BP402T · B.PHARM THEORY

BP402T Medicinal Chemistry

Unit V — Autacoids & Related Drugs

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B.Pharm Semester IV · Unit V · Theory Notes

Antihistamines · Proton Pump Inhibitors · NSAIDs & Antipyretics

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Chapter 7 — Antihistamines

7.1 Learning Objectives

After studying this chapter, you will be able to:

- Define autacoid, histamine, H1-receptor and H2-receptor in your own words.
- Describe how histamine is formed in the body and what it does at H1 and H2 receptors.
- Classify H1-antagonists into the seven chemical classes (aminoalkyl ethers, ethylenediamines, piperazines, propylamines, phenothiazines, tricyclics, second-generation agents).
- Describe the chemical structure (scaffold + key substituents) of every antihistamine in the syllabus.
- Compare first-generation and second-generation H1-antagonists with reasons from their chemistry.
- Write the complete synthesis of Diphenhydramine hydrochloride, Promethazine and Cimetidine with all reagents and intermediates.
- State the uses of each antihistamine and H2-antagonist.
- Explain the pharmacophore (common structural pattern) shared by H1-antagonists.

7.2 Definitions

Autacoid. An autacoid is a chemical messenger made inside the body that acts very close to where it is released (locally), not carried far by blood like a hormone. "Auto" = self, "acos" = remedy. Histamine, serotonin, prostaglandins and kinins are autacoids.

Histamine. Histamine is an autacoid formed from the amino acid histidine. It is stored in mast cells and basophils and released during allergy. It causes itching, redness, swelling, sneezing and stomach-acid secretion.

Histamine receptor. A protein "lock" on a cell surface into which histamine (the "key") fits. There are four types: H1, H2, H3, H4. H1 causes allergy symptoms; H2 causes gastric-acid secretion.

Antagonist. A drug that sits on a receptor and blocks the natural messenger from acting — like sitting on someone's chair so they cannot sit. Antihistamines are H1- or H2-antagonists.

Inverse agonist (note). Modern research shows most "antihistamines" do not just block histamine — they actively switch the H1-receptor OFF (they prefer the inactive shape of the receptor). For exams, "H1-antagonist" is the accepted term.

7.3 Terminology (word-by-word from zero)

Term	What it means in plain words
Mast cell	A tissue cell packed with granules of histamine; bursts open (degranulates) during allergy.
Degranulation	The bursting of mast-cell granules, releasing histamine into surrounding tissue.
Sedation	Drowsiness/sleepiness caused when a drug enters the brain. First-generation antihistamines sedate.
Anticholinergic effect	Dry mouth, blurred vision, constipation, urinary difficulty — caused when a drug also blocks muscarinic receptors.
Blood–brain barrier (BBB)	The tight wall of blood vessels protecting the brain; only small, fat-soluble (lipophilic) drugs cross it easily.
Lipophilic	"Fat-loving" — dissolves in fats; lipophilic drugs cross the BBB and cause sedation.
Salt form (hydrochloride)	The drug combined with HCl to make it water-soluble for tablets/syrups; e.g., diphenhydramine hydrochloride.

Term	What it means in plain words

Table continued

Prodrug	An inactive drug that the body converts into the active form.
Pharmacophore	The minimum structural pattern a molecule needs for activity — for H1 blockers: two aromatic rings + basic amine.
QT prolongation	Dangerous lengthening of the heart's electrical recovery time; caused by astemizole/terfenadine — a reason they were withdrawn.
Tachyphylaxis	Effect wearing off with repeated use (seen with H2-blockers after a few days).

7.4 Explanations

7.4.1 What is histamine and where does it come from? Technical concept: histamine is 2-(1H-imidazol-4-yl)ethanamine, formed by decarboxylation of histidine. Simple explanation: the body takes the amino acid histidine (from food protein) and removes its acid part (COOH) using an enzyme called histidine decarboxylase. What is left is histamine — a small molecule with an imidazole ring and an ethylamine side chain. Example: when pollen touches the nose of an allergic person, mast cells in the nose release stored histamine within seconds. Key takeaway: histidine (amino acid) − CO_2 = histamine (allergy messenger).

7.4.2 What does histamine do at H1 and H2 receptors? Technical concept: H1-receptors mediate the "triple response" and smooth-muscle contraction; H2-receptors stimulate parietal-cell acid secretion via cAMP. Simple explanation: H1 is the "allergy receptor" — when histamine touches it, blood vessels leak (redness, swelling), airways tighten (wheezing) and nerves itch (itching, sneezing). H2 is the "acid receptor" in the stomach — when histamine touches it, the stomach pours out hydrochloric acid. Example: a mosquito bite itches and swells because of H1; acidity after spicy food involves H2. Key takeaway: block H1 → stop allergy; block H2 → stop acidity.

7.4.3 The common pattern (pharmacophore) of H1-antihistamines. Technical concept: classical H1-antagonists share Ar–X–$(CH_2)_n$–$N(R)_2$, where two aryl groups are attached to a central carbon linked through O/N/C to a 2–3 carbon chain ending in a tertiary amine. Simple explanation: almost every first-generation antihistamine looks like this — TWO flat rings (phenyl/pyridyl) joined at one carbon, a short bridge, and a nitrogen with methyl groups (the basic amine). The two rings grip the receptor; the nitrogen (positively charged at body pH) forms the key ionic bond. Diagram (draw this): sketch two hexagons (aromatic rings) sharing one central carbon • — from that carbon draw a short chain –O–CH_2–CH_2– ending in –$N(CH_3)_2$. Label: "two aryl rings = grip; basic nitrogen = anchor." Key takeaway: two rings + basic amine = antihistamine skeleton. Spot this pattern and you can classify any H1 blocker.

7.5 Chemical Classification of H1-Antagonists

Class 1 — Aminoalkyl ethers (two rings joined through an –O– ether link): Diphenhydramine, Dimenhydrinate, Doxylamine, Clemastine, Diphenylpyraline. **Class 2 — Ethylenediamines** (two nitrogens on a 2-carbon chain, one carrying a 2-aminopyridine ring): Tripelennamine. **Class 3 — Piperazines (cyclizines)** (benzhydryl group on a piperazine ring): Chlorcyclizine, Meclizine, Buclizine. (Second-generation piperazines: Cetirizine, Levocetirizine.) **Class 4 — Propylamines (alkylamines)** (aryl + pyridyl on a 3-carbon chain with terminal amine): Chlorpheniramine, Triprolidine, Phenindamine. **Class 5 — Phenothiazines** (tricyclic phenothiazine with aminoalkyl side chain on ring nitrogen): Promethazine, Trimeprazine. **Class 6 — Tricyclics (dibenzocycloheptenes and related)** (three fused rings with piperidinylidene): Cyproheptadine, Azatadine, Astemizole, Loratadine. **Class 7 — Second-generation (non-sedating) agents**: Loratadine, Cetirizine, Levocetirizine, Astemizole (withdrawn). (Chemically they belong to the classes above, but are grouped by property: poor BBB crossing → no sedation.)

> Flowchart (draw this): Histamine released from mast cell → binds H1 → allergy symptoms; Antihistamine → occupies H1 → histamine cannot bind → symptoms blocked. (Same logic for H2 → acid.)

7.6 Mechanism of Action (in simple steps)

1. Allergen (pollen, dust) enters → mast cell degranulates → histamine released.
2. Histamine binds H1-receptors on vessels, airways, nerves → itching, swelling, bronchoconstriction.
3. Antihistamine reaches the same receptor first and occupies it (inverse agonist: locks receptor in OFF shape).
4. Histamine finds the seat taken → no signal → symptoms stop.
5. H2-blockers do the same at stomach parietal cells → less cAMP → less H+/K+ pump activity → less acid.

7.7 Infographic Concept Box

ANTIHISTAMINES AT A GLANCE
🧪 Core pattern: **2 aromatic rings + basic nitrogen** (tertiary amine)
🧠 1st generation: **cross BBB → sleepy** (diphenhydramine, promethazine, chlorpheniramine)
🚫 2nd generation: **cannot cross BBB → non-sleepy** (cetirizine, loratadine, levocetirizine)
🔬 7 chemical families: Ethers | Ethylenediamines | Piperazines | Propylamines | Phenothiazines | Tricyclics | 2nd-gen
⚗️ Star syntheses: **Diphenhydramine** (ether coupling) • **Promethazine** (phenothiazine N-alkylation) • **Cimetidine** (thioether + cyanoguanidine build-up)
🍽️ H2 blockers: **cimetidine, ranitidine, famotidine** → less stomach acid
⚠️ Withdrawn: **astemizole** (heart QT danger) • **ranitidine** (NDMA impurity)

