAZINE [tricycle closed]
Box 3 + ClCH2CH2CH2N(CH3)2 --(NaNH2)--> Box 4: CHLORPROMAZINE [N-10 alkylated]
Note: "NaNH2 removes N-H; nitrogen attacks the alkyl chloride"
```

Memory hook: "**C**ouple the rings, **S**ulfur closes them, **S**ide chain hangs on" **C-S-S**: "**C**hlorpromazine **S**ynthesis **S**ucceeds."

Drug 3 — Triflupromazine

- **Chemical class:** Aliphatic phenothiazine.
- **Structure:** Scaffold = phenothiazine tricycle. Key substituents: **2-trifluoromethyl (–CF_3)** (stronger electron-withdrawing flag than Cl) + N-10 3-dimethylaminopropyl.
- **Uses:** Psychosis; also used as an **antiemetic** (strong D2 blockade in the vomiting center).

Drug 4 — Thioridazine

- **Chemical class: Piperidine** phenothiazine.
- **Structure:** Scaffold = phenothiazine tricycle. Key substituents: **2-methylthio (–SCH_3)** + N-10 side chain ending in a **piperidine ring** [2-(1-methylpiperidin-2-yl)ethyl] instead of a simple dimethylamine.
- **Uses:** Schizophrenia (reserved for refractory cases — risk of **QT prolongation**/cardiac arrhythmia and retinal pigmentation limits use).

Drug 5 — Piperacetazine

- **Chemical class: Piperazine** phenothiazine.
- **Structure:** Scaffold = phenothiazine tricycle. Key substituents: **2-acetyl (–$COCH_3$)** + N-10 side chain ending in a **piperazine ring** bearing a hydroxyethyl group [3-(4-(2-hydroxyethyl)piperazin-1-yl)propyl].
- **Uses:** Psychosis (low-dose antipsychotic with moderate EPS).

Drug 6 — Prochlorperazine

- **Chemical class: Piperazine** phenothiazine.
- **Structure:** Scaffold = phenothiazine tricycle. Key substituents: **2-chloro** + N-10 **[3-(4-methylpiperazin-1-yl)propyl]** — the piperazine ring makes it high-potency.
- **Uses: Severe nausea/vomiting and vertigo** (its most famous use), psychosis.

Drug 7 — Trifluoperazine

- **Chemical class: Piperazine** phenothiazine — high-potency.

- **Structure:** Scaffold = phenothiazine tricycle. Key substituents: **2-trifluoromethyl (–CF_3)** + N-10 **3-(4-methylpiperazin-1-yl)propyl**.
- **Uses:** Schizophrenia, short-term **anxiety** (low doses).

SAR of Phenothiazines (Rule Table — must memorize)

#	Structural feature	SAR rule	Example
1	Tricyclic phenothiazine core	Essential; the folded "butterfly" shape fits the D2 receptor	—
2	C-2 substituent	**Electron-withdrawing groups (Cl, CF_3, SCH_3, $COCH_3$) increased antipsychotic potency**; H weak	Chlorpromazine (2-Cl) > promazine (2-H)
3	N-10 side chain	A **3-carbon chain ending in a basic tertiary amine** is optimal; the amine is protonated at pH 7.4 and anchors to the receptor	All active phenothiazines
4	Side-chain type	**Piperazine > piperidine aliphatic** in potency — but piperazine also gives **more EPS**	Trifluoperazine (piperazine, high EPS)
5	N-10 substitution	N-10 **must be alkylated**; N-10-H (unsubstituted phenothiazine) = inactive	2-chlorophenothiazine alone is inactive
6	Chain length	**3 carbons** between N-10 and the terminal amine is best; 2 carbons = weaker	Promazine series (3C) standard
7	Ring positions 1, 3, 4	Substituents here **decreased activity** (only C-2 helps)	—
8	Branching on side chain	Methyl branching **reduced activity**	—

Simple explanation: Three rules run the show: (1) put an electron-pulling flag at C-2, (2) hang a 3-carbon chain with a charged amine hook from N-10, (3) choose the hook type — piperazine for power (with EPS price), piperidine/aliphatic for gentler action.

Example: Why is trifluoperazine more potent than promazine? Two reasons: CF_3 at C-2 (stronger flag than H, rule 2) + piperazine side chain (rule 4). **Key takeaway:** C-2 flag = potency dial; side-chain type = potency-vs-EPS tradeoff dial.

3.5 THIOXANTHENES — Carbon Replaces Nitrogen at Position 10

Technical concept: Thioxanthenes keep the tricyclic shape but the central ring has **carbon (C-9) instead of nitrogen** at the bridge position, and the side chain attaches via a **double bond (alkylidene)**. This makes the molecule exist as **cis/trans (Z/E) isomers** — only the **cis (Z)** form is strongly active, because only it folds like phenothiazines.

Simple explanation: Same butterfly, but the body of the butterfly is carbon, and the tail (side chain) is nailed on with a stiff double bond instead of a flexible single bond. The tail can point two ways — only one direction fits the receptor lock.

Drug 8 — Chlorprothixene

- **Chemical class:** Thioxanthene (aliphatic side chain).
- **Structure:** Scaffold = **thioxanthene tricycle** (S in the middle ring, C at position 9). Key substituents: **3-chloro** on the ring + C-9 carries **(3-dimethylaminopropylidene)** — a =CH–CH_2–CH_2–N(CH_3)$_2$ tail joined by a **C=C double bond**.
- **Uses:** Psychosis, agitation; strongly sedating.

Drug 9 — Thiothixene

- **Chemical class:** Thioxanthene (piperazine side chain) — high-potency.
- **Structure:** Scaffold = thioxanthene tricycle. Key substituents: **2-sulfonamide (–$SO_2N(CH_3)_2$)** (the electron-withdrawing flag here is a sulfonamide, not Cl) + C-9 **[3-(4-methylpiperazin-1-yl)propylidene]** tail via C=C. The **cis (Z)-isomer** is the active drug.
- **Uses:** Schizophrenia.

3.6 DIBENZODIAZEPINES AND DIBENZOXAZEPINES — The Tricyclic Atypicals

Technical concept: These keep two benzene "wings" but the middle ring is a **seven-membered diazepine (two Ns) or oxazepine (one N + one O)**. At position 11 sits a **C=N double bond linked to N-methylpiperazine**. Clozapine is the first true atypical — the gold standard for treatment-resistant schizophrenia.

Simple explanation: A slightly bigger butterfly (seven-membered middle ring) with a piperazine grappling hook attached through a stiff C=N link. This shape grabs serotonin receptors (5-HT2A) as well as dopamine — the atypical signature.

Drug 10 — Loxapine

- **Chemical class: Dibenzoxazepine** (oxygen in the central seven-membered ring).
- **Structure:** Scaffold = **dibenzo[b,f][1,4]oxazepine**. Key substituents: **8-chloro** + C-11 carries **4-methylpiperazin-1-yl** attached via **C=N**.
- **Uses:** Schizophrenia. (Its metabolite amoxapine is an antidepressant — a fun cross-connection.)

Drug 11 — Clozapine

- **Chemical class: Dibenzodiazepine** (NH in the central seven-membered ring) — the prototype atypical antipsychotic.
- **Structure:** Scaffold = **5H-dibenzo[b,e][1,4]diazepine**. Key substituents: **8-chloro** + C-11 **(4-methylpiperazin-1-yl)** via C=N. Differs from loxapine by **NH replacing O** in the middle ring.
- **Uses: Treatment-resistant schizophrenia** (works when nothing else does); also reduces suicidal behavior. Price: risk of **agranulocytosis** — mandatory regular blood monitoring.

3.7 BUTYROPHENONES — The Four-Carbon Ketone Chain

Technical concept: Butyrophenones are not tricyclic at all. Their scaffold is a **p-fluorobutyrophenone**: a benzene ring with fluorine at the para position, attached to a **four-carbon chain ending in a ketone (C=O)**. The other end of the chain carries a **piperidine (or similar) ring**. They are among the most potent D2 blockers — and the most EPS-prone.

Simple explanation: Forget the butterfly — this is a spear: a fluorine-tipped aromatic head, a four-link shaft with a ketone kink, and a piperidine handle. It jabs the D2 receptor very precisely and very hard. Precision = power, but also = stiffness side effects.

Drug 12 — Haloperidol

- **Chemical class:** Butyrophenone — the reference high-potency typical antipsychotic.
