

Unit 3: Medicinal Chemistry Aspects of Drug Classes and Stereochemistry

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3.1 How a drug class is studied systematically

Every class in this unit is studied the same way, and examination answers should follow the same order:

- 1 **Classification:** the chemical or pharmacological families inside the class.
- 2 **Mechanism of action:** the target, and how engaging it produces the clinical effect.
- 3 **SAR:** the structural features that activity requires, tolerates or forbids, read from analog series.
- 4 **Synthesis:** one representative, preferably new generation, drug built step by step, because a synthesis is SAR made practical: it shows which ring and which group is installed when, and why.

A **new generation** drug in each class below means the later member whose design fixed a named fault of the older drugs: poorer selectivity, shorter action, worse side effects or resistance.

3.2 Anti-hypertensive drugs

Groups: ACE inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, diuretics, direct renin inhibitors and others.

ACE inhibitors. Mechanism: block the angiotensin converting enzyme, so less angiotensin II (vasoconstrictor) is made and less bradykinin is destroyed. SAR: the inhibitor must present a group that binds the active site zinc ion (a carboxylate, or the sulfhydryl of the first drug captopril), a carbonyl that hydrogen bonds in the site, and a carboxylate that mimics the substrate C-terminus. Captopril's free sulfhydryl gave rash and taste disturbance; **enalapril** replaced it with a second carboxylate and is given as its monoethyl ester prodrug (Unit 2). Lisinopril is the lysine analog of enalaprilat and needs no activation.

ARBs. Losartan blocks the angiotensin II AT1 receptor. Its design is a Unit 2 case study: an imidazole based lead carried a carboxylic acid; replacing the acid with a **tetrazole** (a non-classical bioisostere) and mounting it on a biphenyl frame gave losartan. A hydroxymethyl group on the imidazole is oxidised in the body to a carboxylic acid metabolite (EXP3174) that is more potent and longer acting than losartan itself.

Calcium channel blockers. Amlodipine is a 1,4-dihydropyridine that blocks L-type calcium channels in vascular smooth muscle. Dihydropyridine SAR: the ring nitrogen must stay unsubstituted, ester groups at the 3 and 5 positions tune potency, and different esters on the two sides (as in amlodipine) give a long acting, once daily drug.

Synthesis of amlodipine (outline): a Hantzsch dihydropyridine synthesis (the named reaction is in MPC102T) in which 2-chlorobenzaldehyde, two beta-keto ester components (one carrying the protected aminoethoxy side chain) and ammonia close the dihydropyridine ring in one multicomponent step; deprotection then frees the side chain amine, which is what makes amlodipine basic, long lived and well tolerated.

3.3 Psychoactive drugs

Antipsychotics. Typical agents block dopamine D2 receptors. Chlorpromazine SAR is classical: a phenothiazine ring with an electron withdrawing substituent at position 2 (chlorine), and a three carbon

chain to a terminal dimethylamino group (section 2.11). Atypical agents such as **risperidone** combine D2 blockade with strong serotonin 5-HT_{2A} blockade, giving fewer extrapyramidal effects; risperidone joins a benzisoxazole ring to a piperidine bearing a pyrimidinone system and is converted in the body to the equally active paliperidone.

Antidepressants. The selective serotonin reuptake inhibitors (SSRIs) block the serotonin transporter. **Fluoxetine** is a phenoxypropylamine: SAR tolerates the trifluoromethylphenoxy group and a secondary methylamine; it is a racemate whose enantiomers and the long lived metabolite norfluoxetine all contribute. Tricyclics (imipramine) block both serotonin and noradrenaline uptake but also hit many other receptors, which is why the selective agents displaced them.

Synthesis of fluoxetine (outline): a Mannich type route builds the 3-(methylamino)-1-phenylpropan-1-ol skeleton (acetophenone, formaldehyde and methylamine give the Mannich base, which is reduced to the amino alcohol); the alcohol is then etherified with 4-chlorobenzotrifluoride under basic conditions to install the trifluoromethylphenoxy group.

3.4 Anticonvulsant drugs

Mechanisms: most anticonvulsants stabilise neuronal membranes by blocking voltage gated sodium channels in their inactivated state (phenytoin, carbamazepine, lamotrigine), enhancing GABA inhibition (benzodiazepines, vigabatrin), or both (valproate). Newer agents use new targets: levetiracetam binds the synaptic vesicle protein SV2A.