7.8 Drug Tables — H1-Antagonists (drug → class → key structure → uses)

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Diphenhydramine hydrochloride*	Aminoalkyl ether	Benzhydryl (diphenylmethyl) ether of 2-dimethylaminoethanol: (C6H5)2CH–O–CH2CH2–N(CH3)2, HCl salt	Allergy, itching, motion sickness, insomnia (sedative), cough colds
Dimenhydrinate	Aminoalkyl ether (salt)	Diphenhydramine + 8-chlorotheophylline (salt pair)	Motion sickness, nausea/vomiting, vertigo
Doxylamine	Aminoalkyl ether	Like diphenhydramine but one phenyl replaced by 2-pyridyl + extra methyl on ether carbon	Allergy, insomnia; with pyridoxine for pregnancy nausea
Clemastine	Aminoalkyl ether	Chlorophenyl + phenyl ether linked to N-methylpyrrolidine ring	Allergic rhinitis, urticaria (less sedating 1st-gen)
Diphenylpyraline	Aminoalkyl ether	Diphenylmethyl ether of N-methyl-4-piperidinol	Allergy, itching
Tripelennamine	Ethylenediamine	N-benzyl-N′,N′-dimethyl-N-(2-pyridyl)ethylenediamine	Allergy, hay fever (also mild local anaesthetic)
Chlorcyclizine	Piperazine (cyclizine)	p-Chlorobenzhydryl on one piperazine N, methyl on the other	Allergy, motion sickness
Meclizine	Piperazine (cyclizine)	p-Chlorobenzhydryl-piperazine + 3-methylbenzyl on second N	Motion sickness, vertigo (Meniere's)
Buclizine	Piperazine (cyclizine)	p-Chlorobenzhydryl-piperazine + p-tert-butylbenzyl on second N	Motion sickness; appetite stimulant in children
Chlorpheniramine	Propylamine	3-(p-chlorophenyl)-3-(2-pyridyl)propyl-dimethylamine	Allergic rhinitis, common-cold combinations

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Table continued			
Triprolidine	Propylamine	p-Tolyl + 2-pyridyl on propenyl chain ending in pyrrolidine ring	Cold/allergy combos (with pseudoephedrine)
Phenindamine	Propylamine (tricyclic-like)	Indeno-pyridine tricycle with 9-phenyl and N-methyl	Allergy (stimulating — less sedation)
Promethazine*	Phenothiazine	Phenothiazine ring + 2-(dimethylamino)propyl chain on ring N, HCl salt	Allergy, motion sickness, antiemetic, pre-anaesthetic sedation
Trimeprazine (alimemazine)	Phenothiazine	Like promethazine + one extra methyl on the side chain	Allergy, pruritus, sedation
Cyproheptadine	Tricyclic	Dibenzocycloheptene with =C-piperidin-4-yl (N-methyl)	Allergy, appetite stimulant, migraine prophylaxis, serotonin syndrome
Azatadine	Tricyclic (aza-analog)	Cyproheptadine-like but one benzene replaced by pyridine ring	Allergy, rhinitis
Astemizole	Tricyclic/benzimidazole-piperidine	Benzimidazole linked to piperidine bearing p-fluorobenzyl and methoxyphenethyl groups	Was used for allergy — WITHDRAWN (QT prolongation, torsades)
Loratadine	Tricyclic (2nd gen)	Chloro-dibenzocycloheptapyridine with piperidinylidene + N-ethoxycarbonyl	Allergic rhinitis, urticaria — non-sedating
Cetirizine	Piperazine (2nd gen)	p-Chlorobenzhydryl-piperazine with –CH2COOH on second N (carboxylic acid)	Allergy, urticaria — non-sedating; active metabolite of hydroxyzine
Levocetirizine	Piperazine (2nd gen)	R-enantiomer of cetirizine (single active mirror image)	Same as cetirizine, lower dose
Cromolyn (sodium cromoglycate)	Chromone (mast-cell stabilizer — NOT an H1 blocker)	Bis-chromone-2-carboxylate dimer linked through glycerol	Asthma prophylaxis, allergic conjunctivitis/rhinitis — prevents histamine release

7.9 Drug Tables — H2-Antagonists

Drug	Key structure (scaffold + substituents)	Main uses
Cimetidine*	5-Methylimidazole–CH2–S–CH2CH2–NH–C(=N–CN)–NH–CH3 (imidazole + thioether + cyanoguanidine)	Peptic ulcer, GERD, acidity (first H2-blocker; now less used — drug interactions)
Ranitidine	Furan ring with –CH2N(CH3)2, linked –CH2–S–CH2CH2– to nitroethenediamine end	Peptic ulcer, GERD — largely withdrawn worldwide after NDMA impurity found
Famotidine	Thiazole ring with sulfamoyl-amidine, linked –CH2–S–CH2CH2– to sulfamoyl-guanidine end	Peptic ulcer, GERD, acidity (preferred now — fewer interactions)

7.10 Starred Syntheses (every step, reagent and intermediate preserved)

7.10.1 Synthesis of Diphenhydramine Hydrochloride Route: benzhydryl halide + 2-dimethylaminoethanol (Williamson ether synthesis).

- Step 1: Benzhydrol (diphenylmethanol, (C6H5)2CHOH) + thionyl chloride (SOCl2) → diphenylmethyl chloride (benzhydryl chloride, (C6H5)2CHCl) + SO2 + HCl.
- Step 2: 2-Dimethylaminoethanol (HO–CH2CH2–N(CH3)2) + sodium hydride (NaH) → sodium 2-dimethylaminoethoxide + H2.

- Step 3: Benzhydryl chloride + sodium 2-dimethylaminoethoxide → diphenhydramine free base ((C6H5)2CH–O–CH2CH2–N(CH3)2) + NaCl (ether formation).
- Step 4: Diphenhydramine base + dry hydrogen chloride (HCl) → diphenhydramine hydrochloride (water-soluble salt).

Key takeaway: make the ether link between the two-ring piece and the amino-alcohol piece, then form the HCl salt.

7.10.2 Synthesis of Promethazine Route: N-alkylation of phenothiazine.

- Step 1: Phenothiazine (tricyclic S,N ring) + sodamide (NaNH2) in dry toluene → N-sodium phenothiazine + NH3 (ring nitrogen deprotonated).
- Step 2: N-sodium phenothiazine + 1-chloro-2-(dimethylamino)propane (ClCH2–CH(CH3)–N(CH3)2) → promethazine free base (10-[2-(dimethylamino)propyl]phenothiazine) + NaCl (SN2 N-alkylation).
- Step 3: Promethazine base + HCl → promethazine hydrochloride.

Key takeaway: deprotonate the phenothiazine nitrogen, then attach the dimethylaminopropyl side chain.

7.10.3 Synthesis of Cimetidine Route: build the substituted imidazole, attach the thioether side chain, then build the cyanoguanidine end.

- Step 1: Ethyl 2-chloroacetoacetate (CH3CO–CHCl–COOC2H5) + formamide (HCONH2), heat → ethyl 4-methylimidazole-5-carboxylate (imidazole ring formed) + H2O + HCl.
- Step 2: Ethyl 4-methylimidazole-5-carboxylate + reducing agent (LiAlH4) → (5-methyl-1H-imidazol-4-yl)methanol (ester reduced to –CH2OH; tautomer of 4-methyl-5-hydroxymethyl).
- Step 3: (5-Methylimidazol-4-yl)methanol + thionyl chloride (SOCl2) → 4-(chloromethyl)-5-methylimidazole hydrochloride + SO2 + H2O.
- Step 4: 4-(Chloromethyl)-5-methylimidazole·HCl + cysteamine (HS–CH2CH2–NH2, 2-mercaptoethylamine) with base (NaOH) → 2-{[(5-methyl-1H-imidazol-4-yl)methyl]sulfanyl}ethanamine (thioether formed) + NaCl + H2O.
- Step 5: The thioether-amine + dimethyl N-cyanodithioimidocarbonate ((CH3S)2C=N–CN) → N-cyano-S-methyl-N′-{2-[(5-methylimidazol-4-yl)methylsulfanyl]ethyl}isothiourea + CH3SH (first methylthio displaced).
- Step 6: Isothiourea intermediate + methylamine (CH3NH2) → cimetidine + CH3SH (second methylthio displaced; cyanoguanidine completed).

Key takeaway: imidazole ring → thioether side chain → cyanoguanidine end group, built stepwise.

7.11 First-Generation vs Second-Generation H1-Antagonists

Feature	First generation (e.g., diphenhydramine, promethazine, chlorpheniramine)	Second generation (e.g., cetirizine, loratadine, levocetirizine)
BBB crossing	Yes — small, lipophilic → enter brain	No — polar/charged, P-gp efflux → stay outside brain
Sedation	Marked drowsiness	Minimal/non-sedating
Anticholinergic effects	Common (dry mouth, blurred vision)	Rare

Feature	First generation (e.g., diphenhydramine, promethazine, chlorpheniramine)	Second generation (e.g., cetirizine, loratadine, levocetirizine)
Table continued		
H1 selectivity	Low — also block muscarinic, α-adrenergic, serotonin receptors	High — selective for H1
Duration	Short (4–6 h), multiple doses/day	Long (12–24 h), once daily
Cardiac risk	Low	Astemizole/terfenadine withdrawn (QT prolongation)
Driving/machinery	Avoid	Usually safe

7.12 Examples and Analogies

- Example: a student with dust allergy takes cetirizine 10 mg once daily — sneezing stops without sleepiness, so she can attend lectures.
- Example: a bus passenger takes dimenhydrinate 30 minutes before a ghat-road journey — no vomiting.
- Analogy: the H1-receptor is a parking slot; histamine is a car that causes trouble when parked. First-gen antihistamines are big trucks that occupy the slot but also wrongly park in nearby slots (brain, muscarinic) — causing drowsiness and dry mouth. Second-gen are smart cars that park only in the right slot.
- Analogy: cimetidine vs famotidine — both lock the stomach's acid switch, but cimetidine also jams nearby switches (CYP enzymes → drug interactions), while famotidine is a cleaner key.