- **Structure:** Scaffold = **4-(4-fluorophenyl)-4-oxobutyl** chain (p-fluorobenzoyl + 3 carbons + ketone). Key substituents: the chain ends in a **4-hydroxy-4-(4-chlorophenyl)piperidin-1-yl** group — a piperidine ring carrying **–OH and a p-chlorophenyl** on the same carbon.
- **Uses:** Schizophrenia, **acute psychosis/agitation** (IM), delirium, **Tourette's tics**, severe nausea. High EPS — often co-prescribed with anti-Parkinson drugs.

Drug 13 — Droperidol

- **Chemical class:** Butyrophenone with a **benzimidazolone** tail.
- **Structure:** Scaffold = same **p-fluorobutyrophenone** head. Key substituents: the chain ends in a **1,2,3,6-tetrahydropyridin-4-yl** ring fused to a **benzimidazol-2-one** (a fused 5-6 system with a urea-like C=O).
- **Uses: Postoperative nausea/vomiting**, acute psychosis. Use limited by **QT prolongation** risk (heart rhythm) — ECG caution.

3.8 NEWER AND MISCELLANEOUS AGENTS

Drug 14 — Risperidone

- **Chemical class: Benzisoxazole** — the first widely used atypical after clozapine.
- **Structure:** Scaffold = **3-(piperidin-4-yl)-1,2-benzisoxazole** (benzene fused to an isoxazole ring containing N–O). Key substituents: the benzisoxazole carries **6-fluoro**; the piperidine nitrogen connects via a **two-carbon linker** to a **2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one** (a fused bicyclic lactam) at its position 3.
- **Uses:** Schizophrenia, **bipolar mania**, irritability in autism. Strong 5-HT2A + D2 blockade.

Drug 15 — Molindone

- **Chemical class: Dihydroindolone** (tetrahydroindol-4-one) — structurally unique, no tricycle.
- **Structure:** Scaffold = **1,5,6,7-tetrahydro-4H-indol-4-one** (a fused 5-6 system: pyrrole fused to a cyclohexenone). Key substituents: **3-ethyl**, **2-methyl**, and at C-5 a **morpholin-4-ylmethyl (–CH_2–morpholine)** group.
- **Uses:** Schizophrenia. Notable for causing **less weight gain** than most atypicals.

Drug 16 — Sulpiride

- **Chemical class: Benzamide** — substituted 2-methoxybenzamide.
- **Structure:** Scaffold = **benzamide** (benzene–CONH–). Key substituents: on the ring, **2-methoxy (–OCH_3)** and **5-sulfamoyl (–SO_2NH_2)**; the amide nitrogen carries a **(1-ethylpyrrolidin-2-yl)methyl** group (a pyrrolidine ring with an ethyl on nitrogen).
- **Uses:** Schizophrenia (**negative symptoms**), vertigo/dizziness. Selective for D2/D3 — low EPS at low doses.

Drug 17 — Brexpiprazole

- **Chemical class: Quinolinone** — D2 **partial agonist** (third-generation mechanism).
- **Structure:** Scaffold = **quinolin-2(1H)-one** (a benzene fused to a lactam). Key substituents: at position 7, a **butoxy linker (–O–$CH_2CH_2CH_2CH_2$–)** connecting to a **4-(1-benzothiophen-4-yl)piperazin-1-yl** group (piperazine carrying a benzothiophene).
- **Uses:** Schizophrenia, **adjunctive treatment of major depression**. Partial agonism = "dimmer, not off switch" on D2 — fewer EPS and less prolactin rise.
- **Simple explanation:** A partial agonist is like pressing the accelerator **gently and constantly** — it prevents both full racing (psychosis) and full stalling (EPS).

Drug 18 — Lumateperone

- **Chemical class:** Fused **tetracyclic** (pyrido-pyrrolo-quinoxaline) — a newer atypical.
- **Structure:** Scaffold = **3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline** — four fused rings in one rigid block. Key substituents: a **3-methyl** on the scaffold and an N-linked **4-(4-fluorophenyl)-4-oxobutyl** side chain (a mini-butyrophenone tail!).
- **Uses:** Schizophrenia, **bipolar depression**. Notable for low metabolic/EPS burden.

Drug 19 — Pimavanserin

- **Chemical class: Trisubstituted urea** — a selective **5-HT2A inverse agonist** (no D2 blockade at all).
- **Structure:** Scaffold = **urea (–NH–CO–N–)**. Key substituents: one nitrogen carries **4-fluorobenzyl**, the same nitrogen carries **1-methylpiperidin-4-yl**, and the other nitrogen carries **4-(2-methylpropoxy)benzyl** [4-(isobutoxy)benzyl].
- **Uses: Psychosis in Parkinson's disease** — the only antipsychotic that does not worsen Parkinson's motor symptoms, precisely because it avoids D2 blockade.
- **Simple explanation:** It treats psychosis through the serotonin door only, leaving the dopamine movement pipes untouched — ideal when those pipes are already damaged (Parkinson's).

Drug 20 — Samidorphan

- **Chemical class: Morphinan** (opioid-related scaffold) — a μ-opioid **antagonist**.

- **Structure:** Scaffold = **epoxymorphinan** (the rigid 5-ring naltrexone-like skeleton: like morphine's framework). Key substituents: **17-(cyclopropylmethyl)**, **3- and 14-hydroxy groups**, and a **6β-[3-(dimethylamino)-2-hydroxypropoxy]** side chain.
- **Uses:** Combined **with olanzapine** (as a fixed combination) for schizophrenia and bipolar disorder — the opioid blockade **reduces olanzapine-induced weight gain**.
- **Simple explanation:** Olanzapine is an excellent antipsychotic that unfortunately stimulates appetite via opioid pathways; samidorphan sits on those opioid receptors like a cap, blunting the weight gain without touching the antipsychotic effect.

Key takeaway (newer agents): Medicinal chemistry moved from "block D2 harder" "balance 5-HT2A/D2" "partial agonism" (brexpiprazole) "skip D2 entirely" (pimavanserin) "fix the side effect with a second drug" (samidorphan + olanzapine).

3.9 Infographic Concept Box — Chapter 3

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+================================================================+
|  ANTIPSYCHOTICS — ONE-PAGE MIND MAP (draw as a poster)          |
|                                                                 |
|  Center: BRAIN with a VOLUME KNOB labeled "Dopamine D2".        |
|  Arrow: "Turn down = fewer voices; price = stiffness (EPS)".    |
|                                                                 |
|  LEFT — TYPICALS (D2 blockade):                                 |
|    Butterfly icon (phenothiazine, 7 drugs): "C-2 flag (Cl/CF3)  |
|      = power; N-10 hook: piperazine = strong + EPS,             |
|      piperidine/aliphatic = gentle". Star: Chlorpromazine*      |
|      (synthesis: couple -> sulfur-close -> hang side chain).    |
|    Carbon butterfly (thioxanthenes, 2): "C=C tail; cis = active".|
|    Spear icon (butyrophenones, 2): "p-fluoro head + 4-C shaft;  |
|      haloperidol = most EPS".                                   |
|                                                                 |
|  RIGHT — ATYPICALS (5-HT2A + D2):                               |
|    Big butterfly (loxapine O-ring, clozapine NH-ring*):         |
|      "*Clozapine = resistant cases; blood tests (agranulocytosis)".|
|    Benzisoxazole (risperidone), benzamide (sulpiride),          |
|    quinolinone (brexpiprazole = partial agonist "dimmer"),      |
|    tetracycle (lumateperone), urea (pimavanserin = no D2,       |
|    for Parkinson's psychosis), morphinan (samidorphan +         |
|    olanzapine = less weight gain).                              |
|                                                                 |
|  BOTTOM banner: "C-2 FLAG = potency dial. SIDE-CHAIN TYPE =     |
|  potency-vs-EPS tradeoff. More tricks: partial agonism,         |
|  D2-skipping, side-effect antidotes."                           |
+================================================================+
```

