Medicinal Chemistry of Major Drug Classes and Stereochemistry

Introduction to Drug-Class and Stereochemical Design

- Drugs in the same therapeutic class may act on different targets and may have very different chemical structures.
- **Medicinal chemistry** connects the structure of a drug with its biological action, synthesis and behaviour in the body.
- A structure–activity relationship, or SAR, explains how a defined structural change affects a measured biological activity within a chemical family.
    - A useful answer shows the structure, identifies the changed group, explains its likely role and states the limits of the comparison.

How to Study a Drug Class

1. Understand the Therapeutic Aim

- Identify the physiological process that needs to be changed, such as vascular contraction, seizure activity or acid secretion.

2. Identify the Target and Mechanism

- State whether the drug activates a receptor, blocks a receptor, inhibits an enzyme or changes an ion channel.

3. Recognise the Pharmacophore

- Identify the groups that provide essential ionic, hydrogen-bonding and hydrophobic interactions.
    - A pharmacophore describes a recognition pattern rather than a complete drug molecule.

4. Explain Structure–Activity Relationships

- Describe how a structural change affects activity or selectivity, and give the chemical reason where it is known.
    - A relationship established for one scaffold must not be applied automatically to an unrelated scaffold.

5. Explain a Representative Synthesis

- Identify the key starting fragments, the bond that joins them and the functional-group changes that produce the final drug.
    - A representative route explains synthetic logic; it does not imply that every manufacturer uses the same process.

6. Consider Stereochemistry and Disposition

- Examine how configuration, ionisation, metabolism and distribution affect the useful activity of the compound.

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Reading the Reaction Schemes

- Structures show the identity and connectivity of the reacting molecules.
- An arrow indicates a chemical transformation, while a retrosynthetic arrow indicates a planning relationship.
- Some medicinal-chemistry schemes show the main organic transformation and omit work-up reagents or inorganic by-products.

Antihypertensive Drugs

Systematic Study

- Antihypertensive drugs reduce blood pressure by changing vascular tone, cardiac activity, circulating volume or hormonal control.

Classification and Representative Examples

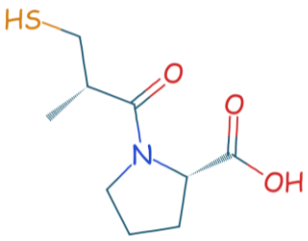
A. Calcium-Channel Blockers

- Dihydropyridines such as **amlodipine** inhibit L-type calcium channels, with prominent effects on vascular smooth muscle.
- Reduced calcium entry decreases contraction and promotes arteriolar relaxation.

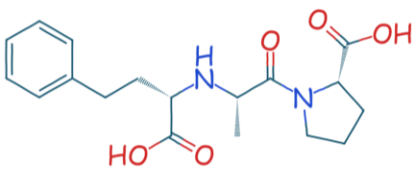
B. Angiotensin-Converting-Enzyme Inhibitors

- ACE inhibitors reduce formation of angiotensin II and affect the breakdown of other ACE substrates, including bradykinin.
- **Captopril** uses a thiol-containing scaffold, while **enalaprilat** uses a carboxylate-containing, peptide-like scaffold.

Two ACE inhibitor scaffolds



Captopril



Enalaprilat

C. Angiotensin-Receptor Blockers

- **Losartan** blocks the angiotensin II AT1 receptor.
- An ARB is a receptor ligand and does not require the same zinc-binding arrangement as an ACE inhibitor.