7.13 Pharmacy Relevance

- Counselling: advise patients on first-gen antihistamines not to drive or operate machinery; take at night if sedating.
- Salt forms matter: hydrochlorides/maleates improve solubility for syrups and fast-dissolving tablets (e.g., cetirizine syrup for children).
- Promethazine injection is a known vesicant — extravasation causes tissue necrosis; pharmacists must label and counsel.
- Cimetidine inhibits CYP1A2/2C19/3A4 — check interactions with warfarin, phenytoin, theophylline before dispensing.
- Levocetirizine shows chirality in action: single enantiomer → same effect at half the dose of racemic cetirizine.

7.14 India Context

- Cetirizine (Cetzine, Zyrtec) and levocetirizine are among India's highest-selling allergy tablets; chlorpheniramine is in countless cold combinations.
- Promethazine (Phenergan) syrup/tablet is widely used for allergy, motion sickness and as a sedative.
- Mefenamic-acid-free note: buclizine is used as a paediatric appetite stimulant in India.
- Ranitidine (Zinetac, Rantac) was one of India's top acidity drugs until 2019–2020, when NDMA (a probable carcinogen) impurity was detected; DCGI/industry withdrew most ranitidine products — a landmark quality-control lesson.
- Doxylamine + pyridoxine (Doxinate) is a first-line prescription for nausea in pregnancy in India.
- Cyproheptadine is (mis)used as an appetite/weight-gain stimulant — pharmacists should counsel against unsupervised use.

7.15 Key Points

1. H1-antagonists block allergy effects; H2-antagonists block gastric-acid secretion.
2. Common pharmacophore: two aromatic rings + basic tertiary amine.
3. Seven H1 chemical classes: aminoalkyl ethers, ethylenediamines, piperazines, propylamines, phenothiazines, tricyclics, second-generation.
4. First-gen = lipophilic → BBB → sedation + anticholinergic effects; second-gen = polar → non-sedating.
5. Starred syntheses: diphenhydramine (ether coupling), promethazine (phenothiazine N-alkylation), cimetidine (imidazole → thioether → cyanoguanidine).
6. Cromolyn is a mast-cell stabilizer, NOT an H1-blocker.
7. Astemizole withdrawn (QT prolongation); ranitidine withdrawn (NDMA impurity).

7.16 Common Confusions

- **Antihistamine vs mast-cell stabilizer:** cetirizine blocks the H1-receptor after histamine is released; cromolyn prevents histamine release itself. Different targets.
- **Dimenhydrinate vs diphenhydramine:** dimenhydrinate IS diphenhydramine + 8-chlorotheophylline salt — not a different drug core.
- **Cetirizine vs levocetirizine:** levocetirizine is the active R-enantiomer of cetirizine — half the dose, same effect.
- **Loratadine vs desloratadine:** desloratadine is loratadine's active metabolite (not in syllabus, but often confused).
- **H1 vs H2 blockers:** both are "antihistamines" chemically, but H1 = allergy, H2 = acidity — never interchange.

7.17 Common Mistakes

- Writing that second-generation antihistamines "do not cross the BBB at all" — they cross poorly; at high doses mild sedation is possible.
- Calling promethazine only an antihistamine — it is also antiemetic and sedative (phenothiazine family).
- Forgetting the HCl in "diphenhydramine hydrochloride" synthesis — the salt-forming step is part of the answer.
- Drawing cimetidine's guanidine without the cyano (–CN) group — the cyanoguanidine is essential (it replaced thiourea, which caused agranulocytosis in earlier drugs like metiamide).
- Confusing tripelennamine (ethylenediamine) with triprolidine (propylamine).

7.18 Mnemonics

- **H1 classes:** "Every Educated Pharmacist Prefers Tasty Sweets" — Ethers, Ethylenediamines, Piperazines, Propylamines, Phenothiazines, Tricyclics, Second-gen.
- **First-gen sedation:** "FIRST makes you doze; SECOND lets you drive."
- **Cimetidine parts:** "I Take Cyanide" — Imidazole + Thioether + Cyanoguanidine.
- **Astemizole warning:** "ASTEmizole — A STrange Effect (on heart)."

7.19 Exam Summary

Antihistamines block histamine at H1 (allergy) or H2 (acid) receptors. Classical H1-blockers share two aromatic rings joined to a basic tertiary amine and fall into seven chemical classes: aminoalkyl ethers (diphenhydramine, dimenhydrinate, doxylamine, clemastine, diphenylpyraline), ethylenediamines (tripelennamine), piperazines (chlorcyclizine, meclizine, buclizine), propylamines (chlorpheniramine, triprolidine, phenindamine), phenothiazines (promethazine, trimeprazine), tricyclics (cyproheptadine, azatadine, astemizole, loratadine) and second-generation agents (cetirizine, levocetirizine, loratadine). First-generation drugs are lipophilic, cross the BBB and cause sedation and anticholinergic effects; second-generation drugs are polar, non-sedating and longer-acting. Cromolyn is a mast-cell stabilizer, not an H1-blocker. H2-blockers (cimetidine, ranitidine, famotidine) reduce gastric acid; cimetidine's synthesis builds imidazole → thioether → cyanoguanidine. Astemizole (QT risk) and ranitidine (NDMA impurity) were withdrawn.

7.20 One-Minute Revision

- Histamine from histidine; H1 = allergy, H2 = acid.
- Pharmacophore: 2 aryl rings + basic N.
- 7 classes: ethers, ethylenediamines, piperazines, propylamines, phenothiazines, tricyclics, 2nd-gen.
- 1st gen sleepy (BBB); 2nd gen non-sleepy.
- Syntheses: diphenhydramine = ether coupling + HCl; promethazine = phenothiazine + ClCH2CH(CH3)NMe2; cimetidine = imidazole–CH2–S–CH2CH2–NH–C(=NCN)–NHMe.
- Cromolyn = mast-cell stabilizer. Astemizole withdrawn (heart). Ranitidine withdrawn (NDMA).

7.21 Exam Questions

Short-answer questions:

1. Define autacoid and histamine. Name the enzyme that forms histamine from histidine.
2. Draw the general pharmacophore of H1-antihistamines and label its parts.
3. Classify H1-antagonists chemically with one example each.
4. Why are second-generation antihistamines non-sedating? Explain using BBB and lipophilicity.
5. Write the structure of diphenhydramine and give its uses.
6. Distinguish between cetirizine and levocetirizine.
7. Why was astemizole withdrawn from the market?
8. Write the structure of cimetidine and label the cyanoguanidine group. Why was cyanoguanidine preferred over thiourea?
9. Give the uses of promethazine other than allergy.
10. What is cromolyn? Why is it not called an H1-antagonist?

Long-answer questions:

1. Classify H1-receptor antagonists based on chemical structure. Describe the structure (scaffold + key substituents) and uses of two drugs from any three classes.
2. Compare first-generation and second-generation H1-antagonists under: BBB penetration, sedation, anticholinergic effects, duration and selectivity. Give examples.
3. Write the complete synthesis of diphenhydramine hydrochloride with all reagents and intermediates. Give its mechanism of action and uses.
4. Describe the synthesis of cimetidine. Explain how H2-antagonists reduce gastric-acid secretion.

MCQs (answers at the end):

1. The common pharmacophore of classical H1-antihistamines is:
   a) One aromatic ring + carboxylic acid b) Two aromatic rings + basic tertiary amine c) Steroid nucleus + ketone d) Pyridine + sulfonamide
2. Diphenhydramine belongs to which chemical class?
   a) Ethylenediamine b) Aminoalkyl ether c) Piperazine d) Phenothiazine
3. Promethazine is a:
   a) Propylamine b) Tricyclic antidepressant c) Phenothiazine antihistamine d) Second-generation agent
4. Which drug is the R-enantiomer of cetirizine?
   a) Loratadine b) Levocetirizine c) Astemizole d) Azatadine
5. Cromolyn sodium acts by:
   a) Blocking H1-receptors b) Blocking H2-receptors c) Stabilizing mast cells d) Blocking muscarinic receptors
6. The cyanoguanidine group is present in:
   a) Ranitidine b) Famotidine c) Cimetidine d) Loratadine
7. Astemizole was withdrawn because of:
   a) Liver failure b) QT prolongation and arrhythmia c) Agranulocytosis d) NDMA impurity
8. Buclizine is used in children in India mainly as a:
   a) Antibiotic b) Appetite stimulant c) Antidiarrhoeal d) Deworming agent
   Answers: 1-b, 2-b, 3-c, 4-b, 5-c, 6-c, 7-b, 8-b

Viva questions:

1. What is the starting material for diphenhydramine synthesis? (Benzhydrol/diphenylmethanol.)
2. Which reagent converts benzhydrol to benzhydryl chloride? (Thionyl chloride.)
3. Name the base used to deprotonate phenothiazine in promethazine synthesis. (Sodamide, NaNH2.)
4. What is cysteamine? (2-Mercaptoethylamine, HS–CH2CH2–NH2.)
5. Why is cimetidine less preferred today? (CYP inhibition → drug interactions; tachyphylaxis.)
6. Which H2-blocker was withdrawn over NDMA? (Ranitidine.)
7. Give one structural difference between promethazine and trimeprazine. (Extra methyl on trimeprazine's side chain.)
8. Is loratadine sedating? Why not? (No — polar, poor BBB crossing, P-gp efflux.)

Application-based questions:

1. A truck driver with allergic rhinitis asks for an antihistamine. Which generation would you dispense and why? What counselling would you give?
2. A patient on warfarin is prescribed cimetidine for acidity. Identify the interaction risk and suggest a safer H2-blocker with reason.
3. A mother asks for an appetite stimulant for her 6-year-old. The doctor prescribed buclizine. Explain its dual identity (antihistamine + appetite stimulant) and counsel on safe use.