3.10 Pharmacy Relevance

1. **EPS management** is a core pharmacist role: recognizing parkinsonism, akathisia, and tardive dyskinesia, and knowing which structures (piperazine phenothiazines, butyrophenones) are highest-risk.
2. **Clozapine monitoring:** pharmacists coordinate the mandatory blood-count surveillance for agranulocytosis — a unique pharmacy responsibility.
3. **QT prolongation:** thioridazine and droperidol carry cardiac risk; pharmacists check ECG status and interacting drugs.

4 **Isomer awareness:** thiothixene's activity resides in the **cis (Z)** isomer — a reminder that 3D shape, not just formula, decides activity.

5 **Combination logic:** the samidorphan + olanzapine combination teaches "side-effect antidote" design — using a second molecule to cancel the first drug's drawback.

3.11 India Context

- **Chlorpromazine (Largactil)** and **haloperidol (Serenace)** remain the backbone of psychosis treatment in Indian public hospitals — effective and extremely cheap.
- **Risperidone** is now among the most prescribed atypical antipsychotics in India for schizophrenia and bipolar disorder.
- **Clozapine** is available in India for treatment-resistant schizophrenia, with blood-monitoring protocols run through hospital pharmacies.
- **Trifluoperazine** is still used in India at low doses for severe anxiety, and **prochlorperazine** for vomiting/vertigo — pharmacists should know these non-psychosis uses to counsel correctly.
- Long-acting injectable forms of haloperidol and risperidone help Indian patients with poor daily-tablet compliance — an adherence strategy pharmacists promote.

3.12 Key Points (Chapter 3)

1 Psychosis = excess dopamine signaling in the mesolimbic pathway; D2 blockade is the core mechanism.

2 Phenothiazine scaffold: S at 5, N at 10; C-2 EWG flag = potency; N-10 3-carbon basic side chain = anchor.

3 Side-chain rule: piperazine = high potency + high EPS; piperidine/aliphatic = lower both.

4 Chlorpromazine synthesis: Ullmann coupling sulfur ring closure N-alkylation ($NaNH_2$).

5 Thioxanthenes: C at position 9, C=C-linked tail; cis isomer active.

6 Clozapine (dibenzodiazepine) = treatment-resistant schizophrenia; agranulocytosis monitoring mandatory.

7 Butyrophenones (haloperidol): p-fluorobutyrophenone scaffold; most potent, most EPS.

8 Atypicals add 5-HT2A blockade; brexpiprazole is a D2 partial agonist; pimavanserin skips D2 (Parkinson's psychosis); samidorphan caps olanzapine's weight gain.

9 EPS = the movement price of D2 blockade (stiffness, tremor, tardive dyskinesia).

10 Loxapine (O-ring) vs. clozapine (NH-ring): one atom changes the class.

3.13 Common Confusions

Confusion	Clarification
Chlorpromazine vs. prochlorperazine	Same 2-Cl flag; different side chains (aliphatic vs. piperazine) very different potency/EPS and uses.
Loxapine vs. clozapine	Dibenzoxazepine (O) vs. dibenzodiazepine (NH) — one ring atom differs; both carry 8-Cl + piperazine via C=N.
Thioridazine's "gentleness"	Lowest EPS among phenothiazines, but carries QT/retinal risks — gentle on movement, not on heart/eyes.
Pimavanserin "isn't an antipsychotic"	It is — but the only one with no D2 blockade (pure 5-HT2A inverse agonist), hence safe in Parkinson's.
Samidorphan's role	It is not itself antipsychotic — it is the weight-gain antidote paired with olanzapine.
Typical vs. atypical = old vs. new	Mostly true, but loxapine (old) behaves atypical-ish and the classification is really about 5-HT2A/D2 pharmacology, not age.

3.14 Common Mistakes (in exams)

1 Drawing phenothiazine with N at position 5 and S at 10 — it is **S at 5, N at 10**.

2 Putting the potency flag at the wrong ring position — it must be **C-2** (not C-1, C-3, or C-4).

3 Forgetting that **N-10 must be alkylated** — unsubstituted phenothiazine is inactive.

4 In chlorpromazine synthesis, using the alkyl chloride **before** the sulfur ring-closure — the tricycle must be built first.

5 Calling thiothixene's active form "trans" — the **cis (Z)** isomer is active.

6 Writing clozapine's use without mentioning **agranulocytosis monitoring**.

7 Confusing the dibenzoxazepine (loxapine, O) with dibenzodiazepine (clozapine, NH).

3.15 Mnemonics

- **7 phenothiazines:** "**P**lease **C**alm **T**he **T**roubled **P**atient; **P**sychosis **T**orments" **P**romazine, **C**hlorpromazine, **T**riflupromazine, **T**hioridazine, **P**iperacetazine, **P**rochlorperazine, **T**rifluoperazine.
- **Side-chain power order:** "**A**mateur < **P**iperidine < **P**iperazine-**P**owerful" (aliphatic < piperidine < piperazine).
- **Chlorpromazine synthesis (C-S-S):** "**C**ouple, **S**ulfur-close, **S**ide-chain."
- **Atypical ladder:** "**C**lozapine **R**isperidone **B**rexpiprazole **P**imavanserin" = "**C**limbing **R**eally **B**ig **P**eaks" (D2 block balance partial skip D2).
- **C-2 flags:** "**C**hlorine, **C**F_3, **S**CH_3, **C**OCH_3" "**C**lever **C**hemists **S**elect **C**arefully."

3.16 Exam Summary (Chapter 3)

- Antipsychotics treat psychosis by blocking D2 (dopamine hypothesis); EPS is the movement price; atypicals add 5-HT2A blockade.

- Phenothiazines (7 drugs): S-5/N-10 tricycle; C-2 EWG flag controls potency; N-10 3-carbon basic side chain is mandatory; piperazine side chains = high potency + high EPS; chlorpromazine synthesized by Ullmann coupling sulfur thionation N-alkylation.
- Thioxanthenes (2): C-9 with C=C-linked tail; cis isomer active.
- Dibenzodiazepine/dibenzoxazepine (2): loxapine (O) and clozapine (NH); clozapine for resistant schizophrenia with blood monitoring.
- Butyrophenones (2): p-fluorobutyrophenone scaffold; haloperidol = highest potency/EPS.
- Newer agents (7): risperidone (benzisoxazole), molindone (indolone), sulpiride (benzamide), brexpiprazole (D2 partial agonist), lumateperone (tetracycle), pimavanserin (5-HT2A-only, Parkinson's psychosis), samidorphan (olanzapine's weight-gain antidote).

3.17 One-Minute Revision (Chapter 3)

Butterfly drug: S-5, N-10; C-2 flag (Cl/CF_3) = power; N-10 hook (3 carbons + charged amine) mandatory; piperazine = strong but stiff (EPS). Chlorpromazine = couple sulfur-close hang chain. Cis-thioxanthenes active. Clozapine (NH-ring) = resistant schizophrenia + blood tests. Haloperidol spear = most EPS. New tricks: 5-HT2A balance (risperidone), partial D2 (brexpiprazole), skip D2 (pimavanserin for Parkinson's), cap weight gain (samidorphan + olanzapine).

3.18 Exam Questions (Chapter 3)

Short-answer questions:

1 State the dopamine hypothesis of psychosis in two sentences.

2 Why does D2 blockade treat hallucinations but cause parkinsonism? (Name the two pathways.)

3 Draw and number the phenothiazine scaffold, marking positions 2, 5, and 10.

4 Rank aliphatic, piperidine, and piperazine phenothiazines by potency and EPS.

5 Why is only the cis isomer of thiothixene clinically useful?

6 What single ring atom differs between loxapine and clozapine?

7 Why does pimavanserin not worsen Parkinson's disease?

8 What is the role of samidorphan in antipsychotic therapy?

Long-answer questions:

1 Classify antipsychotics with examples. Explain the dopamine hypothesis and how typical and atypical agents differ (D2 vs. 5-HT2A/D2), with the EPS tradeoff.

2 Write the complete synthesis of chlorpromazine starting from m-chloroaniline. Give reagents, conditions, and the structure (in words) of each intermediate.

3 Discuss the SAR of phenothiazines with the rule table, using promazine, chlorpromazine, thioridazine, and trifluoperazine as examples.

MCQs (answer key at the end):

1 In phenothiazines, sulfur and nitrogen are at positions:

a) 5 and 10 b) 1 and 4 c) 2 and 10 d) 5 and 9

1 The potency-enhancing substituent position in phenothiazines is:

a) C-1 b) C-2 c) C-3 d) N-10

1 Which side chain gives the highest antipsychotic potency (and most EPS)?

a) Aliphatic dimethylaminopropyl b) Piperidine c) Piperazine d) Morpholine

1 The sulfur ring-closure step in chlorpromazine synthesis is called:

a) Ullmann coupling b) Bernthsen-type thionation c) Friedel–Crafts d) Grignard addition

1 The base used for N-alkylation in chlorpromazine synthesis is:

a) NaOH b) $NaNH_2$ c) NaOEt d) Pyridine

1 The active isomer of thiothixene is:

a) Trans (E) b) Cis (Z) c) Racemic d) Meso

1 Clozapine requires regular monitoring for:

a) Liver enzymes b) Agranulocytosis c) QT interval only d) Blood sugar only

1 Pimavanserin is unique because it:

a) Blocks D2 strongly b) Is a 5-HT2A inverse agonist with no D2 blockade c) Is a prodrug d) Contains sulfur

1 Brexpiprazole's D2 action is best described as:

a) Full antagonist b) Partial agonist c) Inverse agonist d) Allosteric activator

1 Samidorphan is combined with olanzapine to:

a) Increase sedation b) Reduce weight gain c) Treat EPS d) Shorten half-life

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

Viva questions:

1 What are positive and negative symptoms of psychosis?

2 Name the two dopamine pathways relevant to therapy vs. EPS.

3 Which reagent closes the phenothiazine ring in chlorpromazine synthesis?

4 Why is N-10 alkylation essential for phenothiazine activity?

5 Which phenothiazine has a methylthio group at C-2?

6 What is tardive dyskinesia?

7 Why is clozapine reserved for treatment-resistant schizophrenia?

8 How does a D2 partial agonist differ from a full antagonist?

Application-based questions:

1 A Parkinson's patient develops hallucinations. Why is pimavanserin preferred over haloperidol here? (Answer: haloperidol's D2 blockade would worsen motor symptoms; pimavanserin treats psychosis via 5-HT2A inverse agonism without touching D2.)