Phenytoin is 5,5-diphenylhydantoin; the hydantoin ring with two phenyl groups is its pharmacophore, and it is made by the Bucherer-Bergs reaction of benzil chemistry routes or from benzophenone with urea and cyanide chemistry in the classical preparation. **Carbamazepine** is a tricyclic relative of the antidepressants with a carbamoyl group on the ring nitrogen. **Lamotrigine**, a new generation agent, is a diaminotriazine that blocks sodium channels and reduces glutamate release, with a broad spectrum including absence seizures where phenytoin fails.

3.5 H1 and H2 receptor antagonists

H1 antagonists (antihistamines). First generation agents (chlorpheniramine, promethazine) cross into the brain and sedate. Second generation agents were designed not to: **cetirizine** is the carboxylic acid metabolite of hydroxyzine, a zwitterion at body pH that crosses the blood brain barrier poorly, so it blocks peripheral H1 receptors with little sedation, and it is sold as the single active enantiomer levocetirizine as well (Unit 3.10).

H2 antagonists suppress gastric acid by blocking histamine H2 receptors on parietal cells, and their discovery is the classic of rational design. Burimamide, built by modifying histamine itself, worked but was weak orally. Adding a methyl group and the thioether chain gave metiamide, potent but causing granulocytopenia from its thiourea group. Replacing thiourea with its bioisostere **cyanoguanidine** gave **cimetidine**, safe and effective: the design chain histamine to burimamide to metiamide to cimetidine is analog design taught by example. Ranitidine then replaced the imidazole ring with a furan bearing a dimethylaminomethyl group and used a nitroethenediamine in place of cyanoguanidine, giving a more potent agent; famotidine is more potent still.

3.6 COX-1 and COX-2 inhibitors

Mechanism: non-steroidal anti-inflammatory drugs inhibit cyclo-oxygenase (COX), the enzyme that converts arachidonic acid to prostaglandins (Unit 5). Aspirin is unique: it **acetylates** a serine (Ser530) in the COX channel irreversibly, so its antiplatelet effect lasts the life of the platelet.

SAR of the classical agents: the arylalkanoic acids (ibuprofen, naproxen, diclofenac) need the acidic group held at a defined distance from a flat aromatic surface that sits in the hydrophobic COX channel; ibuprofen's alpha methyl group is largely a spacer, and its inactive R enantiomer is converted to the active S form in the body (section 3.10).

COX-2 selective inhibitors. COX-1 protects the stomach lining while COX-2 is induced at inflammation sites, so selective COX-2 blockade promised anti-inflammatory action without gastric damage. **Celecoxib** achieves it with a pyrazole ring carrying a sulfonamide group that fits a side pocket present in COX-2 but blocked in COX-1. The class lesson includes the failure: rofecoxib was withdrawn because selective COX-2 blockade also suppresses protective prostacyclin in blood vessels, raising cardiovascular risk, the comparison that every student of this unit should be able to explain.

3.7 Adrenergic and cholinergic agents

Adrenergic agonists. The catecholamine frame (phenethylamine with catechol hydroxyls) is read by all adrenoceptors; selectivity is engineered by substitution. **Salbutamol** is the model: replacing one catechol hydroxyl by a hydroxymethyl group (a bioisosteric change) makes it resist COMT methylation, and a bulky tert-butyl group on nitrogen directs it to beta-2 receptors, giving a long acting bronchodilator. **Beta blockers** share the aryloxypropanolamine frame of propranolol; atenolol's para substituent pattern gives beta-1 selectivity and water solubility, hence renal excretion and once daily dosing.

Cholinergic agents. Acetylcholine itself is useless as a drug (hydrolysed in seconds, active everywhere). **Bethanechol** fixes both faults of the muscarinic agonist: a carbamate ester resists cholinesterase where acetate fails, and a beta methyl group gives muscarinic over nicotinic selectivity and blocks hydrolysis further. Anticholinesterases work from the other side: **donepezil** reversibly inhibits acetylcholinesterase in the brain and is the standard symptomatic treatment in Alzheimer's disease, while the carbamate physostigmine carbamylates the enzyme reversibly and organophosphates phosphorylate it essentially irreversibly.