7.22 References

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Chapter 8 — Gastric Proton Pump Inhibitors

8.1 Learning Objectives

After studying this chapter, you will be able to:

- Define proton pump, prodrug and GERD in your own words.
- Classify proton pump inhibitors chemically and draw their common scaffold.
- Describe the structure (benzimidazole + substituted pyridine + sulfinyl bridge) of omeprazole, lansoprazole, rabeprazole and pantoprazole.
- Explain the acid-activation mechanism of PPIs in simple steps.
- State the SAR rules governing PPI activity.
- List the therapeutic uses of PPIs and their counselling points.

8.2 Definitions

Proton pump (H+/K+ ATPase). The enzyme in stomach parietal cells that pumps hydrogen ions (H+, acid) into the stomach in exchange for potassium ions — the final step of acid production. "ATPase" means it uses ATP energy.

Proton pump inhibitor (PPI). A drug that permanently switches off the proton pump, stopping acid secretion at its final step.

Prodrug. An inactive compound that the body (here, stomach acid itself) converts into the active drug. All PPIs are prodrugs activated by acid.

GERD. Gastro-oesophageal reflux disease — acid flowing back from stomach into the food pipe, causing heartburn.

Sulfoxide. A sulfur atom double-bonded to oxygen (–S(=O)–); the bridge linking the two rings in every PPI.

8.3 Terminology (word-by-word from zero)

Term	What it means in plain words
Parietal cell	Stomach-lining cell containing proton pumps; the PPI's target.
Secretory canaliculus	Tiny acidic channel (pH ≈ 1) inside the parietal cell where PPIs concentrate and activate.
Sulfenamide	The reactive ring-closed form of the PPI that permanently binds the pump.
Disulfide bond	A strong S–S link; the PPI forms this with a cysteine of the pump — irreversible.
Cysteine	An amino acid with a –SH group on the pump protein; the PPI's anchor point (Cys813).
pKa	A number telling how easily a molecule picks up a proton; PPI pyridine pKa (~4) controls how fast it activates.
Racemic / enantiomer	Racemic = 50:50 mixture of mirror images; enantiomer = one mirror image (esomeprazole = S-omeprazole).
H. pylori	Bacterium causing most ulcers; PPIs are part of its eradication therapy.

8.4 Explanations

8.4.1 Why is the proton pump the best target for acidity? Technical concept: histamine (H2), gastrin and acetylcholine all stimulate acid via different receptors, but all signals converge on the H+/K+ ATPase. Simple explanation: three different switches (H2, gastrin, muscarinic) can turn on acid, but there is only ONE tap at the end — the proton pump. H2-blockers close one switch; PPIs close the tap itself. That is why PPIs are stronger. Example: a patient still acidic on famotidine gets complete relief on omeprazole. Key takeaway: one final common tap → blocking it beats blocking one switch.

8.4.2 The common scaffold of PPIs. Technical concept: substituted benzimidazole linked via a sulfinylmethyl bridge (–CH2–S(=O)–) to a substituted pyridine. Simple explanation: every PPI has TWO ring systems — a benzimidazole (fused benzene + imidazole) on the left and a pyridine on the right — joined by a short bridge containing sulfur with an oxygen (–CH2–S(=O)–). Substituents on the two rings decide which drug it is. Diagram (draw this): draw benzimidazole ring (left) — CH2 — S(=O) — CH2 — pyridine ring (right). Label: "benzimidazole | sulfinylmethyl bridge | substituted pyridine". Mark variable positions: 5/6 on benzimidazole, 3/4/5 on pyridine. Key takeaway: benzimidazole + S(=O) bridge + pyridine = PPI skeleton.

8.5 Chemical Classification

Substituted benzimidazoles — all four syllabus PPIs belong to this single class:

- Omeprazole: 5-methoxy on benzimidazole; 4-methoxy-3,5-dimethyl on pyridine (racemic sulfoxide).
- Lansoprazole: unsubstituted benzimidazole; 3-methyl-4-(2,2,2-trifluoroethoxy) on pyridine.
- Rabeprazole: unsubstituted benzimidazole; 3-methyl-4-(3-methoxypropoxy) on pyridine (sodium salt used).
- Pantoprazole: 5-difluoromethoxy on benzimidazole; 3,4-dimethoxy on pyridine (sodium salt used).

8.6 Mechanism of Action — Acid Activation (step by step)

1. PPI swallowed as inactive prodrug (weak base, absorbed into blood).
2. Blood carries it to parietal cells; being a weak base, it concentrates ~1000-fold in the acidic secretory canaliculi (pH ~1).
3. Strong acid protonates the pyridine nitrogen → triggers rearrangement: sulfoxide → sulfenic acid → cyclic sulfenamide.
4. Sulfenamide (highly reactive) attacks the –SH of cysteine-813 on the H+/K+ ATPase → forms a disulfide (S–S) bond.
5. Pump permanently blocked (irreversible). Acid stops until new pumps are made (~24 hours) → once-daily dosing works.
   Flowchart (draw this): Inactive PPI → (acid pH<2) → sulfenamide → + pump–SH → pump–S–S–drug → acid OFF (irreversible).
   Key takeaway: acid itself switches the drug ON, exactly where acid is made — a self-targeting prodrug.

8.7 Infographic Concept Box

PPIs AT A GLANCE
🧪 Scaffold: **benzimidazole –CH2–S(=O)– pyridine** (substituted benzimidazoles)
⚗️ Prodrug trick: **acid turns it ON** inside the parietal cell canaliculus
🔒 Action: **sulfenamide + pump cysteine → disulfide bond → pump dead (irreversible)**
⏱️ Effect lasts ~24 h (new pumps must be made) → **once-daily dosing**
💊 Four drugs: **Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole**
🍽️ Take **30 min before breakfast** (pumps must be active to be blocked)

8.8 Drug Table (drug → class → key structure → uses)

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Omeprazole	Substituted benzimidazole	5-Methoxybenzimidazole + (4-methoxy-3,5-dimethylpyridin-2-yl)methyl sulfoxide; racemic	GERD, peptic ulcer, Zollinger–Ellison syndrome, H. pylori combos, NSAID-ulcer prevention
Lansoprazole	Substituted benzimidazole	Benzimidazole + [3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl sulfoxide	GERD, ulcer, H. pylori eradication
Rabeprazole	Substituted benzimidazole	Benzimidazole + [3-methyl-4-(3-methoxypropoxy)pyridin-2-yl]methyl sulfoxide (Na salt)	GERD, ulcer; fastest activation
Pantoprazole	Substituted benzimidazole	5-(Difluoromethoxy)benzimidazole + [(3,4-dimethoxypyridin-2-yl)methyl] sulfoxide (Na salt)	GERD, ulcer, IV form for bleeding ulcers/Zollinger–Ellison

8.9 SAR Highlights (rule table)

#	SAR rule	Explanation in simple words
1	The sulfoxide (–S(=O)–) bridge is essential	Sulfide (–S–) and sulfone (–SO2–) analogs are inactive — the sulfoxide is needed for acid rearrangement.
2	Pyridine nitrogen must be basic (pKa ~4)	It picks up a proton in acid → concentrates the drug in canaliculi and triggers activation. Non-basic analogs fail.
3	Higher pyridine pKa → faster activation	Rabeprazole (pKa ~5.0, most basic) activates fastest; pantoprazole (pKa ~3.9) slowest. Electron-donating groups raise pKa.
4	Benzimidazole 5/6-substituents tune stability and metabolism	5-OCH3 (omeprazole), 5-OCHF2 (pantoprazole) affect chemical stability and CYP2C19 metabolism; difluoromethoxy resists metabolism.
5	Benzimidazole N–H is required	Needed for the acid-catalyzed rearrangement to sulfenamide; N-substituted analogs are inactive.
6	Chiral sulfoxide → single enantiomers improve consistency	S-omeprazole (esomeprazole) and R-lansoprazole (dexlansoprazole) avoid variable CYP2C19 metabolism of the other enantiomer.
7	Pyridine 4-substituent controls lipophilicity/distribution	Trifluoroethoxy (lansoprazole), methoxypropoxy (rabeprazole) fine-tune tissue penetration and half-life.

8.10 Examples and Analogies

- Example: a GERD patient takes pantoprazole 40 mg 30 minutes before breakfast — heartburn gone all day with one tablet.
- Example: H. pylori eradication = PPI + clarithromycin + amoxicillin for 14 days (triple therapy); the PPI raises stomach pH so antibiotics work.
- Analogy: the PPI is a "sleeper agent" — harmless in blood, but the enemy's own acid wakes it up inside the acid factory, where it welds the machinery shut (disulfide bond).
- Analogy: H2-blocker vs PPI — turning off one light switch vs cutting the main power line.

8.11 Pharmacy Relevance

- Counselling: take 30–60 minutes BEFORE food (pumps must be actively secreting to be trapped); swallow whole — do not crush enteric-coated tablets.
- Drug interactions: omeprazole inhibits CYP2C19 → reduces clopidogrel activation (avoid combo; prefer pantoprazole/rabeprazole).

- Long-term use: vitamin B12, magnesium and calcium monitoring; rebound acidity on sudden stop — taper if used for months.
- IV pantoprazole is used in hospitals for upper-GI bleeding — a critical-care drug pharmacists prepare.