2 A student draws a phenothiazine with the side chain on C-2 and chlorine on N-10. Identify two SAR violations. (Answer: the basic side chain must hang from N-10, not C-2 (rule 3/5); the EWG flag belongs at C-2, not on nitrogen (rule 2).)

3 A patient on clozapine misses blood tests for two months. What is the pharmacist's concern and action? (Answer: risk of undetected agranulocytosis; withhold/flag supply and urgently arrange blood-count monitoring per protocol.)

3.19 References (Chapter 3)

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CHAPTER 4: ANTICONVULSANTS (ANTIEPILEPTICS)

4.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define seizure, epilepsy, and convulsion, and name the major seizure types in simple words.

2 Classify anticonvulsants by chemical class with examples.

3 Explain the three main mechanisms (Na^+ channel blockade, GABA enhancement, Ca^{2+} channel blockade) using simple analogies.

4 Draw the numbered hydantoin, succinimide, and oxazolidinedione scaffolds.

5 Write the complete syntheses of phenytoin (Biltz) and carbamazepine with reagents, conditions, and intermediates.

6 Apply the anticonvulsant SAR rule tables (hydantoins, succinimides/oxazolidinediones, general pharmacophore).

7 Describe the scaffold, key substituents, and one use of each of the 20 drugs.

8 Match each drug to its seizure type (tonic-clonic vs. absence).

9 Explain why ethosuximide works for absence seizures but phenytoin does not.

4.2 Definitions — Starting From Zero

- **Seizure:** A sudden, uncontrolled burst of electrical activity in the brain — neurons firing all together when they shouldn't.
- **Epilepsy:** A disorder of **repeated** seizures (a single seizure is not epilepsy).
- **Convulsion:** A seizure with visible jerking movements of the body (not all seizures convulse — some are brief "blank stares").
- **Tonic-clonic (grand mal) seizure:** The classic seizure — body stiffens (tonic), then jerks rhythmically (clonic), with loss of consciousness.
- **Absence (petit mal) seizure:** A brief 5–10 second "blank stare" — the person freezes mid-sentence, then continues as if nothing happened. Common in children.
- **Focal (partial) seizure:** Starts in one brain region (may spread). **Generalized seizure:** involves the whole brain from the start.
- **Status epilepticus:** A seizure that won't stop (or repeated seizures without waking up) — a medical emergency.
- **Ion channel:** A protein tunnel in the neuron membrane that lets charged particles (Na^+, Ca^{2+}, Cl^-) pass. Seizures = channels misbehaving; anticonvulsants = channel disciplinarians.

Simple explanation: Think of the brain as a city at night. Normally, lights (neurons) turn on and off in an orderly pattern. A seizure is a **city-wide blackout followed by every light flashing at once** — a power surge. Anticonvulsants are the surge protectors: they don't rewire the city, but they stop the surges.

Three surge-protector strategies (mechanisms):

1 **Block voltage-gated Na^+ channels** (phenytoin, carbamazepine): lock some "fire-signal doors" so the electrical storm can't spread. Best for tonic-clonic/focal seizures.

2 **Boost GABA** (phenobarbital, benzodiazepines, valproate): strengthen the brain's brakes.

3 **Block T-type Ca^{2+} channels** in the thalamus (ethosuximide, trimethadione): silence the "pacemaker" rhythm that drives absence seizures.

Analogy: Na^+ blockers are like **speed breakers** on a road — the seizure signal can't race through. GABA boosters are like **more traffic police** calming every junction. T-type Ca^{2+} blockers switch off the **faulty traffic light** that keeps blinking the absence-seizure rhythm.

Key takeaway: Match the mechanism to the seizure: Na^+ blockade for tonic-clonic/focal; T-type Ca^{2+} blockade for absence; GABA boosting helps broadly.

```
DIAGRAM — DRAW THIS: "Three locks, three keys"
Draw a neuron with three labeled tunnels: "Na+ channel (fire door)",
"GABA-A Cl- channel (brake)", "T-type Ca2+ channel (pacemaker)".
Draw a key labeled "Phenytoin/Carbamazepine" locking the Na+ door.
Draw a key labeled "Phenobarbital/Valproate" opening the GABA door wider.
Draw a key labeled "Ethosuximide" locking the Ca2+ pacemaker.
Caption: "Right key, right seizure: Na+ = tonic-clonic; Ca2+ = absence."
```

4.3 Classification (Flowchart)

```
FLOWCHART — DRAW THIS:
                ANTICONVULSANTS (20 drugs)
                            |
    +---------+--------+------+------+------+------+
    |         |        |      |      |      |      |
Barbitu-  Hydan-  Oxazo-  Suc-  Diben-  Carbox-  Miscel-
rates     toins   lidi-   cini- zazepine ylic     laneous
(3):      (3):    nediones mides (1):    acids    (7):
1. Pheno- 4. Phen- (2):    (3):  12. Car- (2):    11. Phena-
   barbi-    ytoin* 6. Tri- 8. Phen-  bamaze- 15. Val- cemide
   tone      5. Me-    metha-   suxi-  pine*    proic 13. Clona-
2. Metha-    pheny-   dione  mide            acid     zepam
   barbital  toin    7. Para- 9. Meth-       16. Gaba- 14. Primidone
3. (see     6. Etho-  metha-   suxi-        pentin    17. Felbamate
   Ch.2)     toin     dione    mide                   18. Perampanel
                            10. Etho-                 19. Lacosamide
                                suximide              20. Retigabine
Seizure-type map (draw as arrows):
Tonic-clonic/focal <---- Phenytoin, Carbamazepine, Phenobarbital, Valproate, Primidone
Absence <---- Ethosuximide, Trimethadione/Paramethadione, Valproate
```

4.4 BARBITURATES AS ANTICONVULSANTS

Technical concept: The same barbiturate scaffold from Chapter 2, but here the **phenyl-substituted** members are prized: the phenyl group confers anticonvulsant (not just hypnotic) activity via prolonged Na^+-channel inactivation plus GABA potentiation.

Drug 1 — Phenobarbitone (= Phenobarbital — same drug as Chapter 2)

- **Chemical class:** Long-acting **phenylbarbiturate**.
- **Structure:** Scaffold = **barbituric acid ring**; C-5 carries **ethyl + phenyl** (5-ethyl-5-phenyl). (Full details in Chapter 2, section 2.4.)
- **Uses (anticonvulsant focus): Tonic-clonic seizures**, **neonatal seizures** (drug of choice in newborns), status epilepticus (second-line). The phenyl group is what makes it an antiepileptic rather than just a sleeping pill.

Drug 2 — Methabarbital

- **Chemical class: N-methyl phenylbarbiturate** (the N-methyl analog of phenobarbital).
- **Structure:** Scaffold = barbituric acid ring; C-5 **ethyl + phenyl** (same as phenobarbital) + **methyl on N-1**. (Note: the syllabus lists it in both Unit I chapters 2 and 4 — it is one and the same compound.)
- **Uses:** Epilepsy (tonic-clonic); demethylated in the body to phenobarbital, acting as a slower, milder form.

Drug 14 (listed here for class logic) — Primidone — see section 4.7.

Key takeaway: In barbiturates, **phenyl at C-5 = seizure control**; the rest of the molecule decides sleep vs. seizure selectivity.