3.8 Antineoplastic agents

Groups and mechanisms: alkylating agents damage DNA directly; antimetabolites impersonate the building blocks of DNA synthesis; intercalators and topoisomerase inhibitors block DNA handling; antimitotics attack the spindle; targeted small molecules block the specific signalling protein a cancer depends on.

Antimetabolites: methotrexate mimics folic acid and inhibits dihydrofolate reductase (Unit 4), starving dividing cells of thymidylate; 5-fluorouracil is converted to a metabolite that irreversibly inhibits thymidylate synthase and is also built into RNA. **Alkylating agents:** cyclophosphamide is a bioprecursor prodrug (Unit 2) oxidised in the liver to phosphoramidate mustard, which cross links DNA.

New generation, targeted design: **imatinib** inhibits the BCR-ABL tyrosine kinase that drives chronic myeloid leukaemia, a drug designed against a defined molecular target rather than against dividing cells generally. Its resistance story (the T315I gatekeeper mutation, section 2.8) and the later inhibitors designed to defeat that mutation make it the complete case study of this subject: target, design, success, resistance, redesign.

3.9 Antiviral agents

Aciclovir is a guanosine analog missing part of the sugar ring (an acyclic side chain instead of ribose). Its selectivity is built in two steps: it is phosphorylated efficiently only by the herpes virus thymidine kinase, so the active form concentrates in infected cells, and the resulting triphosphate then both inhibits the viral DNA

polymerase and terminates the growing DNA chain because the chain has no 3-prime hydroxyl to continue from.

Antiretrovirals: zidovudine (AZT), a thymidine analog with an azido group in place of the 3-prime hydroxyl, terminates HIV reverse transcription the same way; modern therapy combines nucleoside analogs with non-nucleoside reverse transcriptase inhibitors (which bind an allosteric pocket of the enzyme) and protease inhibitors (Unit 4 transition state design, saquinavir).

Oseltamivir inhibits influenza neuraminidase, the enzyme that releases new virus particles from the cell; it was designed as a carbocyclic mimic of the sialic acid transition state, and is given as an ethyl ester prodrug hydrolysed to the active carboxylate.

3.10 Stereochemistry and drug action

Molecules with a chiral centre exist as **enantiomers**, mirror images with identical physical properties in an ordinary environment but different behaviour in a chiral one, and the body is chiral throughout: its enzymes, receptors and transporters are built from L-amino acids. The Easson-Stedman three point model (section 1.6) explains why one enantiomer can fit its receptor at three points while its mirror image manages only two.

Stage	Enantioselectivity example
Absorption	L-DOPA is carried by an amino acid transporter; D-DOPA is not, one reason levodopa is the drug
Distribution	Plasma protein binding differs between warfarin enantiomers, changing free concentrations
Metabolism	S-warfarin is the more potent anticoagulant and is cleared mainly by CYP2C9; R-warfarin uses other enzymes, so interactions differ by enantiomer
Elimination and safety	D-penicillamine is the therapeutic chelator; the L form is far more toxic. Naproxen is marketed as the single S enantiomer, the active COX inhibitor

Case studies every student should know:

- **Thalidomide:** sold as a racemate; one enantiomer is sedative, the other teratogenic, but the two interconvert in the body, so giving a single enantiomer would not have prevented the tragedy. The honest lesson is about testing in pregnancy, not just separation.
- **Ibuprofen:** only the S enantiomer inhibits COX, but the body inverts much of the R dose into S (a unidirectional metabolic inversion), so the racemate works and the single enantiomer (dexibuprofen) is an option, not a necessity.
- **Chiral switches:** omeprazole was remarketed as its S enantiomer esomeprazole, cetirizine as levocetirizine, and ofloxacin as levofloxacin (the antibacterial activity of ofloxacin lives almost entirely in the S form). A chiral switch is justified when the single enantiomer is genuinely cleaner, faster or safer, not merely newer.
- **Geometric isomerism:** diethylstilbestrol is active in the trans form, whose two hydroxyls sit at the distance the oestrogen receptor expects; the cis form is far weaker, a distance and geometry lesson that links back to section 2.11.

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