8.12 India Context

- Omeprazole (Omez), pantoprazole (Pan), rabeprazole (Razo) and lansoprazole (Lan) are among India's top-selling acidity drugs — available OTC in many pharmacies, so counselling on correct timing matters.
- Fixed-dose combinations with domperidone (e.g., Pan-D, Omez-D) are hugely popular in India for acidity with nausea/bloating.
- Self-medication is rampant — pharmacists should warn against years-long unsupervised use (B12 deficiency, bone effects).

8.13 Key Points

1. All PPIs are substituted benzimidazoles: benzimidazole–CH2–S(=O)–pyridine.
2. They are prodrugs activated by acid in parietal-cell canaliculi.
3. Active sulfenamide forms an irreversible disulfide bond with Cys813 of H+/K+ ATPase.
4. Effect lasts ~24 h → once-daily dosing, taken before breakfast.
5. SAR: sulfoxide essential; basic pyridine needed; pyridine pKa sets activation speed; benzimidazole substituents tune metabolism.
6. Uses: GERD, peptic ulcer, Zollinger–Ellison, H. pylori triple therapy, NSAID-ulcer prophylaxis.

8.14 Common Confusions

- **PPI vs H2-blocker:** both reduce acid, but PPIs block the final pump irreversibly (stronger, longer); H2-blockers block one receptor reversibly.
- **Prodrug confusion:** the PPI tablet is INACTIVE — stomach acid activates it. Antacids (e.g., Gelusil) are not prodrugs; they neutralize acid directly.
- **Omeprazole vs esomeprazole:** esomeprazole is the S-enantiomer of omeprazole — same scaffold, more predictable metabolism.
- **Why take before food?** PPIs only trap ACTIVE pumps; food stimulates pumps, so the drug must be waiting beforehand.

8.15 Common Mistakes

- Saying PPIs "neutralize acid" — they STOP acid production; antacids neutralize.
- Claiming the effect is reversible — the disulfide bond is irreversible; recovery needs new pump synthesis.
- Forgetting the sulfoxide oxygen in the structure — sulfide/sulfone analogs are inactive.
- Advising to take PPIs after meals — wrong; before breakfast is correct.

8.16 Mnemonics

- **Four PPIs:** "Only Lazy Rabbits Panic" — Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole.
- **Scaffold:** "Benzi–Sulfur–Pyri" (benzimidazole + sulfinyl + pyridine).
- **Activation:** "Acid Awakens, Sulfenamide Seals" (acid → sulfenamide → disulfide seal).

8.17 Exam Summary

Gastric proton pump inhibitors are substituted benzimidazoles sharing a benzimidazole–CH2–S(=O)–pyridine scaffold. They are prodrugs: as weak bases they concentrate in the acidic parietal-cell canaliculi, where acid converts them to a reactive sulfenamide that forms an irreversible disulfide bond with cysteine-813 of the H+/K+ ATPase, shutting off acid secretion for ~24 hours. Omeprazole (5-methoxybenzimidazole; 4-methoxy-3,5-dimethylpyridine), lansoprazole (trifluoroethoxy pyridine), rabeprazole (methoxypropoxy pyridine; fastest activation) and pantoprazole (difluoromethoxy benzimidazole) differ only in ring substituents. SAR: the sulfoxide bridge and basic pyridine nitrogen are essential; pyridine pKa controls activation speed; benzimidazole substituents tune stability/metabolism. Used in GERD, peptic ulcer, Zollinger–Ellison syndrome, H. pylori eradication and NSAID-ulcer prophylaxis; taken 30 minutes before breakfast.

8.18 One-Minute Revision

- Class: substituted benzimidazoles; scaffold benzimidazole–CH2–S(=O)–pyridine.
- Prodrug → acid activates → sulfenamide → disulfide with pump Cys → irreversible block.
- Once daily, before breakfast; effect ~24 h.
- SAR: sulfoxide essential; basic pyridine; pKa sets speed (rabeprazole fastest).
- 4 drugs: omeprazole, lansoprazole, rabeprazole, pantoprazole.
- Uses: GERD, ulcer, Zollinger–Ellison, H. pylori, NSAID-ulcer prevention.

8.19 Exam Questions

Short-answer questions:

1. Draw the general scaffold of proton pump inhibitors and label the three parts.
2. Why are PPIs called prodrugs? What activates them and where?
3. Write the structure of omeprazole highlighting the sulfinyl bridge.
4. How does lansoprazole differ structurally from omeprazole?
5. Why are PPIs dosed once daily? Explain using pump turnover.
6. Why should PPIs be taken before food?
7. State two SAR rules for PPIs.
8. Give the uses of pantoprazole, including its IV use.

Long-answer questions:

1. Classify PPIs chemically. Describe the structure of omeprazole, lansoprazole, rabeprazole and pantoprazole, pointing out the substituent differences.
2. Explain the mechanism of action of proton pump inhibitors with a neat labelled flowchart. Add SAR highlights.
3. Compare PPIs with H2-receptor antagonists under: site of action, reversibility, potency and dosing.

MCQs (answers at the end):

1. The chemical class of omeprazole is:
   a) Imidazoline b) Substituted benzimidazole c) Quinoline d) Thiazole
2. The bridge linking the two rings in PPIs is:
   a) –CH2–S(=O)– b) –CH2–CH2– c) –O– d) –NH–CO–
3. PPIs are activated by:
   a) Liver enzymes b) Stomach acid c) Intestinal bacteria d) Blood esterases

1. The PPI binds which amino acid of the H+/K+ ATPase?
   a) Serine b) Cysteine c) Lysine d) Aspartate
2. The nature of PPI binding to the pump is:
   a) Reversible competitive b) Irreversible covalent (disulfide) c) Allosteric d) Ionic only
3. Which PPI activates fastest?
   a) Pantoprazole b) Omeprazole c) Rabeprazole d) Lansoprazole
4. Esomeprazole is:
   a) A different scaffold b) The S-enantiomer of omeprazole c) A prodrug of pantoprazole d) An H2-blocker
5. Omeprazole + clopidogrel interaction occurs because omeprazole:
   a) Induces CYP2C19 b) Inhibits CYP2C19 c) Chelates clopidogrel d) Increases gastric pH only
   Answers: 1-b, 2-a, 3-b, 4-b, 5-b, 6-c, 7-b, 8-b

Viva questions:

1. Expand GERD. (Gastro-oesophageal reflux disease.)
2. What is the pH inside the parietal-cell canaliculus? (~1.)
3. Name the reactive species formed from PPIs in acid. (Sulfenamide.)
4. Which cysteine does the PPI bind? (Cys813.)
5. Why is the sulfoxide essential? (Needed for acid rearrangement; sulfide/sulfone inactive.)
6. Which substituent makes pantoprazole's benzimidazole unique? (5-Difluoromethoxy.)
7. Name the IV PPI used in GI bleeding. (Pantoprazole.)

Application-based questions:

1. A patient on clopidogrel after a stent needs a PPI for acidity. Which PPI would you recommend avoiding, and which is safer? Justify using CYP2C19.
2. A patient takes omeprazole after dinner and complains it "doesn't work." Identify the counselling error and correct it.
3. Design H. pylori triple therapy for a peptic-ulcer patient and explain the PPI's role in it.

8.20 References

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Chapter 9 — NSAIDs and Antipyretics

9.1 Learning Objectives

After studying this chapter, you will be able to:

- Define NSAID, inflammation, prostaglandin, COX-1 and COX-2 in your own words.
- Describe the arachidonic-acid cascade and the role of cyclooxygenase.
- Classify NSAIDs into the seven chemical classes with examples.
- Describe the structure (scaffold + key substituents) of every NSAID in the syllabus.
- Write the complete synthesis of Mefenamic acid and Ibuprofen with all reagents and intermediates.
- State the SAR rules of representative agents class by class.
- Explain how aspirin differs from other NSAIDs (irreversible acetylation) and how selective COX-2 inhibitors work.
- List uses, India-context brands and counselling points for NSAIDs.

9.2 Definitions

NSAID. Non-Steroidal Anti-Inflammatory Drug — a pain, fever and inflammation reliever that is NOT a steroid (unlike cortisone). Examples: aspirin, ibuprofen, diclofenac.

Inflammation. The body's redness–heat–swelling–pain response to injury or infection, driven largely by prostaglandins.

Prostaglandin. A lipid messenger made from arachidonic acid that causes pain, fever and inflammation (PGE2 is the main one).

Cyclooxygenase (COX). The enzyme that converts arachidonic acid into prostaglandins. Two forms: COX-1 (protects stomach, helps platelets — always present) and COX-2 (made at injury sites — causes pain/inflammation).

Antipyretic. A fever-reducing drug (e.g., paracetamol). **Analgesic** = pain reliever.

9.3 Terminology (word-by-word from zero)

Term	What it means in plain words
Arachidonic acid	A fatty acid stored in cell membranes; the raw material for prostaglandins.
Phospholipase A2	The enzyme that cuts arachidonic acid out of the membrane — the cascade's first step.
Constitutive vs inducible	Constitutive = always present (COX-1); inducible = made on demand at injury (COX-2).
Ulcerogenic	Tending to cause stomach ulcers — the main side effect of non-selective NSAIDs.
Chiral centre / enantiomer	A carbon with four different groups; mirror-image forms (R/S). For ibuprofen, S is active.
Prodrug (NSAID)	Inactive form converted in the body — e.g., sulindac (sulfoxide → active sulfide).
Enteric coating	Tablet coating that survives stomach acid and dissolves in intestine — protects the stomach.
Reye's syndrome	Rare, dangerous brain–liver illness — aspirin is avoided in children with viral fever because of it.