4.5 HYDANTOINS — The Imidazolidine-2,4-dione Family

Technical concept: Hydantoins share a **five-membered ring with two nitrogens and two carbonyls** (imidazolidine-2,4-dione). Like barbiturates, activity needs **disubstitution at C-5** — and here **two phenyl groups** give the classic Na^+-channel-blocking antiepileptic. Hydantoins block Na^+ channels **without general sedation** — the patient stays alert, which was revolutionary.

Simple explanation: A smaller, tighter ring than barbiturates, with the same "two teeth at carbon-5" rule. Two phenyl teeth = stops seizures without putting the patient to sleep. That selectivity (no drowsiness) is why phenytoin dominated epilepsy treatment for decades.

```
DIAGRAM — DRAW THIS: Numbered hydantoin scaffold
Draw a pentagon. Number: N1 (top-right), C2=O (top), N3 (top-left),
C4=O (bottom-left), C5 (bottom-right) with two lines down labeled R1, R2.
Caption: "Hydantoin: 5-membered, 2 nitrogens, 2 ketones. C-5 disubstitution required.
Phenytoin: R1 = R2 = phenyl."
```

Drug 4 — Phenytoin

- **Chemical class: Hydantoin** — the prototype Na^+-channel-blocking antiepileptic.
- **Structure:** Scaffold = **hydantoin (imidazolidine-2,4-dione)**. Key substituents: C-5 carries **two phenyl groups** (5,5-diphenyl). N-1 and N-3 are unsubstituted (–NH).
- **Uses: Tonic-clonic and focal seizures** (first-line classic), **status epilepticus** (IV, as the prodrug fosphenytoin), trigeminal neuralgia, cardiac arrhythmias (historical). No good for absence seizures.

Synthesis of Phenytoin (Biltz synthesis — one pot, two mechanistic stages)

Starting materials: Benzil (1,2-diphenylethane-1,2-dione: Ph–CO–CO–Ph) + **urea**.

Stage 1 — Addition of urea to benzil.

- Reagents/conditions: **Urea**, **sodium hydroxide (NaOH)** in **ethanol**, heated.
- What happens: One $–NH_2$ of urea attacks one carbonyl carbon of benzil, forming a C–N bond (an addition intermediate with an –OH on that carbon).
- **Intermediate (not isolated):** The urea–benzil adduct — Ph–C(OH)($NHCONH_2$)–CO–Ph.

Stage 2 — Benzilic-acid-type rearrangement + cyclization.

- What happens: A **1,2-phenyl shift** occurs — one phenyl group migrates from its carbon to the neighboring carbon (exactly like the classic benzilic acid rearrangement of benzil with hydroxide). Simultaneously, the second $–NH_2$ of urea attacks the remaining carbonyl, closing the five-membered ring with loss of water.

- **Product: Phenytoin — 5,5-diphenylhydantoin (5,5-diphenylimidazolidine-2,4-dione).** Both phenyls end up on C-5; the ring now has its two C=O groups (from urea's carbonyl and benzil's second carbonyl).

```
FLOWCHART — DRAW THIS: Phenytoin synthesis (Biltz)
Box 1: Benzil (Ph-CO-CO-Ph) + urea --(NaOH, EtOH, heat)-->
Box 2: [urea-benzil adduct] --(1,2-phenyl shift; -H2O)-->
Box 3: PHENYTOIN [5,5-diphenylhydantoin]
Write under arrow 2: "Phenyl migrates; second NH2 closes the ring"
```

Memory hook: "**B**enzil + **U**rea, **B**ase, **B**oom — phenyl jumps, ring closes" **B-U-B-B**: "**B**iltz **U**ses **B**enzil **B**ravely."

Key takeaway: The Biltz synthesis is a rearrangement-driven ring closure — the phenyl migration is the star step that places both phenyls exactly at C-5.

Drug 5 — Mephenytoin

- **Chemical class: N-methyl hydantoin**.
- **Structure:** Scaffold = hydantoin. Key substituents: C-5 carries **ethyl + phenyl** (one phenyl replaced by ethyl vs. phenytoin) + **methyl on N-3**.
- **Uses:** Tonic-clonic/focal seizures (less used today; risk of blood disorders).

Drug 6 — Ethotoin

- **Chemical class: N-ethyl hydantoin**.
- **Structure:** Scaffold = hydantoin. Key substituents: C-5 carries **one phenyl + one hydrogen** (5-phenyl only — the exception that proves the C-5 rule still gives some activity) + **ethyl on N-3**.
- **Uses:** Tonic-clonic/focal seizures; milder, with fewer gum/blood side effects than phenytoin.

SAR of Hydantoins (Rule Table)

#	Structural feature	SAR rule	Example
1	C-5 disubstitution	Two substituents at C-5 required for full activity; mono-substituted = weaker	Phenytoin (di-Ph) > ethotoin (mono-Ph)
2	Aryl groups at C-5	**Phenyl/aryl groups** strong activity against tonic-clonic seizures (Na^+ blockade)	Phenytoin
3	Alkyl at C-5	Small alkyl groups retained but milder activity	Mephenytoin (ethyl)
4	N-alkylation	N-methyl/N-ethyl altered metabolism and duration; can reduce side effects	Mephenytoin, ethotoin
5	Ring carbonyls	Both C=O groups needed for H-bonding to the receptor	—

4.6 OXAZOLIDINEDIONES AND SUCCINIMIDES — The Absence-Seizure Specialists

Technical concept: These are **five-membered rings with two carbonyls** like hydantoins, but the ring heteroatoms differ: **oxazolidinedione** has N + O in the ring; **succinimide** (pyrrolidine-2,5-dione) has one N. Small **alkyl** (not phenyl) substituents at C-3/C-5 give selective activity against **absence seizures** via T-type Ca^{2+} channel blockade in the thalamus.

Simple explanation: Same five-membered "two-ketone" idea as hydantoins, but with small oily methyl/ethyl teeth instead of big phenyl teeth. Small teeth = fits the thalamus pacemaker lock (T-type calcium channels) = stops the blank-stare seizures. Big phenyl teeth would be too bulky for this lock.

Drug 7 — Trimethadione

- **Chemical class: Oxazolidine-2,4-dione**.
- **Structure:** Scaffold = **oxazolidine-2,4-dione** (five-membered: N at 3, O at 1, C=O at 2 and 4). Key substituents: **3-methyl** (on nitrogen), **5,5-dimethyl** (two methyls at C-5) — hence "tri-methyl".
- **Uses: Absence seizures** (historical). Limited by **teratogenicity** (causes birth defects — "fetal trimethadione syndrome").

Drug 8 — Paramethadione

- **Chemical class: Oxazolidine-2,4-dione** (homolog of trimethadione).
- **Structure:** Scaffold = oxazolidine-2,4-dione. Key substituents: **3-methyl**, C-5 carries **methyl + ethyl** (5-ethyl instead of 5-methyl vs. trimethadione).
- **Uses:** Absence seizures (historical; same teratogenicity concerns).

Drug 9 — Phensuximide

- **Chemical class: Succinimide** (N-substituted).
- **Structure:** Scaffold = **pyrrolidine-2,5-dione** (succinimide: five-membered, one N, two C=O). Key substituents: **N-methyl** + **3-phenyl** (phenyl at C-3, not C-5).
- **Uses:** Absence seizures (historical; largely replaced by ethosuximide).

Drug 10 — Methsuximide

- **Chemical class: Succinimide**.
- **Structure:** Scaffold = succinimide. Key substituents: **N-methyl** + C-3 carries **methyl + phenyl** (3-methyl-3-phenyl).
- **Uses:** Absence and other generalized seizures (adjunct).

Drug 11 — Ethosuximide

- **Chemical class: Succinimide** — the gold standard for absence seizures.

- **Structure:** Scaffold = succinimide. Key substituents: **N–H** (no N-methyl!) + C-3 carries **ethyl + methyl** (3-ethyl-3-methyl). Small, simple, no phenyl.
- **Uses: Absence seizures — first-line drug of choice**, especially in children. Blocks T-type Ca^{2+} channels; ineffective for tonic-clonic seizures.

Compare the three succinimides (table):

Feature	Phensuximide	Methsuximide	Ethosuximide
N-substituent	Methyl	Methyl	H
C-3 groups	Phenyl	Methyl + phenyl	Ethyl + methyl
Phenyl present?	Yes	Yes	**No**
Absence-seizure use	Historical	Adjunct	**First-line**

Key takeaway: For absence seizures, **small alkyl > phenyl** — ethosuximide's tiny ethyl+methyl pair is the perfect fit for the T-type calcium lock.

