CHAPTER 19 · ORGANIC CHEMISTRY · LESSON 19.10

Stereochemistry in Drug Development

Lesson Notes — Case Study: Thalidomide and the Chirality of Life

Student Learning Outcomes

By the end of this lesson, students will be able to:

- Explain why chirality matters in drug design, using the receptor–drug "chiral lock and key" analogy.
- Describe the thalidomide case as a real-world example of enantiomer-dependent biological activity.
- Explain the concept of in vivo racemisation and why it made a single-enantiomer thalidomide impossible.

Main Content

1. Why Chirality Matters in Drug Design

Biological systems are chiral. Proteins and receptors in the body are built from chiral building blocks, so a receptor behaves like a highly specific ***"chiral lock."***

A chiral drug is the ***"key."*** Only one enantiomer may fit the receptor correctly — so the two mirror-image forms of the same drug (enantiomers) can produce **vastly different biological effects.**

KEY IDEA

One enantiomer may be therapeutic while its mirror image is inactive — or even toxic — in the very same biological system. Enantiomers are non-superimposable mirror images: identical in molecular formula, different in 3-D spatial arrangement.

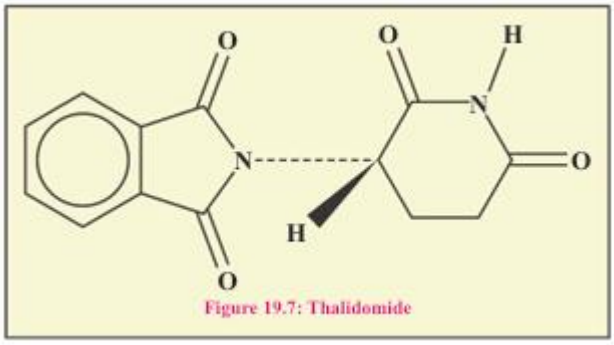

Figure 19.7: Thalidomide

2. The Thalidomide Case (Figure 19.7)

Thalidomide, a tranquilliser, was originally distributed as a racemic mixture — a 50:50 blend of both enantiomers.

- It appeared to be a very successful, non-toxic sedative with no known side effects.
- In the early 1960s, women prescribed the drug for nausea ("morning sickness") in early pregnancy gave birth to badly deformed babies.
- The drug was immediately withdrawn from the market.
- Research showed that the (+) isomer was an effective, safe tranquilliser — while the (–) isomer was the culprit responsible for damaging the fetus.

3. In Vivo Racemisation — The Real Danger

It was originally thought that the problem was due to contamination by the (–) isomer in some production batches.

Subsequent research revealed something far more serious: **racemisation of the pure (+) isomer occurs rapidly as soon as it enters the bloodstream.**

> **CRITICAL DATA POINT**
>
> *Within 10 minutes, racemisation of pure (+)-thalidomide is over 50% complete. This means giving patients only the "safe" (+) enantiomer could never have prevented the tragedy — the body converts it into the harmful form anyway.*

Thalidomide itself will never be marketed again. However, chirality-stable analogues are being investigated as possible anti-inflammatory drugs.

Multiple Choice Questions (with Answers)

Q1. Why do the two enantiomers of a chiral drug often have different biological effects?

A) They have different molecular formulas B) Biological receptors are chiral and interact selectively with one enantiomer

C) Enantiomers have different melting points D) Enantiomers react with different enzymes only in plants

✓ Answer: B

Q2. In what form was thalidomide originally marketed?

A) Pure (+) isomer B) Pure (–) isomer

C) Racemic mixture D) A polymer blend

✓ Answer: C

Q3. Which enantiomer of thalidomide was found to cause birth defects?

A) (+) isomer B) (–) isomer

C) Both equally D) Neither; a metabolite was responsible

✓ Answer: B

Q4. What phenomenon made it impossible to prevent thalidomide's toxic effects by administering only the safe enantiomer?

A) Hydrolysis B) Oxidation

C) In vivo racemisation D) Esterification

✓ Answer: C

Q5. Approximately how much racemisation of pure (+)-thalidomide occurs within 10 minutes in the bloodstream?

A) Less than 10% B) About 25%

C) Over 50% D) 100%

✓ Answer: C

Short Questions

For discussion or written response — no answers provided.

1. Explain the “chiral lock and key” analogy and why it is important in drug–receptor interactions.

2. Describe what happened when thalidomide was prescribed to pregnant women in the early 1960s, and explain the biochemical reason behind the outcome.

3. Why can’t the thalidomide tragedy be avoided today simply by administering only the (+) enantiomer of the drug?