9.4 Explanations

9.4.1 The arachidonic-acid cascade (the story of pain). Technical concept: membrane phospholipids → (phospholipase A2) → arachidonic acid → (COX-1/COX-2) → PGG2 → PGH2 → prostaglandins (PGE2, PGI2), thromboxane A2. Simple explanation: when tissue is injured, an enzyme (phospholipase A2) cuts a fatty acid — arachidonic acid — out of the cell membrane. Then COX enzymes convert it into prostaglandins, the chemicals that cause pain, swelling and fever. NSAIDs block COX, so prostaglandins are never made. Flowchart (draw this): Cell membrane → [phospholipase A2] → Arachidonic acid → [COX-1 / COX-2] → PGH2 → PGE2 (pain, fever, inflammation) + PGI2 (protects stomach) + TXA2 (platelet clotting). NSAIDs block the COX step ✖. Example: a sprained ankle swells because COX-2 at the injury makes PGE2; ibuprofen blocks COX-2 → swelling and pain fall. Key takeaway: no COX → no prostaglandins → no pain/fever/inflammation.

9.4.2 COX-1 vs COX-2 — why selectivity matters. Technical concept: COX-1 is constitutive (gastric mucosal protection via PGE2/PGI2, platelet TXA2, kidney function); COX-2 is induced by inflammatory stimuli. Non-selective NSAIDs inhibit both → GI ulcers and bleeding; COX-2-selective drugs spare COX-1 → fewer GI effects but possible cardiovascular risk. Simple explanation: COX-1 is the "good housekeeper" — it protects your stomach lining and helps blood clot. COX-2 is the "fire alarm" — it appears at injuries and causes pain. Ordinary NSAIDs silence both: pain goes, but the stomach loses protection (ulcers). COX-2-selective drugs (celecoxib, etoricoxib) silence only the alarm. Example: an arthritis patient with a past ulcer is given celecoxib instead of diclofenac. Key takeaway: COX-1 = protection, COX-2 = inflammation; selective drugs protect the stomach but need heart-risk caution.

9.4.3 How aspirin is special. Technical concept: aspirin irreversibly acetylates Ser530 of COX-1 (transfers its acetyl group), permanently disabling the enzyme; platelets cannot make new COX → low-dose aspirin is a lasting antiplatelet. Simple explanation: most NSAIDs sit on COX temporarily and leave. Aspirin permanently "tattoos" the enzyme by sticking its acetyl group onto it — the enzyme is dead forever. Since platelets cannot make new enzyme, even a tiny daily dose (75 mg) keeps blood thin. Diagram (draw this): COX enzyme with serine –OH → aspirin donates $CH_3CO–$ → serine–O–$COCH_3$ (acetylated, dead enzyme) + salicylic acid released. Key takeaway: aspirin = irreversible; all other NSAIDs in this chapter = reversible.

9.5 Chemical Classification of NSAIDs

Class 1 — Salicylates (salicylic-acid based): Sodium salicylate, Aspirin (acetylsalicylic acid), Diflunisal. **Class 2 — Anthranilates / Fenamates** (N-phenylanthranilic acid): Mefenamic acid, Niflumic acid, Meclofenamate (meclofenamic acid). **Class 3 — Indole/Indene acetic acids** (indole or indene + CH_2COOH): Indomethacin, Sulindac, Tolmetin, Zomepirac. **Class 4 — Arylacetic / Arylpropionic acids** (aryl + CH_2COOH or aryl + $CH(CH_3)COOH$): Diclofenac, Ketorolac, Ibuprofen, Naproxen. **Class 5 — Oxicams** (enolic-acid benzothiazines): Piroxicam. **Class 6 — Pyrazolones** (pyrazole/pyrazolidine-dione): Antipyrine, Phenylbutazone. **Class 7 — Para-aminophenol derivatives** (acetanilide based; analgesic–antipyretic, weak anti-inflammatory): Phenacetin, Acetaminophen (paracetamol). **Class 8 — Selective COX-2 inhibitors** (coxibs; vicinal diaryl heterocycles): Celecoxib, Etoricoxib.

9.6 Infographic Concept Box

NSAIDs AT A GLANCE
🔥 Cascade: **membrane → arachidonic acid → COX → prostaglandins** (pain/fever/swelling)
💊 Action: **block COX → no prostaglandins**
🧪 8 classes: **Salicylates | Fenamates | Indole-acetic acids | Aryl-acetic/propionic acids | Oxicams | Pyrazolones | Para-aminophenols | COX-2 selective (coxibs)**
⭐ Aspirin = **irreversible** (acetylates COX); rest = reversible
⚗️ Star syntheses: **Mefenamic acid** (Ullmann coupling) • **Ibuprofen** (Boots 6-step)
⚠️ Stomach rule: **COX-1 blocked → ulcers**; coxibs spare the stomach, watch the heart
🧒 Aspirin **avoided in children** (Reye's syndrome) — paracetamol instead

9.7 Drug Tables (drug → class → key structure → uses)

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Sodium salicylate	Salicylate	Sodium salt of 2-hydroxybenzoic acid (o-hydroxybenzoate)	Rheumatic fever, pain/fever (older drug)
Aspirin (acetylsalicylic acid)	Salicylate	2-Acetoxybenzoic acid: salicylic acid with –OCOCH3 at ortho position	Pain, fever, inflammation; LOW dose (75–150 mg): antiplatelet — heart attack/stroke prevention
Diflunisal	Salicylate	5-(2,4-Difluorophenyl)salicylic acid: biphenyl with F at 2′,4′	Pain, osteoarthritis (longer-acting salicylate; no acetylation)
Mefenamic acid*	Fenamate (anthranilate)	N-(2,3-Xylyl)anthranilic acid: benzoic acid –NH– (2,3-dimethylphenyl)	Pain, dysmenorrhoea (Meftal — very popular in India)
Niflumic acid	Fenamate	2-(3-Trifluoromethylanilino)nicotinic acid: pyridine ring + 3-CF3 phenyl	Inflammation, pain (topical/systemic)
Meclofenamate	Fenamate	N-(2,6-Dichloro-3-methylphenyl)anthranilic acid	Arthritis, pain
Indomethacin	Indole acetic acid	1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid	Rheumatoid arthritis, gout, ankylosing spondylitis; closes PDA in newborns
Sulindac	Indene acetic acid	Indene with p-(methylsulfinyl)benzylidene at 1-position + CH2COOH at 3 (sulfoxide prodrug → active sulfide)	Arthritis (prodrug — gentler on stomach)
Tolmetin	Pyrrole acetic acid	1-Methyl-5-(p-toluoyl)pyrrole-2-acetic acid	Rheumatoid/osteoarthritis
Zomepirac	Pyrrole acetic acid	5-(p-Chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid	Was used for pain — WITHDRAWN (anaphylaxis risk)
Diclofenac	Aryl-acetic acid	2-(2,6-Dichloroanilino)phenylacetic acid	Pain, arthritis, post-operative pain (Voveran — India's top NSAID)
Ketorolac	Aryl-acetic acid (pyrrolizine)	5-Benzoyl-2,3-dihydro-pyrrolizine-1-carboxylic acid	Moderate–severe short-term pain (injectable/oral; ≤5 days — GI/bleed risk)
Ibuprofen*	Aryl-propionic acid	2-(4-Isobutylphenyl)propanoic acid: phenyl + p-isobutyl + –CH(CH3)COOH (racemic; S active)	Pain, fever, inflammation, dysmenorrhoea (Brufen)
Naproxen	Aryl-propionic acid	(S)-2-(6-Methoxy-2-naphthyl)propanoic acid: naphthalene + 6-OCH3	Arthritis, gout, dysmenorrhoea (long-acting)
Piroxicam	Oxicam	4-Hydroxy-2-methyl-N-(pyridin-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (enolic acid)	Rheumatoid/osteoarthritis — once daily (t½ ~50 h)
Phenacetin	Para-aminophenol	p-Ethoxyacetanilide: CH3CONH–C6H4–OCH2CH3 (para)	Was an antipyretic — WITHDRAWN (kidney damage, carcinogenic)

Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
Table continued			
Acetaminophen (paracetamol)	Para-aminophenol	p-Hydroxyacetanilide: CH3CONH–C6H4–OH (para); active metabolite of phenacetin	Fever, mild–moderate pain (Crocin/Calpol); weak anti-inflammatory
Antipyrine (phenazone)	Pyrazolone	1-Phenyl-2,3-dimethyl-5-pyrazolone	Analgesic–antipyretic (older; ear-drop combos)
Phenylbutazone	Pyrazolone	4-Butyl-1,2-diphenylpyrazolidine-3,5-dione	Severe arthritis — RESTRICTED (agranulocytosis, GI bleed)
Celecoxib	Selective COX-2 inhibitor	4-[5-(p-Tolyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide: diaryl-pyrazole + p-SO2NH2	Arthritis with low GI risk; sulfonamide — caution in sulfa allergy
Etoricoxib	Selective COX-2 inhibitor	5-Chloro-3-(4-methanesulfonylphenyl)-6′-methyl-2,3′-bipyridine: bipyridine + p-SO2CH3	Arthritis, gout, dental pain (once daily)

9.8 Starred Syntheses (every step, reagent and intermediate preserved)

9.8.1 Synthesis of Mefenamic Acid Route: Ullmann–Goldberg condensation (copper-catalyzed N-arylation).

- Step 1: o-Chlorobenzoic acid (2-chlorobenzoic acid) + 2,3-dimethylaniline (2,3-xylidine), anhydrous potassium carbonate (K2CO3), copper powder/copper(I) catalyst, heat (~150–200 °C) → N-(2,3-xylyl)anthranilic acid = mefenamic acid [2-(2,3-dimethylphenylamino)benzoic acid] + KCl + H2O + CO2 (Ullmann condensation; aryl chloride displaced by the aniline nitrogen).