SAR of Oxazolidinediones and Succinimides (Rule Table)

#	Structural feature	SAR rule	Example
1	Five-membered dione ring	The cyclic imide (two C=O) is essential — H-bonding pharmacophore	All three succinimides
2	C-3/C-5 substituents	**Small alkyl groups (methyl, ethyl)** selective absence-seizure activity	Ethosuximide (Et, Me)
3	Phenyl substitution	Phenyl shifts profile away from pure absence activity, more toxicity	Phensuximide (older, replaced)
4	N-substitution	N–H (ethosuximide) vs. N-methyl — both active; N-methyl alters metabolism	Ethosuximide (N–H) is first-line
5	Ring oxygen (oxazolidinediones)	O in the ring tolerated but brings teratogenicity in this class	Trimethadione

4.7 MISCELLANEOUS ANTICONVULSANTS

Drug 12 — Carbamazepine

- **Chemical class: Dibenzazepine-5-carboxamide** (tricyclic, structurally related to imipramine-type antidepressants but with a C10=C11 double bond and a carboxamide).
- **Structure:** Scaffold = **5H-dibenzo[b,f]azepine** — two benzene rings fused to a central seven-membered azepine ring containing one nitrogen. Key substituents: a **C10=C11 double bond** in the central ring (this distinguishes it from imipramine) and a **carboxamide (–$CONH_2$)** on the ring nitrogen (N-5).
- **Uses: Focal and tonic-clonic seizures**, **trigeminal neuralgia** (first-line), bipolar mania prophylaxis. Na^+-channel blocker like phenytoin.

Synthesis of Carbamazepine (4 steps)

Step 1 — Base-catalyzed dimerization 2,2'-dinitrodibenzyl.

- Reagents/conditions: **o-nitrotoluene**, **sodium hydroxide (NaOH)**, heat.
- What happens: Two molecules of o-nitrotoluene condense — the acidic methyl group of one attacks the other — joining them through a $–CH_2–CH_2–$ bridge.
- **Intermediate: 2,2'-dinitrodibenzyl** (2,2'-dinitrobibenzyl) — structure: two o-nitrophenyl rings linked by an ethylene ($–CH_2CH_2–$) bridge.

Step 2 — Reductive cyclization iminodibenzyl.

- Reagents/conditions: **Zinc (Zn)** and **NaOH** (reducing conditions), heat.
- What happens: The nitro groups are reduced and the molecule cyclizes, forming the central seven-membered nitrogen ring.
- **Intermediate: Iminodibenzyl — 10,11-dihydro-5H-dibenzo[b,f]azepine** — structure: the tricycle with a saturated $–CH_2–CH_2–$ bridge (positions 10–11) and –NH– at position 5.

Step 3 — Dehydrogenation iminostilbene.

- Reagents/conditions: **Bromine (Br_2)** followed by base (dehydrobromination), or heating with **sulfur**.
- What happens: Two hydrogens are removed from the C10–C11 bridge, creating the double bond.
- **Intermediate: Iminostilbene — 5H-dibenzo[b,f]azepine** — structure: same tricycle, now with **C10=C11**.

Step 4 — Carbamoylation carbamazepine.

- Reagents/conditions: **Phosgene ($COCl_2$)**, then **ammonia (NH_3)**.
- What happens: Phosgene attaches a –COCl group to the ring nitrogen (forming the carbamoyl chloride); ammonia displaces chloride, giving the $–CONH_2$ amide.
- **Product: Carbamazepine — 5H-dibenzo[b,f]azepine-5-carboxamide.**

```
FLOWCHART — DRAW THIS: Carbamazepine synthesis
Box 1: 2 o-nitrotoluene --(NaOH, heat)--> Box 2: 2,2'-dinitrodibenzyl
Box 2 --(Zn, NaOH, heat)--> Box 3: IMINODIBENZYL [tricycle, saturated bridge]
Box 3 --(Br2, then base / S, heat)--> Box 4: IMINOSTILBENE [C10=C11]
Box 4 --(i) COCl2; (ii) NH3--> Box 5: CARBAMAZEPINE [N-5 CONH2]
Note: "Steps 1-3 build the tricycle; step 4 installs the carboxamide"
```

Memory hook: "**D**imerize, **R**educe-close, **D**ehydrogenate, **C**arbamoylate" **D-R-D-C**: "**D**octors **R**arely **D**efer **C**arbamazepine."

Drug 13 — Clonazepam

- **Chemical class: Nitrobenzodiazepine** (benzodiazepine with a nitro flag and ortho-chloro phenyl).
- **Structure:** Scaffold = **1,4-benzodiazepin-2-one** (same family as Chapter 2). Key substituents: **7-nitro ($–NO_2$)** (instead of 7-chloro), **5-(2-chlorophenyl)** (ortho-chloro phenyl), N-1 hydrogen.

- **Uses: Absence and myoclonic seizures**, panic disorder. The nitro group gives strong anticonvulsant potency.

Drug 15 — Valproic Acid (Valproate)

- **Chemical class: Branched short-chain fatty acid** — the simplest anticonvulsant structure.
- **Structure:** Scaffold = a **carboxylic acid** on a branched 8-carbon skeleton: **2-propylpentanoic acid** [$CH_3CH_2CH_2$–CH(COOH)–$CH_2CH_2CH_3$]. Key substituents: the **α-carbon carries two propyl chains** (branching is essential — straight-chain octanoic acid is inactive).
- **Uses: Broad-spectrum** — effective in **all seizure types** (tonic-clonic, absence, myoclonic), **bipolar disorder**, migraine prophylaxis. Multiple mechanisms: Na^+ blockade + GABA boosting + (weak) T-type Ca^{2+} blockade.
- **Simple explanation:** A tiny branched fatty acid that does a little of everything — the Swiss Army knife of epilepsy.

Drug 16 — Gabapentin

- **Chemical class: GABA analog** (structurally resembles GABA but does not act on GABA receptors — it binds the $\alpha_2\delta$ subunit of calcium channels).
- **Structure:** Scaffold = **cyclohexane ring** with two substituents on the same carbon (C-1): an **aminomethyl group (–CH_2NH_2)** and an **acetic acid group (–CH_2COOH)**. If you trace N–C–C–C–COOH through the ring, you can "see" the GABA skeleton folded into a ring.
- **Uses: Focal seizures** (adjunct), **neuropathic pain** (postherpetic neuralgia, diabetic neuropathy) — its biggest use today.

Drug 17 — Felbamate

- **Chemical class: Dicarbamate** (like meprobamate from Chapter 2, but antiepileptic).
- **Structure:** Scaffold = **2-phenylpropane-1,3-diol** backbone. Key substituents: **both –OH groups converted to carbamates (–$OCONH_2$)**; a **phenyl** on C-2.
- **Uses: Lennox–Gastaut syndrome** (severe childhood epilepsy) — reserved for refractory cases because of **aplastic anemia** and liver failure risks.

Drug 18 — Perampanel

- **Chemical class: Bipyridone** — a selective **AMPA receptor antagonist** (blocks the glutamate "fire!" signal at AMPA receptors).
- **Structure:** Scaffold = **pyridin-2(1H)-one** (a six-membered lactam). Key substituents: **1-phenyl** (on nitrogen), **3-(2-cyanophenyl)** (–C_6H_4–CN ortho), **5-(pyridin-2-yl)**. Three aromatic rings around one pyridone core.
- **Uses: Focal seizures** (adjunct). First antiepileptic to target AMPA receptors.

Drug 19 — Lacosamide

- **Chemical class: Functionalized amino acid** (a modified D-serine derivative).
- **Structure:** Scaffold = a **propanamide** backbone: **(R)-2-acetamido-N-benzyl-3-methoxypropanamide**. Key substituents: **N-acetyl (–$NHCOCH_3$)**, **O-methyl ether (–OCH_3)**, and an **N-benzyl (–CH_2–C_6H_5)** amide. The **R-configuration** is essential.
- **Uses: Focal seizures** (monotherapy or adjunct). Enhances **slow inactivation** of Na^+ channels (a subtly different Na^+ mechanism).

Drug 20 — Retigabine (Ezogabine)

- **Chemical class: Triaminobenzene carbamate** — a **KCNQ potassium-channel opener** (the only antiepileptic that opens K^+ channels to quiet neurons).
- **Structure:** Scaffold = a **1,2,4-trisubstituted benzene** (three nitrogens around the ring). Key substituents: **2-amino (–NH_2)**, **4-(4-fluorobenzylamino)** (–NH–CH_2–C_6H_4–F para), and **1-(ethoxycarbonylamino)** (–$NHCOOCH_2CH_3$, a carbamate).
- **Uses: Focal seizures** (adjunct) — use severely limited/withdrawn in many countries because of **retinal pigmentation and skin discoloration** with long-term use.