D. Other Classes

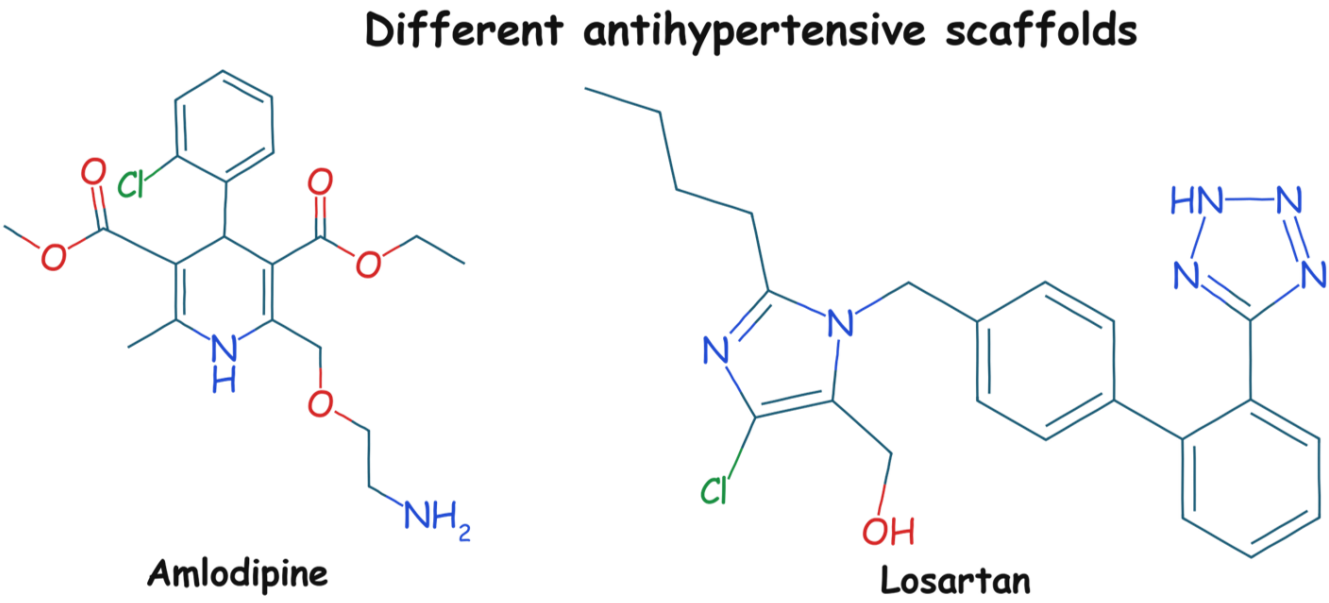
- Beta blockers reduce selected cardiac and renin responses to sympathetic stimulation.

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- Diuretics increase renal salt excretion through their individual nephron targets.

Comparison of Representative Scaffolds



Different antihypertensive mechanisms use different ring systems and ionisable groups

- **Amlodipine** and **losartan** both lower blood pressure, but the structures illustrate two different chemical families.
- **Amlodipine** has a dihydropyridine ring with ester groups and an aminoethoxy side chain; **losartan** has an imidazole linked to a biphenyl–tetrazole region.
- The comparison shows why drugs with the same therapeutic purpose can require different recognition groups and synthetic routes.

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Mechanism of Action

Amlodipine

- **Amlodipine** reduces calcium entry through L-type channels in vascular smooth muscle.
- Reduced intracellular calcium decreases smooth-muscle contraction, causing arteriolar dilatation and a fall in peripheral resistance.