Key takeaway: one copper-catalyzed coupling joins o-chlorobenzoic acid to 2,3-xylidine — the fenamate skeleton in a single step.

9.8.2 Synthesis of Ibuprofen (Boots 6-step route) Route: Friedel–Crafts acylation → Darzens glycidic ester → hydrolysis/decarboxylation → oxime → nitrile → hydrolysis.

- Step 1: Isobutylbenzene + acetyl chloride (CH3COCl), anhydrous aluminium chloride (AlCl3), Friedel–Crafts acylation → p-isobutylacetophenone (4′-isobutylacetophenone) + HCl.
- Step 2: p-Isobutylacetophenone + ethyl chloroacetate (ClCH2COOC2H5), sodium ethoxide (NaOC2H5), Darzens condensation → ethyl 3-(4-isobutylphenyl)-3-methyloxirane-2-carboxylate (α,β-epoxy/glycidic ester) + NaCl.
- Step 3: Epoxy ester + aqueous acid (H3O+), heat → hydrolysis and decarboxylation → 2-(4-isobutylphenyl)propanal (propionaldehyde) + CO2 + ethanol.
- Step 4: Aldehyde + hydroxylamine (NH2OH) → oxime [2-(4-isobutylphenyl)propanal oxime] + H2O.
- Step 5: Oxime + acetic anhydride ((CH3CO)2O), heat → dehydration → 2-(4-isobutylphenyl)propionitrile + acetic acid.
- Step 6: Nitrile + concentrated HCl, aqueous, heat → acid hydrolysis → ibuprofen [2-(4-isobutylphenyl)propanoic acid] + NH4Cl.

Key takeaway: build the ketone, extend by two carbons via the Darzens epoxide, then convert –CHO → –CN → –COOH. *Note (green upgrade): the modern BHC 3-step route (isobutylbenzene → Friedel–Crafts acylation with acetic anhydride/HF → catalytic hydrogenation to the alcohol → palladium-catalyzed carbonylation) makes the same drug with ~99% atom economy — a landmark green-chemistry example.*

9.9 SAR of Representative Agents by Class (rule tables)

Class 1 — Salicylates (representative: aspirin)

#	Rule
1	Free –COOH (or hydrolyzable ester) is needed for ionic binding to Arg120 of COX.
2	Ortho-acetoxy (–OCOCH3) is essential for aspirin's irreversible action — it acetylates Ser530; salicylic acid alone is reversible only.
3	The aromatic ring is required; 5-position substitution is tolerated (diflunisal: 5-(2,4-difluorophenyl) → longer half-life, no GI acetylation damage).
4	Esterifying the –COOH (e.g., methyl salicylate) gives topical-only agents — hydrolyzed too fast systemically.

Class 2 — Fenamates (representative: mefenamic acid)

#	Rule
1	N-Phenylanthranilic acid scaffold is essential — benzoic acid –NH– aryl.
2	Ortho substitution on the N-phenyl ring increases activity (forces a twisted, active conformation).
3	2,3-Dimethyl (mefenamic), 2,6-dichloro-3-methyl (meclofenamate), or nicotinic-acid + 3-CF3 (niflumic) substitution enhances potency.
4	Free –COOH is essential; esterification kills activity.

Class 3 — Indole/indene acetic acids (representative: indomethacin)

#	Rule
1	Acetic-acid side chain (–CH2COOH) at indole 3-position is essential.
2	N-Aroyl group is essential; p-chlorobenzoyl is optimal (electron-withdrawing para substituent).
3	2-Methyl group is essential — fills a hydrophobic pocket and blocks metabolism.
4	5-Methoxy enhances anti-inflammatory activity.
5	Sulindac is a sulfoxide prodrug: reduced in vivo to the active sulfide; the sulfone metabolite is inactive.

Class 4 — Aryl-acetic/aryl-propionic acids (representative: ibuprofen, diclofenac)

#	Rule
1	The α-methyl group is essential — propionic acids out-perform acetic acids and resist β-oxidation.
2	The S-(+) enantiomer is the active form (ibuprofen is racemic; the R form converts to S in vivo; naproxen is used as pure S).
3	A para lipophilic substituent (isobutyl in ibuprofen; naphthyl in naproxen) fits the COX hydrophobic channel.
4	Free –COOH is needed for the Arg120 ionic bond.
5	Diclofenac rule: 2,6-dichloro substitution on the N-phenyl ring (twisted conformation) gives high potency.

Class 5 — Oxicams (representative: piroxicam)

#	Rule
1	The enolic 4-OH (acidic, pKa ~6) is essential — the "enolic acid" pharmacophore; exists as a zwitterion.
2	The 1,2-benzothiazine 1,1-dioxide core is required.

#	Rule

Table continued

3	The N-(2-pyridyl) carboxamide is essential for activity.
4	Very long half-life (~50 h) is built into the scaffold → once-daily dosing.

Class 6 — Pyrazolones (representative: phenylbutazone, antipyrine)

#	Rule
1	The pyrazolidine-3,5-dione core is essential.
2	A 4-position substituent (n-butyl in phenylbutazone) is essential for anti-inflammatory activity.
3	N1,N2-diphenyl substitution is needed; the p-hydroxy metabolite (oxyphenbutazone) is also active.
4	Antipyrine (1-phenyl-2,3-dimethyl-5-pyrazolone) keeps analgesic–antipyretic activity with weak anti-inflammatory action.

Class 7 — Para-aminophenols (representative: acetaminophen)

#	Rule
1	p-Hydroxyacetanilide scaffold: para –NHCOCH3 and –OH are both needed.
2	Phenacetin (p-ethoxy) is metabolized to acetaminophen (p-hydroxy) — the active species; phenacetin itself caused renal damage → withdrawn.
3	Weak COX inhibition in inflamed tissue → good antipyretic/analgesic but poor anti-inflammatory.
4	Overdose saturates safe metabolism → toxic NAPQI metabolite → liver necrosis (antidote: N-acetylcysteine).

Class 8 — Selective COX-2 inhibitors (representative: celecoxib)

#	Rule
1	Vicinal (adjacent) diaryl groups on a central heterocycle (pyrazole in celecoxib; pyridine in etoricoxib) are essential — the cis-diaryl pharmacophore.
2	One phenyl must carry a para-sulfonamide (–SO2NH2, celecoxib) or methylsulfone (–SO2CH3, etoricoxib) — this fits the extra side pocket of COX-2 (Val523; COX-1 has bulkier Ile523).
3	A 3-trifluoromethyl on the pyrazole enhances COX-2 selectivity and potency.
4	Sulfonamide → avoid in sulfa-allergic patients; class carries cardiovascular-risk caution (rofecoxib withdrawn for heart attacks).

9.10 Examples and Analogies

- Example: a rheumatoid-arthritis patient takes diclofenac 50 mg twice daily — joint pain and morning stiffness fall within days.
- Example: a child with 102 °F fever gets paracetamol syrup 15 mg/kg — fever falls in 30–45 minutes.
- Example: after a tooth extraction, ketorolac injection controls severe pain for a few days (never beyond 5 days).
- Analogy: COX-1 and COX-2 are twin factories. COX-1 makes "protective bricks" for the stomach; COX-2 makes "fire alarms" (pain). Non-selective NSAIDs shut both factories — no alarm, but the stomach wall crumbles. Coxibs shut only the alarm factory.
- Analogy: aspirin vs other NSAIDs — a padlock (reversible NSAIDs: lock and unlock) vs welding the door shut (aspirin: acetylation is permanent).

9.11 Pharmacy Relevance

- Counselling: take NSAIDs after food or with milk; report black stools, vomiting blood, or severe stomach pain (GI bleed signs).
- Dose logic: ibuprofen is racemic but only S works — the body converts R→S, so the racemate is still effective.
- Paracetamol overdose is the #1 cause of acute liver failure — counsel on maximum 4 g/day adult dose and hidden paracetamol in cold combos.
- Aspirin + children with viral fever = Reye's risk — always recommend paracetamol instead.
- Ketorolac: maximum 5 days total therapy — flag longer prescriptions.
- Phenylbutazone is restricted (agranulocytosis) — dispense only on prescription with blood-count monitoring advice.

9.12 India Context

- Diclofenac (Voveran), ibuprofen (Brufen) and paracetamol (Crocin, Calpol, Dolo-650) dominate Indian pharmacies; Dolo-650 became a household name during COVID-19.
- Mefenamic acid (Meftal, Meftal-Spas with dicyclomine) is India's go-to prescription for dysmenorrhoea and dental pain.
- Aspirin (Disprin, Ecosprin 75) is widely used as a low-dose antiplatelet after heart attacks.
- Nimesulide is NOT in the syllabus — note it is banned for children in India (liver risk); do not confuse with syllabus drugs.
- Self-medication with NSAIDs for every body ache is rampant — pharmacists must screen for ulcer history, asthma (aspirin-sensitive), pregnancy and kidney disease.

