MODULE NOTES

Course: Drug Design & Structure–Activity Relationship (SAR)

Module 8: Case Studies in Drug Design

1. Introduction

Drug design is a systematic and rational approach to discovering new therapeutic agents based on knowledge of biological targets and molecular interactions. Modern drug discovery has shifted from empirical screening to mechanism-based and target-oriented drug development.
Case studies in drug design provide practical insight into how theoretical SAR principles are applied in real-world drug development.

2. Fundamental Concepts

2.1 Drug Design

Drug design involves:

- Identification of biological target (It may be: Enzymes, Receptors, Ion channels, Transport proteins, DNA or RNA).
- Selection of lead compound- A lead compound is a chemical molecule that shows desired biological activity against the selected target.
  Sources of lead compounds: Natural products, Synthetic compound libraries, High-throughput screening (HTS), Existing drugs (drug repurposing), Endogenous ligands.
- Structural modification- Once a lead compound is identified, systematic structural changes are made to improve its pharmacological properties.
  Common Structural Modifications: Addition or removal of functional groups, Substituent modification, Ring expansion or contraction, Bioisosteric replacement, Alteration of stereochemistry.
- Optimization of potency, selectivity, and safety.

Types of Drug Design

1. Ligand-Based Drug Design (LBDD)- Ligand-Based Drug Design is used when the structure of the biological target is unknown but information about active molecules (ligands) is available. **Principle:** "Similar structures produce similar biological activity."
2. Structure-Based Drug Design (SBDD)- Structure-Based Drug Design relies on knowledge of the three-dimensional structure of the biological target.
   This structural information is obtained using: X-ray crystallography, NMR spectroscopy, Cryo-electron microscopy. **Principle:** Design molecules that fit precisely into the active site of the target.
3. Rational Drug Design- Rational drug design is a logical approach based on: Understanding of disease mechanism, Knowledge of target structure, Molecular interaction principles.

2.2 Structure–Activity Relationship (SAR)

SAR is the correlation between the chemical structure of a molecule and its biological activity.

Factors Influencing SAR

- Electronic effects
- Steric effects
- Hydrophobicity (log P)
- Hydrogen bonding
- Bioisosterism

SAR studies help identify:

- Essential pharmacophore- A pharmacophore is the minimum structural framework required for a molecule to produce biological activity. It represents: The spatial arrangement of functional groups, Key interaction points with the biological target, Hydrogen bond donors/acceptors, Hydrophobic regions, Ionic interaction sites.
  Through SAR analysis, non-essential parts of the molecule can be removed, and the essential pharmacophoric features can be retained or optimized.

- Functional groups responsible for activity- SAR studies determine which functional groups are critical for binding and activity.
  Examples: Hydroxyl (-OH) group for hydrogen bonding, Amine ($-NH_2$) for ionic interaction, Carboxyl (-COOH) for enzyme binding, Aromatic ring for hydrophobic interaction.
  By modifying or substituting functional groups, scientists can observe: Increase or decrease in activity, Change in selectivity, Alteration in pharmacokinetics,
  This helps in identifying: Active groups, Inactive or detrimental groups, Groups causing adverse effects.

- Modifications that enhance potency or reduce toxicity- SAR enables systematic structural changes to improve drug performance.
  To Enhance Potency: Increase binding affinity, Improve molecular fit in active site, Add groups that strengthen interactions.
  To Improve Selectivity: Introduce steric bulk, Modify substituents to target specific receptor subtypes.
  To Reduce Toxicity: Remove reactive functional groups, Replace toxic moieties with bioisosteres, Modify metabolic pathways, Reduce off-target interactions.

