# Lecture Notes: Session 7 - Physicochemical Properties: Geometrical Isomerism

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## Introduction

This lecture focuses on geometrical isomerism, a key physicochemical property influencing drug activity, selectivity, and pharmacokinetics. Geometrical isomerism arises in molecules with restricted rotation, leading to distinct spatial arrangements (cis-trans or E-Z isomers) that can significantly alter biological effects. Using tamoxifen as a primary example, this session explores cis-trans isomerism, E-Z notation, and their implications in medicinal chemistry.

## 1 Geometrical Isomerism

Geometrical isomerism occurs when molecules have the same molecular formula and connectivity but differ in the spatial arrangement of atoms due to restricted rotation, typically around double bonds or in cyclic systems. This property is critical in drug design, as isomers may exhibit different pharmacological profiles.

### 1.1 Cis-Trans Isomers

**Definition:** Cis-trans isomerism describes the relative orientation of substituents around a double bond or in a cyclic structure.

- **Cis (Z, Zusammen):** Substituents are on the same side of the double bond or ring.
- **Trans (E, Entgegen):** Substituents are on opposite sides.

**Pharmacological Relevance:**

- Different spatial arrangements affect receptor binding, solubility, and metabolism.
- Isomers may have distinct therapeutic effects or side effect profiles.

**Structural Requirements:**

- Restricted rotation, typically due to a carbon-carbon double bond or rigid cyclic systems.
- Two different substituents on each atom of the double bond or ring.

### 1.2 E-Z Notation

**Definition:** The E-Z notation is a systematic method to assign stereochemistry based on the Cahn-Ingold-Prelog (CIP) priority rules.

- Assign priorities to substituents on each carbon of the double bond based on atomic number (higher atomic number = higher priority).
- **Z (Zusammen):** Higher-priority substituents on the same side.
- **E (Entgegen):** Higher-priority substituents on opposite sides.

**Application:**

- More precise than cis-trans for complex molecules with multiple substituents.
- Ensures unambiguous stereochemical description.

## 2 Example: Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), is a classic example of geometrical isomerism impacting pharmacological activity. It is used in breast cancer treatment and exists as E and Z isomers.

**Chemical Structure:** 1-(4-(2-(Dimethylamino)ethoxy)phenyl)-1,2-diphenylbut-1-ene.

**Stereochemistry:**

- The central double bond (C=C) restricts rotation, leading to E and Z isomers.
- **Z-Tamoxifen (Active):** The phenyl groups are on the same side of the double bond.
- **E-Tamoxifen (Less Active):** The phenyl groups are on opposite sides.

**E-Z Assignment:**

- For the double bond carbons:
  - Carbon 1: Substituents are phenyl (C1) and 4-(2-(dimethylamino)ethoxy)phenyl (C2). Phenyl has higher priority (carbon vs. carbon, but phenyl's substituents considered).
  - Carbon 2: Substituents are phenyl (C1) and ethyl (C2). Phenyl has higher priority.
- **Z-Tamoxifen:** Higher-priority groups (phenyl on C1, phenyl on C2) on the same side.
- **E-Tamoxifen:** Higher-priority groups on opposite sides.

**Pharmacological Properties:**

- *Mechanism:* Z-Tamoxifen acts as an estrogen receptor antagonist in breast tissue, inhibiting cancer cell proliferation, but has partial agonist activity in other tissues (e.g., endometrium).
- *Pharmacokinetics:* Half-life of 5–7 days, metabolized via CYP2D6 to active metabolites (e.g., 4-hydroxytamoxifen). Z-isomer is more potent.
- *Clinical Use:* Hormone receptor-positive breast cancer, chemoprevention in high-risk patients.

**SAR Notes:**

- The Z-isomer's spatial arrangement allows optimal binding to the estrogen receptor's ligand-binding domain.
- The dimethylaminoethoxy side chain enhances receptor affinity and tissue selectivity.
- The E-isomer has weaker antagonistic activity, contributing less to therapeutic effects.

## 3 Other Drug Examples

- **Stilbestrol (Diethylstilbestrol, DES):**
  - Structure: Contains a double bond with E and Z isomers.
  - Relevance: E-DES is more estrogenic due to better receptor fit, historically used in hormone therapy but discontinued due to carcinogenicity.
- **Fumaric Acid vs. Maleic Acid:**
  - Fumaric acid (trans, E) is used in psoriasis treatment; maleic acid (cis, Z) is less active and more toxic.
  - SAR: Trans configuration enhances receptor interaction and stability.

## 4 Clinical Implications

- **Receptor Binding:** Geometrical isomers differ in their fit to target receptors, as seen with Z-Tamoxifen's superior estrogen receptor antagonism.
- **Pharmacokinetics:** Isomers may have different solubility, metabolism, or clearance rates (e.g., Z-Tamoxifen's favorable binding vs. E-Tamoxifen).
- **(**Formulation Challenges: Separation of isomers is critical to ensure therapeutic efficacy and minimize side effects (e.g., pure Z-Tamoxifen in commercial preparations).
- **Toxicity:** Incorrect isomers may cause adverse effects (e.g., E-DES's reduced efficacy and safety concerns).

## 5 Key Learning Points

- Geometrical isomerism arises from restricted rotation, leading to cis-trans or E-Z isomers with distinct spatial arrangements.
- E-Z notation uses CIP priority rules for precise stereochemical assignment.
- Tamoxifen illustrates how Z-isomer potency drives therapeutic efficacy in breast cancer treatment.
- Understanding geometrical isomerism is critical for designing drugs with optimal receptor binding and pharmacokinetic profiles.