9.13 Key Points

1. NSAIDs block COX → no prostaglandins → less pain, fever, inflammation.
2. COX-1 = protective (stomach, platelets); COX-2 = inflammatory. Selectivity decides side effects.
3. Eight chemical classes: salicylates, fenamates, indole/indene acetic acids, aryl-acetic/propionic acids, oxicams, pyrazolones, para-aminophenols, coxibs.
4. Aspirin is the only irreversible NSAID (acetylates Ser530) → low-dose antiplatelet.
5. Starred syntheses: mefenamic acid (Ullmann: o-chlorobenzoic acid + 2,3-xylidine, Cu/K2CO3); ibuprofen (Boots 6-step: Friedel–Crafts → Darzens → aldehyde → oxime → nitrile → acid).
6. SAR essentials: free –COOH; α-methyl in propionics; S-enantiomer active; sulfonamide/methylsulfone for COX-2 selectivity; sulfoxide prodrug (sulindac).
7. Withdrawn/restricted: phenacetin (kidney), zomepirac (anaphylaxis), phenylbutazone restricted (agranulocytosis), rofecoxib (cardiac).

9.14 Common Confusions

- **Paracetamol vs NSAID:** paracetamol relieves pain/fever but is a weak anti-inflammatory — it is not a true NSAID.
- **Aspirin dose:** 75–150 mg = antiplatelet; 300–600 mg = pain/fever — same drug, different doses, different jobs.
- **Celecoxib vs diclofenac:** both relieve arthritis, but celecoxib spares the stomach (COX-2 selective) while diclofenac can ulcerate it.
- **Sulindac prodrug:** the tablet contains inactive sulfoxide; the body reduces it to the active sulfide.

- **Ibuprofen enantiomers:** the bottle is racemic (R+S) but only S blocks COX — R converts to S inside the body.

9.15 Common Mistakes

- Writing "all NSAIDs are reversible" — aspirin is irreversible; state the exception.
- Forgetting the α-methyl in ibuprofen's structure — it is a propionic acid, not acetic.
- Drawing mefenamic acid without the 2,3-dimethyl groups — those methyls define the drug.
- Saying coxibs have "no side effects" — they spare the stomach but carry cardiovascular caution.
- Recommending aspirin for a child's viral fever — Reye's syndrome risk; paracetamol is correct.

9.16 Mnemonics

- **NSAID classes:** "Silly Ants In Argentina Ate Oranges, Pineapples, Pears, Cherries" — Salicylates, Anthranilates, Indoles, Aryl-acids, Oxicams, Pyrazolones, Para-aminophenols, Coxibs.
- **Aspirin special:** "Aspirin Acetylates — Always" (irreversible acetylation of Ser530).
- **Ibuprofen synthesis:** "Fred Dances Happily Over New Acres" — Friedel–Crafts, Darzens, Hydrolysis/decarboxylation, Oxime, Nitrile, Acid hydrolysis.
- **COX-2 selectivity:** "Sulfonamide Seeks Side-pocket" (SO2NH2/SO2Me fits COX-2's Val523 pocket).

9.17 Exam Summary

NSAIDs relieve pain, fever and inflammation by blocking cyclooxygenase in the arachidonic-acid cascade, stopping prostaglandin synthesis. COX-1 is constitutive and protective (stomach, platelets); COX-2 is induced at injury sites. Eight chemical classes cover the syllabus: salicylates (sodium salicylate, aspirin — irreversible Ser530 acetylator and low-dose antiplatelet, diflunisal), fenamates (mefenamic acid — Ullmann synthesis from o-chlorobenzoic acid + 2,3-xylidine; niflumic acid; meclofenamate), indole/indene acetic acids (indomethacin, sulindac prodrug, tolmetin, zomepirac withdrawn), aryl-acetic/propionic acids (diclofenac, ketorolac, ibuprofen — Boots 6-step synthesis, S-enantiomer active; naproxen), oxicams (piroxicam, enolic acid, t½ ~50 h), pyrazolones (antipyrine, phenylbutazone restricted), para-aminophenols (phenacetin withdrawn, acetaminophen), and selective COX-2 inhibitors (celecoxib, etoricoxib — vicinal diaryl + sulfonamide/methylsulfone fitting the COX-2 side pocket). Key SAR: free carboxylic acid, α-methyl in propionics, ortho substitution in fenamates, N-aroyl/2-methyl/5-methoxy in indomethacin, enolic OH in oxicams. Paracetamol overdose causes NAPQI liver injury; aspirin is avoided in children (Reye's).

9.18 One-Minute Revision

- Cascade: membrane → arachidonic acid → COX → prostaglandins; NSAIDs block COX.
- COX-1 protective, COX-2 inflammatory.
- 8 classes: salicylates, fenamates, indole-acetic, aryl-acetic/propionic, oxicams, pyrazolones, para-aminophenols, coxibs.
- Aspirin irreversible (acetylates Ser530); low dose = antiplatelet.
- Syntheses: mefenamic acid = Ullmann coupling; ibuprofen = Boots 6-step.
- SAR: free COOH; α-methyl; S active; sulfonamide → COX-2 pocket.
- Withdrawn: phenacetin, zomepirac, rofecoxib; restricted: phenylbutazone.

9.19 Exam Questions

Short-answer questions:

1. Draw the arachidonic-acid cascade flowchart and mark the NSAID blockade point.

1. Distinguish COX-1 from COX-2 under: occurrence, function and clinical significance.
2. Why is aspirin called an irreversible NSAID? Which residue does it acetylate?
3. Write the structure of ibuprofen and circle the chiral centre. Which enantiomer is active?
4. Classify NSAIDs chemically with two examples each.
5. What is a coxib? Name two and state their advantage.
6. Why is paracetamol a poor anti-inflammatory?
7. Write the Ullmann synthesis of mefenamic acid with reagents.
8. Why was phenacetin withdrawn? Name its active metabolite.
9. State the 5-day rule for ketorolac and the reason behind it.

Long-answer questions:

1. Classify NSAIDs based on chemical structure. Describe the structure (scaffold + key substituents) and uses of one drug from any five classes.
2. Write the complete Boots synthesis of ibuprofen with all reagents and intermediates. Explain the role of the Darzens step.
3. Discuss the SAR of (a) fenamates, (b) arylpropionic acids and (c) selective COX-2 inhibitors as rule tables.
4. Explain why COX-2-selective inhibitors cause fewer gastric ulcers than diclofenac, and why they still need cardiovascular caution.

MCQs (answers at the end):

1. NSAIDs act by inhibiting:
   a) Phospholipase A2 b) Cyclooxygenase c) Lipoxygenase d) Thrombin
2. Aspirin irreversibly inhibits COX by acetylating:
   a) Cys813 b) Ser530 c) Arg120 d) Val523
3. The active enantiomer of ibuprofen is:
   a) R b) S c) Both equal d) Neither
4. Mefenamic acid is synthesized by:
   a) Friedel–Crafts acylation b) Ullmann condensation c) Darzens reaction d) Williamson ether synthesis
5. Sulindac is a:
   a) Direct COX-2 inhibitor b) Sulfoxide prodrug activated to sulfide c) Irreversible inhibitor d) Topical agent
6. The COX-2 selectivity of celecoxib comes from:
   a) Carboxylic acid b) p-Sulfonamide fitting the COX-2 side pocket c) Steroid nucleus d) Sulfoxide bridge
7. Piroxicam's long duration is due to:
   a) Irreversible binding b) Half-life ~50 h c) Prodrug activation d) Enteric coating
8. Phenacetin was withdrawn because of:
   a) Cardiac arrhythmia b) Renal damage and carcinogenicity c) NDMA impurity d) Agranulocytosis
9. Which is NOT a true NSAID (weak anti-inflammatory)?
   a) Diclofenac b) Paracetamol c) Ibuprofen d) Naproxen
10. Low-dose aspirin (75 mg) is used as:
    a) Antipyretic b) Antiplatelet c) Uricosuric d) Antacid
    Answers: 1-b, 2-b, 3-b, 4-b, 5-b, 6-b, 7-b, 8-b, 9-b, 10-b

Viva questions:

1. Name the enzyme that releases arachidonic acid from membranes. (Phospholipase A2.)
2. Which prostaglandin mainly causes pain and fever? (PGE2.)

1. Reagents for the Darzens step in ibuprofen synthesis? (Ethyl chloroacetate + sodium ethoxide.)
2. What does the oxime become in step 5 of the Boots route? (Nitrile, via acetic anhydride.)
3. Starting materials of mefenamic acid synthesis? (o-Chlorobenzoic acid + 2,3-dimethylaniline.)
4. Why is the α-methyl important in ibuprofen? (Activity + blocks β-oxidation.)
5. Which drug closes PDA in newborns? (Indomethacin.)
6. Antidote for paracetamol poisoning? (N-acetylcysteine.)
7. Why is aspirin avoided in children with viral fever? (Reye's syndrome.)
8. One structural feature that makes etoricoxib COX-2 selective? (p-Methylsulfone on the diaryl scaffold.)

Application-based questions:

1. A 60-year-old with a healed gastric ulcer needs long-term arthritis therapy. Compare diclofenac vs celecoxib for this patient, including the cardiac caution you would counsel.
2. A patient took 20 paracetamol tablets after an argument. Explain the biochemical danger (NAPQI), the antidote, and the pharmacist's role.
3. A dentist prescribes ketorolac for 10 days post-extraction. Identify the problem and counsel the patient on safe duration and warning signs.

9.20 References

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