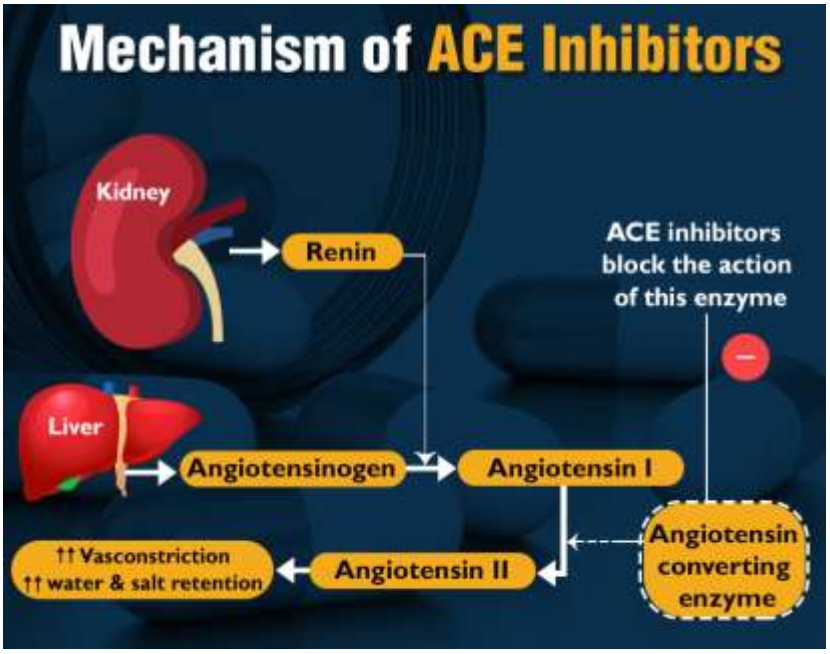
3. Case Study 1: ACE Inhibitors

Examples:

- Captopril
- Enalapril

3.1 Disease Background

Hypertension is associated with activation of the Renin–Angiotensin–Aldosterone System (RAAS).
Angiotensin-Converting Enzyme (ACE) converts Angiotensin I to Angiotensin II, a potent vasoconstrictor.



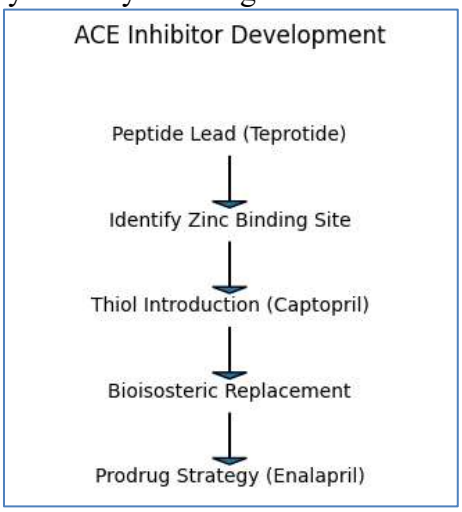
3.2 Lead Identification

Initial lead: Peptide inhibitor (teprotide).

Limitation: Poor oral bioavailability.

3.3 SAR Development

- Zinc-binding group essential (ACE is a zinc metalloprotease).
- Thiol (-SH) group binds strongly to zinc.
- Proline moiety necessary for enzyme recognition.

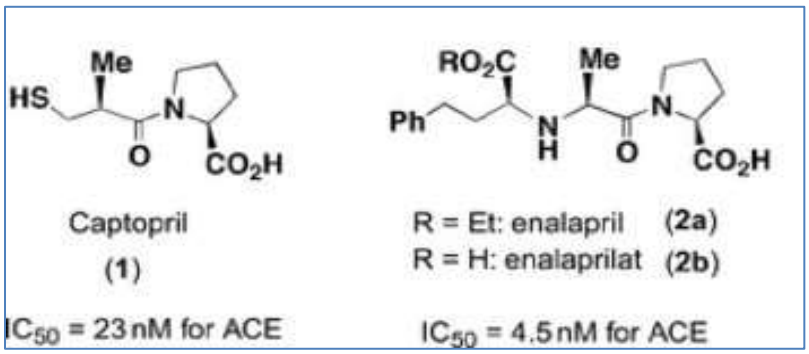


Development of Captopril

- First orally active ACE inhibitor.
- Contains thiol group for zinc binding.
- Side effects: Metallic taste, skin rash.

Development of Enalapril

- Thiol replaced by carboxyl group (bioisosterism).
- Reduced adverse effects.
- Developed as prodrug for improved absorption.