Drug 11 — Phenacemide

- **Chemical class: Phenylacetylurea** (an open-chain ureide).
- **Structure:** Scaffold = **urea** linked to phenylacetyl: **C_6H_5–CH_2–CO–NH–CO–NH_2**. Key substituents: a **phenylacetyl** group on one urea nitrogen.
- **Uses:** Severe epilepsy unresponsive to safer drugs (high toxicity — behavioral and blood disorders); essentially historical.

Key takeaway (miscellaneous): Modern anticonvulsants explore new locks — AMPA blockade (perampanel), K^+ opening (retigabine), $\alpha_2\delta$ calcium binding (gabapentin) — while old ones (valproate, carbamazepine) succeed by hitting several targets at once.

4.8 General SAR / Pharmacophore of Anticonvulsants (Rule Tables)

Technical concept: Across all classes, one pattern repeats — the **anticonvulsant pharmacophore**: (a) a **hydrophobic aryl/alkyl region**, (b) a **hydrogen-bonding domain** (imide/amide/urea C=O and N–H), and (c) an **electron-donor group**. If a molecule has these three arranged correctly, it has a good chance of stopping seizures.

#	Pharmacophore element	SAR rule	Example
1	Hydrophobic aryl group	One or two **lipophilic phenyl rings** Na^+-channel blockade, tonic-clonic activity	Phenytoin (2 Ph), carbamazepine (2 fused Ph)
2	H-bond donor/acceptor	**–NH–CO– (imide/amide/urea)** motif anchors to the receptor/channel	Hydantoins, succinimides, phenacemide
3	Electron-donor atom	A **carbonyl oxygen or equivalent** positioned near the hydrophobic region	All dione classes

#	Pharmacophore element	SAR rule	Example
4	Size of hydrophobic group	**Large (phenyl)** tonic-clonic/focal; **small (methyl/ethyl)** absence seizures	Phenytoin vs. ethosuximide
5	Lipophilicity balance	Enough lipid solubility to **cross the blood–brain barrier**, but not so much that the drug gets trapped in fat	Valproate (branched = just right)
6	Stereochemistry	**Chirality can decide activity** — one enantiomer active, the other weak	Lacosamide (R-active), (S)-ketamine noted in Ch. 1

Simple explanation: Every successful anticonvulsant is built like a grappling hook: a greasy aromatic head that lodges in the channel wall, plus an H-bonding handle (–NH–CO–) that grips the protein. Big head = stops big seizures (tonic-clonic); small head = stops absence seizures.

Example: Phenytoin (two phenyls + hydantoin H-bonding) fits the tonic-clonic lock; ethosuximide (ethyl+methyl + succinimide H-bonding) fits the absence lock. Same handle, different head size. **Key takeaway:** Learn the pharmacophore once — hydrophobic aryl + H-bonding imide/amide + electron donor — and you can rationalize nearly every drug in this chapter.

4.9 Infographic Concept Box — Chapter 4

```
+================================================================+
|  ANTICONVULSANTS — ONE-PAGE MIND MAP (draw as a poster)         |
|                                                                |
|  Center: BRAIN with a LIGHTNING BOLT labeled "Seizure = power  |
|  surge". Three shields around it: "Na+ block", "GABA boost",   |
|  "Ca2+ (T-type) block".                                        |
|                                                                |
|  LEFT — BIG-HEAD drugs (tonic-clonic/focal, Na+ blockade):      |
|    Hydantoin ring (2 Ph): Phenytoin* (Biltz: benzil + urea,    |
|      phenyl jumps). Dibenzazepine: Carbamazepine* (tricycle +  |
|      CONH2; build tricycle, then carbamoylate). Phenylbarbital |
|      (Ph = anticonvulsant), Valproate (branched acid, does all).|
|                                                                |
|  RIGHT — SMALL-HEAD drugs (absence, T-type Ca2+ blockade):      |
|    Succinimide ring: Ethosuximide (Et + Me, FIRST-LINE).       |
|    Oxazolidinedione: Trimethadione (teratogenic — avoid).      |
|                                                                |
|  BOTTOM strip — NEW LOCKS: Perampanel (AMPA block), Retigabine |
|  (K+ opener, withdrawn many places), Gabapentin (Ca2+ a2d, pain),|
|  Lacosamide (R-amino acid, slow Na+ inactivation), Felbamate   |
|  (dicarbamate, Lennox-Gastaut, toxic), Clonazepam (nitro-BZD), |
|  Phenacemide (phenylacetylurea, historical).                   |
|                                                                |
|  BOTTOM banner: "PHARMACOPHORE: greasy aryl head + -NH-CO-     |
|  handle + electron donor. Big head = tonic-clonic; small head =|
|  absence."                                                     |
+================================================================+
```

4.10 Pharmacy Relevance

1 **Seizure-type matching** is the pharmacist's key counseling checkpoint: phenytoin/carbamazepine for tonic-clonic, ethosuximide for absence — giving the wrong one can worsen seizures.

2 **Narrow therapeutic index:** Phenytoin shows **saturable (Michaelis–Menten) metabolism** — a small dose increase can cause a huge blood-level jump. Pharmacists monitor levels and counsel on strict adherence.

3 **Teratogenicity counseling:** Valproate and trimethadione/paramethadione are teratogenic — pharmacists must counsel women of childbearing age on contraception and folate.

4 **Enzyme induction:** Phenytoin, carbamazepine, and phenobarbital induce liver enzymes, reducing the effect of contraceptives, anticoagulants, and many other drugs — a classic interaction-checking duty.

5 **Adherence aids:** Once-daily options and fixed combinations help; pharmacists promote seizure diaries and never advise abrupt discontinuation (withdrawal seizures).

4.11 India Context

- **Phenytoin (Eptoin)** and **phenobarbital (Gardenal)** are the cheapest, most widely available epilepsy drugs in India and remain first-line in government hospitals and rural practice.
- **Carbamazepine (Tegretol/Mazetol)** is the standard drug for **trigeminal neuralgia** ("tic douloureux") in Indian neurology practice, as well as for focal seizures.
- **Sodium valproate (Encorate)** is one of the most prescribed broad-spectrum antiepileptics in India for both epilepsy and bipolar disorder.
- **Gabapentin** is widely prescribed in India for **neuropathic pain** (diabetic neuropathy is common), often more than for epilepsy.
- **Clonazepam** is commonly used in India for myoclonic/absence seizures and panic disorder; pharmacists counsel on its dependence potential.

4.12 Key Points (Chapter 4)

1 Seizure = abnormal electrical burst; epilepsy = repeated seizures.

2 Three mechanisms: Na^+ blockade (tonic-clonic), GABA boost (broad), T-type Ca^{2+} blockade (absence).

3 Hydantoin scaffold: 5-membered dione; C-5 disubstitution; phenyls = tonic-clonic power.

4 Phenytoin synthesis (Biltz): benzil + urea → 1,2-phenyl shift → ring closure.

5 Carbamazepine: dibenzazepine + N-5 carboxamide; synthesis = dimerize → reductive cyclization → dehydrogenate → carbamoylate.

6 Succinimides/oxazolidinediones: small alkyl groups = absence seizures (ethosuximide first-line).

7 Valproate: branched fatty acid, broad-spectrum (all seizure types).

8 New locks: perampanel (AMPA), retigabine (K^+ opener), gabapentin ($\alpha_2\delta$ Ca^{2+}), lacosamide (R-amino acid).

9 Pharmacophore: hydrophobic aryl + H-bonding (–NH–CO–) + electron donor.

10 Big head = tonic-clonic; small head = absence.

4.13 Common Confusions

Confusion	Clarification
Phenobarbital (Ch. 2) vs. phenobarbitone (Ch. 4)	Same drug — INN vs. older BAN name; hypnotic in Ch. 2, antiepileptic in Ch. 4.
Mephobarbital vs. methabarbital	The same compound (N-methyl phenobarbital) appears under both names in the two unit lists.
Primidone vs. phenobarbital	Different drugs — primidone is the 2-deoxy analog (C=O replaced by CH_2 at position 2); the body converts primidone partly into phenobarbital.
Ethotoin vs. ethosuximide	Different classes! Ethotoin = hydantoin (tonic-clonic); ethosuximide = succinimide (absence).
Trimethadione vs. ethosuximide	Both for absence, but trimethadione = oxazolidinedione (teratogenic, historical); ethosuximide = succinimide (first-line).
Gabapentin "is GABA"	It only *looks* like GABA folded into a ring — it does not act on GABA receptors (binds $\alpha_2\delta$ calcium-channel subunit).
Carbamazepine vs. imipramine	Same tricyclic skeleton, but carbamazepine has the C10=C11 double bond + carboxamide (antiepileptic); imipramine lacks both (antidepressant).

