Lecture Notes: Session 6 - Physicochemical Properties: Optical Isomerism

SNS College of Pharmacy and Health Sciences

August 2025

Introduction

This lecture explores optical isomerism, a critical physicochemical property in medicinal chemistry that influences drug activity, selectivity, and safety. Optical isomerism arises from chirality, leading to enantiomers with distinct pharmacological profiles. Using warfarin as a primary example, this session covers chirality, enantiomers, and their pharmacological differences, highlighting the importance of stereochemistry in drug design and clinical applications.

1 Optical Isomerism

Optical isomerism occurs when molecules with identical molecular formulas and connectivity differ in their three-dimensional arrangement, leading to non-superimposable mirror images (enantiomers). These isomers rotate plane-polarized light and exhibit distinct biological activities due to stereospecific interactions with chiral biological targets.

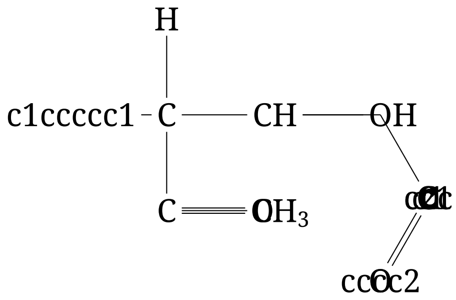
1.1 Chirality

Definition: Chirality refers to the property of a molecule that lacks an internal plane of symmetry, making it non-superimposable on its mirror image. A chiral molecule typically contains a stereogenic center, such as a carbon atom with four different substituents (chiral carbon).
Pharmacological Relevance:

- Chiral drugs interact differently with biological targets (e.g., enzymes, receptors), which are also chiral.
- Enantiomers may differ in potency, selectivity, toxicity, or metabolism.
- Racemic mixtures (50:50 mix of enantiomers) may have combined or distinct effects compared to pure enantiomers.

Example - Warfarin:

- Chemical Structure: Warfarin (4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one) has a chiral carbon at the butyl side chain.

- 

- The chiral carbon is bonded to four groups: phenyl, ketone, hydroxyl, and hydrogen.

1.2 Enantiomers

Definition: Enantiomers are pairs of molecules that are non-superimposable mirror images, differing only in their spatial arrangement around a chiral center. They have identical physical properties (e.g., melting point, solubility) but differ in optical activity (rotation of plane-polarized light) and biological interactions.
Properties:

- **Optical Activity:** One enantiomer rotates plane-polarized light to the right (dextrorotatory, (+)) and the other to the left (levorotatory, (-)).
- **Nomenclature:** Designated as (R) or (S) based on Cahn-Ingold-Prelog priority rules.
- **Biological Activity:** Enantiomers may bind differently to chiral receptors or enzymes, leading to varied pharmacological effects.

Example - Warfarin Enantiomers:

- Warfarin exists as (R)-warfarin and (S)-warfarin, with the chiral center at the carbon bearing the phenyl and ketone groups.
- (S)-Warfarin is 3–5 times more potent than (R)-warfarin as an anticoagulant.

1.3 Pharmacological Differences: (S)-Warfarin vs. (R)-Warfarin

Warfarin, an anticoagulant, inhibits vitamin K epoxide reductase, preventing blood clotting. Its enantiomers exhibit significant pharmacological differences due to stereospecific interactions with biological targets.
(S)-Warfarin:

- *Potency:* More potent inhibitor of vitamin K epoxide reductase.
- *Pharmacokinetics:* Metabolized primarily by CYP2C9; half-life 20–30 hours.
- *Clinical Use:* Contributes most to warfarin's anticoagulant effect in racemic mixtures.
- *Metabolism:* Undergoes 7-hydroxylation, forming inactive metabolites.

(R)-Warfarin:

- *Potency:* Less potent, with weaker binding to the target enzyme.
- *Pharmacokinetics:* Metabolized by CYP1A2 and CYP3A4; longer half-life (35–45 hours).
- *Clinical Use:* Contributes less to therapeutic effect but extends duration of action.
- *Metabolism:* Undergoes 6- and 8-hydroxylation, with some metabolites retaining minor activity.

Clinical Implications:

- Warfarin is administered as a racemic mixture, but (S)-warfarin dominates therapeutic efficacy.
- Stereoselective metabolism (e.g., CYP2C9 polymorphisms) affects dosing and bleeding risk.
- Example Case: Patients with CYP2C9 mutations may accumulate (S)-warfarin, increasing anticoagulation effects and requiring dose adjustments.

SAR Notes:

- The chiral center in warfarin influences receptor binding due to spatial orientation.
- The (S)-enantiomer's configuration aligns better with the active site of vitamin K epoxide reductase, enhancing potency.
- Structural modifications at the chiral center (e.g., altering substituents) could modulate activity but risk altering specificity.

2 Additional Examples

To reinforce the concept, consider other chiral drugs:

- **(S)-Ibuprofen vs. (R)-Ibuprofen:**
  - (S)-Ibuprofen is the active COX inhibitor for analgesia and anti-inflammatory effects.
  - (R)-Ibuprofen is less active but converts to (S)-ibuprofen in vivo via chiral inversion.
- **Thalidomide Tragedy:**
  - Racemic thalidomide caused birth defects due to the (S)-enantiomer's teratogenicity, while (R)-thalidomide was sedative.
  - Highlights the need for enantiopure drugs or racemic safety testing.

3 Clinical and Drug Design Considerations

- **Enantiopure vs. Racemic Drugs:** Developing single enantiomers (e.g., (S)-warfarin) can improve efficacy and safety but increases production costs. Racemic mixtures are common when both enantiomers are safe or interconvert (e.g., ibuprofen).
- **Stereoselective Pharmacokinetics:** Enantiomers may differ in absorption, distribution, metabolism, and excretion, requiring careful monitoring (e.g., warfarin's CYP2C9 metabolism).
- **Chiral Synthesis and Analysis:** Advances in chiral chromatography and asymmetric synthesis enable enantiopure drug development, critical for avoiding adverse effects (e.g., thalidomide).
- **Regulatory Implications:** Regulatory agencies (e.g., FDA) require stereochemical characterization to ensure safety and efficacy.

4 Key Learning Points

- Optical isomerism arises from chirality, producing enantiomers with identical physical properties but distinct biological activities.
- Enantiomers, such as (S)- and (R)-warfarin, differ in potency and metabolism due to stereospecific interactions with biological targets.
- Warfarin exemplifies how (S)-enantiomer potency drives therapeutic effects, while (R)-enantiomer influences duration.
- Understanding chirality is essential for designing safer, more effective drugs and predicting pharmacokinetic variability.