SAR Table: ACE Inhibitors

Drug	Key Functional Group	Effect on Activity	Limitation
Captopril	Thiol (-SH)	Strong Zinc Binding, High Potency	Metallic taste, rash
Enalapril	Carboxylate	Reduced toxicity, Good potency	Prodrug required

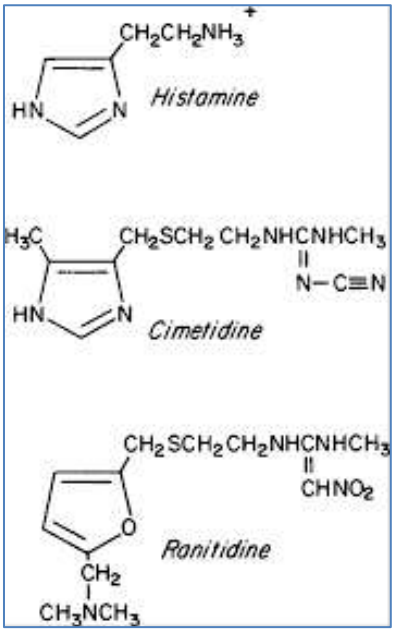
3.4 Key Learning

- Transition from peptide to non-peptide drug.
- Importance of zinc-binding groups.
- Application of bioisosteric replacement.

4. Case Study 2: H2-Receptor Antagonists

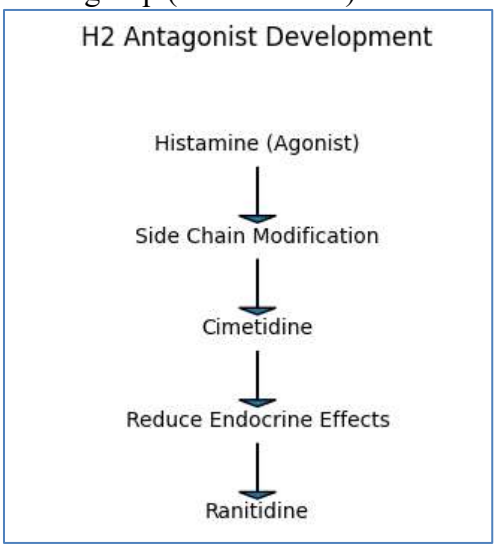
Examples:

- Cimetidine
- Ranitidine



4.1 Disease Background
Peptic ulcer disease due to excessive gastric acid secretion.
Target: Histamine H2 receptor.
4.2 Lead Compound
Histamine (agonist).
Goal: Convert agonist into antagonist.
4.3 SAR Development

- Modification of side chain.
- Addition of bulky substituents.
- Introduction of cyanoguanidine group (in cimetidine).



Issues with Cimetidine

- Antiandrogenic effects.
- CYP450 inhibition → drug interactions.

Development of Ranitidine

- Removal of imidazole ring.
- Reduced endocrine side effects.
- Improved safety profile.

SAR Table: H2 Antagonists

Drug	Structural Feature	Advantage	Limitation
Cimetidine	Imidazole ring	Effective acid suppression	CYP inhibition
Ranitidine	Modified ring system	Reduced endocrine effects	Less CYP inhibition

4.4 Key Learning

- Ligand-based drug design.
- Importance of receptor selectivity.
- Reduction of off-target effects.

5. Case Study 3: β-Blockers
Example:

- Propranolol

5.1 Disease Background
Used in hypertension, arrhythmia, angina.
Target: β-adrenergic receptors.

5.2 Lead Compound
Isoproterenol (β-agonist).
Goal: Develop antagonist.
5.3 SAR Findings

- Aryloxypropanolamine structure essential.
- Bulky substituents on amine → antagonistic activity.
- Lipophilic aromatic ring enhances potency.

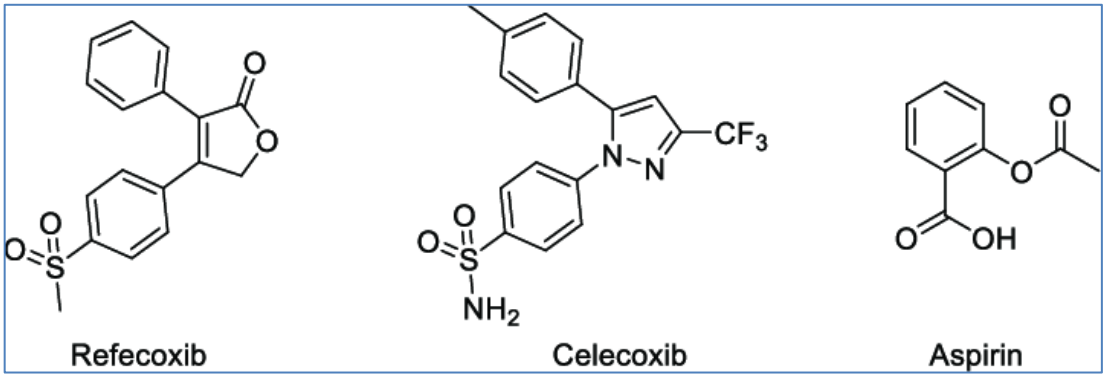
Later modifications led to β1-selective blockers.
5.4 Key Learning

- Agonist → antagonist transformation.
- Structural basis of receptor selectivity.