4.14 Common Mistakes (in exams)

1. Drawing phenytoin with phenyls at N-1/N-3 — they belong at **C-5**.
2. In the Biltz synthesis, forgetting the **1,2-phenyl shift** — the rearrangement is the whole point.
3. Writing carbamazepine synthesis without the **dehydrogenation step** (iminodibenzyl iminostilbene) — the C10=C11 double bond is essential.
4. Attaching the carboxamide to a ring carbon — it goes on the **ring nitrogen (N-5)**.
5. Prescribing logic errors: giving phenytoin for absence seizures (it doesn't work and can worsen them).
6. Drawing ethosuximide with a phenyl group — its power is in the **small ethyl+methyl** pair.
7. Calling valproic acid "straight-chain" — the **α-branching (two propyls)** is essential for activity.

4.15 Mnemonics

- **3 hydantoins:** "**P**lease **M**anage **E**pilepsy" **P**henytoin, **M**ephenytoin, **E**thotoin.
- **3 succinimides:** "**P**apa **M**akes **E**veryone **S**leepy" **P**hensuximide, **M**ethsuximide, **E**thosuximide (for absence "stares").
- **2 oxazolidinediones:** "**T**wo **P**ills" **T**rimethadione, **P**aramethadione.
- **Phenytoin synthesis (B-U-B-B):** "**B**enzil + **U**rea, **B**ase phenyl **B**ounces (shifts)."
- **Carbamazepine synthesis (D-R-D-C):** "**D**imerize, **R**educe-close, **D**ehydrogenate, **C**arbamoylate."
- **Seizure-type match:** "**B**ig head = **B**ig seizures (tonic-clonic); **S**mall head = **S**tares (absence)."
- **New locks:** "**P**erampanel **P**lugs **A**MPA; **R**etigabine **R**aises K^+ (potassium)."

4.16 Exam Summary (Chapter 4)

- Anticonvulsants stop seizure power-surges via Na^+ blockade (tonic-clonic/focal), GABA boosting (broad), or T-type Ca^{2+} blockade (absence).
- Barbiturates: phenyl at C-5 = anticonvulsant (phenobarbitone, methabarbital); primidone is the deoxy analog metabolized to phenobarbital.
- Hydantoins (5-membered dione, C-5 disubstituted): phenytoin (5,5-diphenyl; Biltz synthesis via benzilic-type phenyl shift), mephenytoin, ethotoin.
- Oxazolidinediones (trimethadione, paramethadione) and succinimides (phensuximide, methsuximide, ethosuximide): small alkyl groups = absence seizures; ethosuximide is first-line.
- Carbamazepine (dibenzazepine-5-carboxamide): 4-step synthesis (dimerize reductive cyclization dehydrogenate carbamoylate); used for focal/tonic-clonic seizures and trigeminal neuralgia.
- Miscellaneous: phenacemide (phenylacetylurea), clonazepam (nitro-BZD), valproic acid (branched fatty acid, broad-spectrum), gabapentin (GABA-lookalike, $\alpha_2\delta$ binder), felbamate (dicarbamate, Lennox–Gastaut), perampanel (AMPA antagonist), lacosamide (R-amino acid), retigabine (K^+ opener).
- Universal pharmacophore: hydrophobic aryl + H-bonding imide/amide + electron donor; head size selects seizure type.

4.17 One-Minute Revision (Chapter 4)

Seizure = brain power surge. Na^+ blockers (phenytoin, carbamazepine) = speed breakers for tonic-clonic. T-type Ca^{2+} blockers (ethosuximide) = switch off the absence pacemaker. Phenytoin = benzil + urea, phenyl jumps (Biltz). Carbamazepine = build tricycle (dimerize close dehydrogenate) then add $CONH_2$ on N. Big phenyl head = tonic-clonic; small alkyl head = absence. Valproate = branched acid, works on everything. New: perampanel (AMPA), retigabine (K^+), gabapentin (pain + seizures), lacosamide (R-form). Pharmacophore: greasy head + –NH–CO– handle.

4.18 Exam Questions (Chapter 4)

Short-answer questions:

1 Differentiate tonic-clonic and absence seizures in two lines each.

2 Name the three anticonvulsant mechanisms and one drug class for each.

3 Draw and number the hydantoin scaffold, marking C-5.

4 Why is ethosuximide effective in absence seizures but phenytoin is not?

5 What is the key rearrangement step in the Biltz synthesis of phenytoin?

6 Why is the C10=C11 double bond important in carbamazepine?

7 How does primidone differ structurally from phenobarbital?

8 State the anticonvulsant pharmacophore in one sentence.

Long-answer questions:

1 Classify anticonvulsants by chemical class with two examples each. Explain the three mechanisms of action with simple analogies and match each to its seizure type.

2 Write the complete synthesis of phenytoin starting from benzil. Give reagents, conditions, and explain the 1,2-phenyl shift with a stepwise description.

3 Write the complete synthesis of carbamazepine starting from o-nitrotoluene. Give reagents, conditions, and the structure (in words) of each intermediate.

4 Discuss the SAR of hydantoins and of succinimides/oxazolidinediones with rule tables, explaining why head-group size selects seizure type.

MCQs (answer key at the end):

1 The Biltz synthesis of phenytoin starts from:

a) Benzil + urea b) Benzophenone + urea c) Benzil + thiourea d) Benzaldehyde + urea

1 The key step in the Biltz synthesis is a:

a) Friedel–Crafts acylation b) 1,2-phenyl shift (benzilic-type rearrangement) c) Grignard addition d) Ullmann coupling

1 In phenytoin, the two phenyl groups are at:

a) N-1 and N-3 b) C-5 c) C-2 and C-4 d) N-1 and C-5

1 First-line drug for absence seizures:

a) Phenytoin b) Ethosuximide c) Carbamazepine d) Phenacemide

1 Carbamazepine differs from imipramine by:

a) An extra benzene ring b) C10=C11 double bond + N-5 carboxamide c) A nitro group d) A sulfur atom

1 In carbamazepine synthesis, the carboxamide is installed using:

a) Urea + heat b) Phosgene then ammonia c) Chloroacetyl chloride d) Dimethyl sulfate

1 Valproic acid's essential structural feature is:

a) Straight 8-carbon chain b) Alpha-branching with two propyl groups c) A phenyl ring d) A nitro group

1 Perampanel acts by blocking:

a) Na^+ channels b) AMPA receptors c) T-type Ca^{2+} channels d) K^+ channels

1 Retigabine's unique mechanism is:

a) GABA potentiation b) KCNQ K^+ channel opening c) NMDA blockade d) 5-HT2A blockade

1 The anticonvulsant pharmacophore consists of:

a) Hydrophobic aryl + H-bonding imide/amide + electron donor b) Two basic amines + one acid c) A steroid nucleus d) A phosphate + a sugar

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

Viva questions:

1 What is status epilepticus?

2 Why do hydantoins need C-5 disubstitution?

3 Name the intermediate with the saturated bridge in carbamazepine synthesis.

4 Which drug is a prodrug-like "deoxy" barbiturate converted to phenobarbital?

5 Why is trimethadione avoided in pregnancy?

6 How does gabapentin's actual target differ from what its structure suggests?

7 Which enantiomer of lacosamide is active?

8 What does "slow inactivation" of Na^+ channels mean for lacosamide (in one line)?

Application-based questions:

1 A 7-year-old has brief blank-stare episodes 20 times a day; EEG shows 3-Hz spike-and-wave. Choose between phenytoin and ethosuximide and justify with SAR. (Answer: ethosuximide — absence seizures need T-type Ca^{2+} blockade; its small ethyl+methyl head fits that lock, while phenytoin's bulky diphenyl head targets Na^+ channels for tonic-clonic seizures and can worsen absence.)

2 A student proposes synthesizing carbamazepine by adding the carboxamide before building the tricycle. Why is this poor planning? (Answer: phosgene/ammonia conditions and the $–CONH_2$ group would interfere with the dimerization, reductive cyclization, and dehydrogenation steps; the robust tricycle (iminostilbene) must be built first, then functionalized at N-5 last.)

3 A woman with epilepsy on valproate plans pregnancy. What are the pharmacist's two key counseling points? (Answer: valproate is teratogenic — urgent neurologist referral for a safer regimen before conception; ensure folate supplementation and contraception until the switch is complete. Never stop abruptly — withdrawal seizures endanger mother and fetus.)

4.19 References (Chapter 4)

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