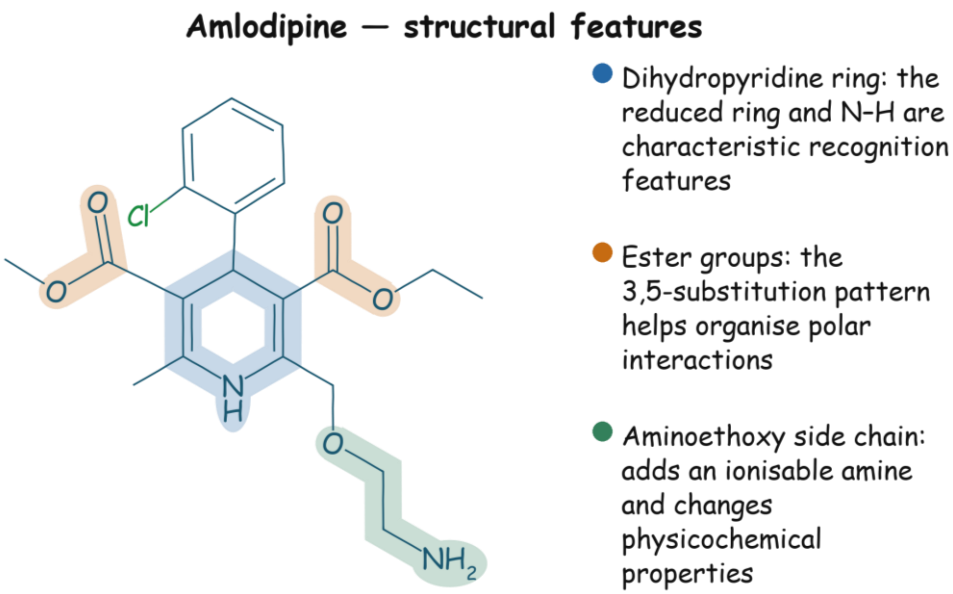
Losartan

- **Losartan** and its active carboxylic-acid metabolite inhibit angiotensin II signalling at AT1 receptors.
- This reduces angiotensin-II-mediated vasoconstriction and aldosterone-related sodium retention.

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Structure–Activity Relationships

Amlodipine



Structural features used to interpret the medicinal chemistry of amlodipine

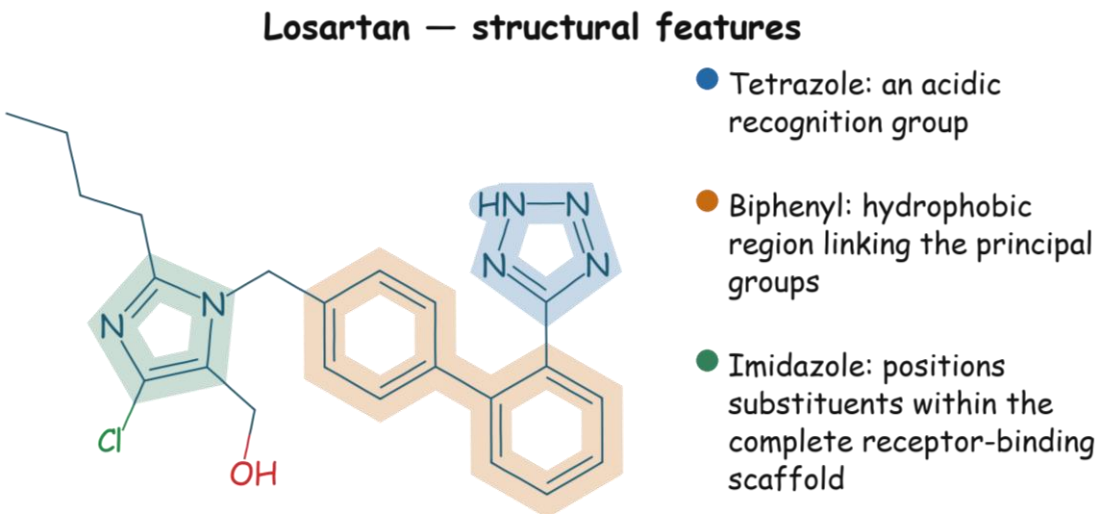
A. The Dihydropyridine Ring

- The 1,4-dihydropyridine ring and its 3,5-dicarboxylate groups are central features of this calcium-channel-blocker family.
- Oxidation to the corresponding aromatic pyridine substantially changes the pharmacological profile.

B. Substituents and Stereochemistry

- The aryl group at position 4 contributes hydrophobic interactions and affects the preferred conformation.
- Different substituents on the two sides of the ring make the position-4 carbon stereogenic.
- The aminoethoxy side chain contributes ionisable character and distinguishes **amlodipine** from simpler dihydropyridines.

Losartan



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- **Losartan** contains a substituted imidazole, a biphenyl group and an acidic tetrazole.
- The hydrophobic region and acidic group contribute to recognition at the AT1 receptor.
- The **tetrazole** provides an acidic recognition group, while the **biphenyl** region helps position a hydrophobic surface.
- Oxidation of **losartan**'s hydroxymethyl group gives an active carboxylic-acid metabolite; a metabolic change can therefore preserve activity rather than simply inactivate a drug.