6. Case Study 4: NSAIDs and COX Selectivity
Examples:

- Aspirin
- Celecoxib

6.1 Disease Background
Inflammation mediated by prostaglandins.
Target: Cyclooxygenase (COX-1 and COX-2).



6.2 Aspirin

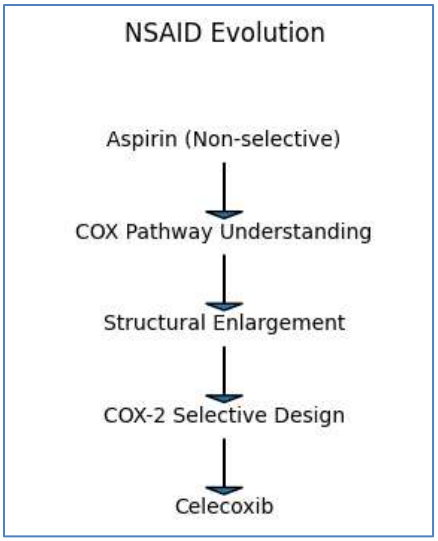
- Acetyl group irreversibly inhibits COX.
- Non-selective inhibition → GI irritation.

6.3 COX-2 Selective Inhibitors

- Larger side chains fit into COX-2 side pocket.
- Reduced gastric toxicity.

Celecoxib:

- Selective COX-2 inhibition.
- Improved GI safety.



SAR Table: NSAIDs

Drug	Structural Feature	Selectivity	Safety Profile
Aspirin	Acetyl group	Non-selective COX	GI irritation
Celecoxib	Bulky sulfonamide	COX-2 selective	Reduced GI toxicity

6.4 Key Learning

- Enzyme selectivity via structural modification.
- Safety-oriented drug design.

7. Case Study 5: Antiviral Drug Design

Example:

- Acyclovir

7.1 Disease Background

Herpes virus infection.

Target: Viral DNA polymerase.

7.2 SAR Insights

- Guanine analogue.
- Incomplete sugar moiety.
- Activated only in infected cells.
- Causes chain termination.

Valacyclovir:

- Prodrug to enhance oral bioavailability.

7.3 Key Learning

- Selective toxicity.
- Prodrug strategy.
- Target-specific activation.

8. Case Study 6: Anticancer Drug Design

Example:

- Cisplatin

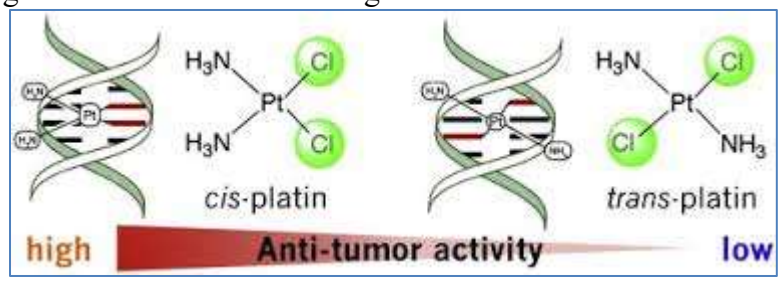
8.1 Disease Background

Cancer cells undergo rapid division.

Target: DNA crosslinking.

8.2 SAR Observations

- Cis configuration essential for activity.
- Trans isomer inactive.
- Chloride ligands facilitate DNA binding.



Limitations:

- Nephrotoxicity.
- Neurotoxicity.

Analogues developed to reduce toxicity.

8.3 Key Learning

- Structure-dependent biological activity.
- Mechanism-based optimization.

9. Overall Lessons from Case Studies

1. Minor structural changes significantly alter activity.
2. Bioisosterism reduces toxicity.
3. Increased steric bulk may improve selectivity.
4. Prodrug strategy enhances bioavailability.
5. Understanding target structure improves rational design.
6. Mechanism-based design leads to safer and more effective drugs.

10. Conclusion

Case studies in drug design demonstrate the practical application of SAR principles in transforming lead compounds into clinically useful drugs. They illustrate the evolution from empirical discovery to rational, target-based drug development and highlight the importance of continuous structural optimization to improve therapeutic efficacy and safety.