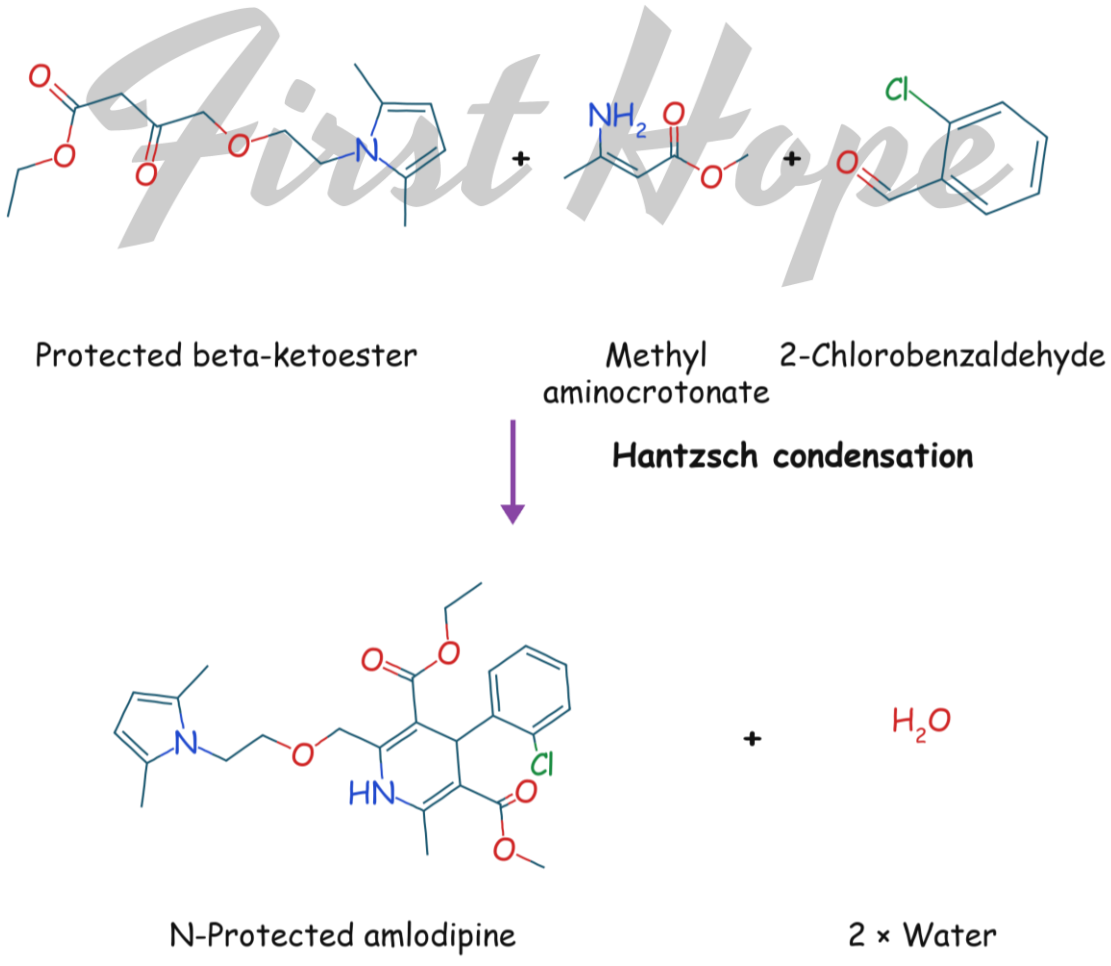
Synthesis of Representative Molecules

Amlodipine

A. Dihydropyridine Ring Construction

- A Hantzsch-type condensation joins an aryl aldehyde, a substituted β-ketoester and an aminocrotonate to construct the dihydropyridine ring.
- The selection of the carbonyl fragments determines which ester and side-chain groups appear in the product.

Hantzsch construction of the protected amlodipine ring



B. Amino-Group Deprotection

- A protected aminoethoxy substituent can be carried through ring formation and then deprotected.

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