Al-Mustaqbal University

College of Science

Drug Stereochemistry

Third Year Students / 2nd Semester

2025-2026

Relation Between Stereochemistry and Drug action

By

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Thalidomide Tragedy: The Story

2- Thalidomide History

- story of the drug Thalidomide is heartbreaking, but it illustrates why we pay so much attention to stereochemistry.
- The compound was identified in the 1950s as a neurologically active molecule that had the ability to quell morning sickness in pregnant women.
- After the drug began to be marketed, children born to women taking it displayed horrific birth defects--often extremely shortened arms and hands that were not functional.
- The drug was pulled from the market after these problems, along with death rates approaching 50%, were reported. This disaster helped lead to the creation of the modern drug testing and approval regime in the United States and Europe.
- The part of the story that pertains to stereochemistry is that the original drug was made and sold as a mixture. These are mirror images of each other, as you can see; they are not identical. researchs revealed that only the form on the right (the "R" form) was therapeutically active; the one on the left (the "S" form) was not only ineffective, it was the source of the birth defects!

Thalidomide Stereochemistry

- **Thalidomide has just one chiral atom and so exists as two enantiomers.**

- **Thalidomide exists in two mirror-image forms: it is a racemic mixture of (R)- and (S)-enantiomers.**
- **The (R)-enantiomer, shown in the figure, has sedative effects, whereas the (S)-isomer is teratogenic. Under biological conditions, the isomers interconvert, so separating the isomers before use is ineffective.**

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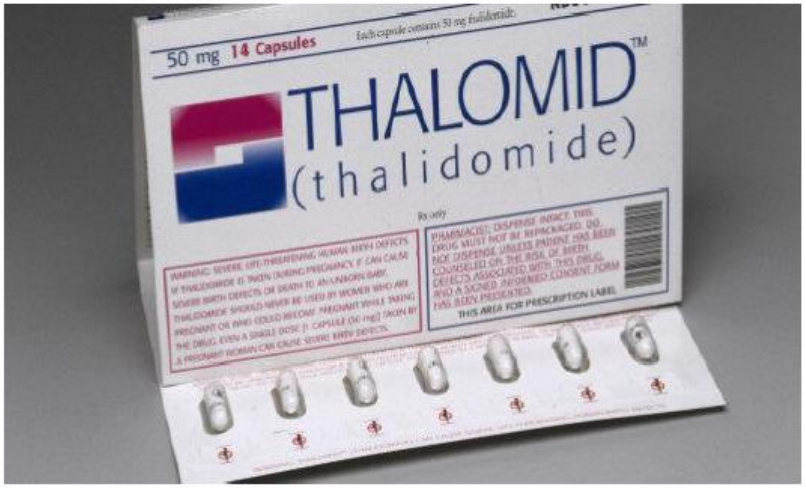
Thalidomide biological effects:

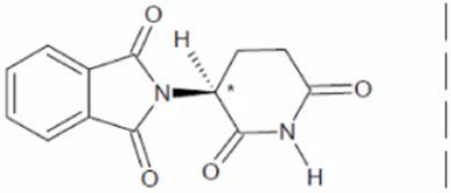


Mirror image of thalidomide caused limb deformation

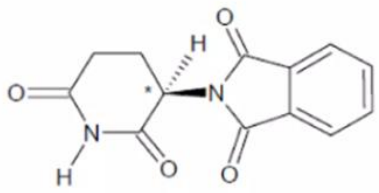
Optical isomers (Thalidomide) tragedy due to Mirror Image

Thalidomide drug exist as optical isomers,

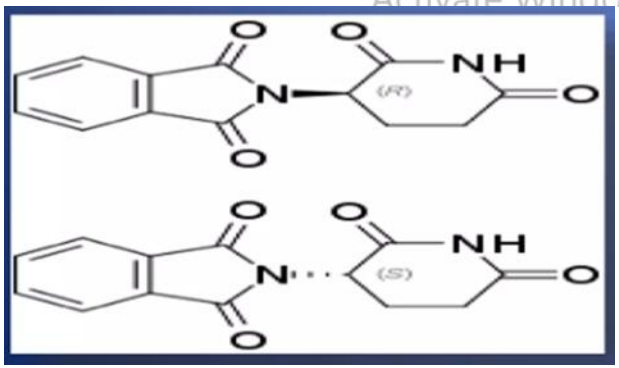
- **Enantiomers (R) and (S)**
- **(R) effective against insomnia and morning sickness**
- **(S) teratogenic, birth and limb defect**



(-)(*S*)-thalidomide



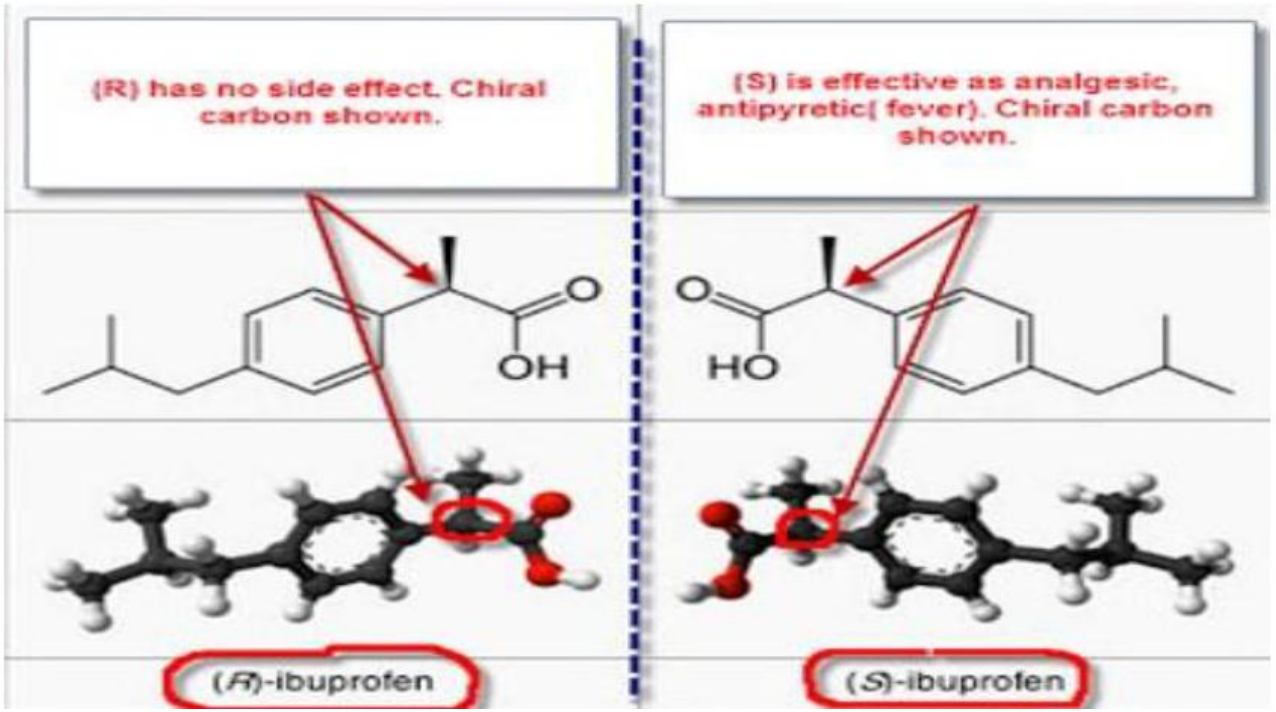
(+)(*R*)-thalidomide



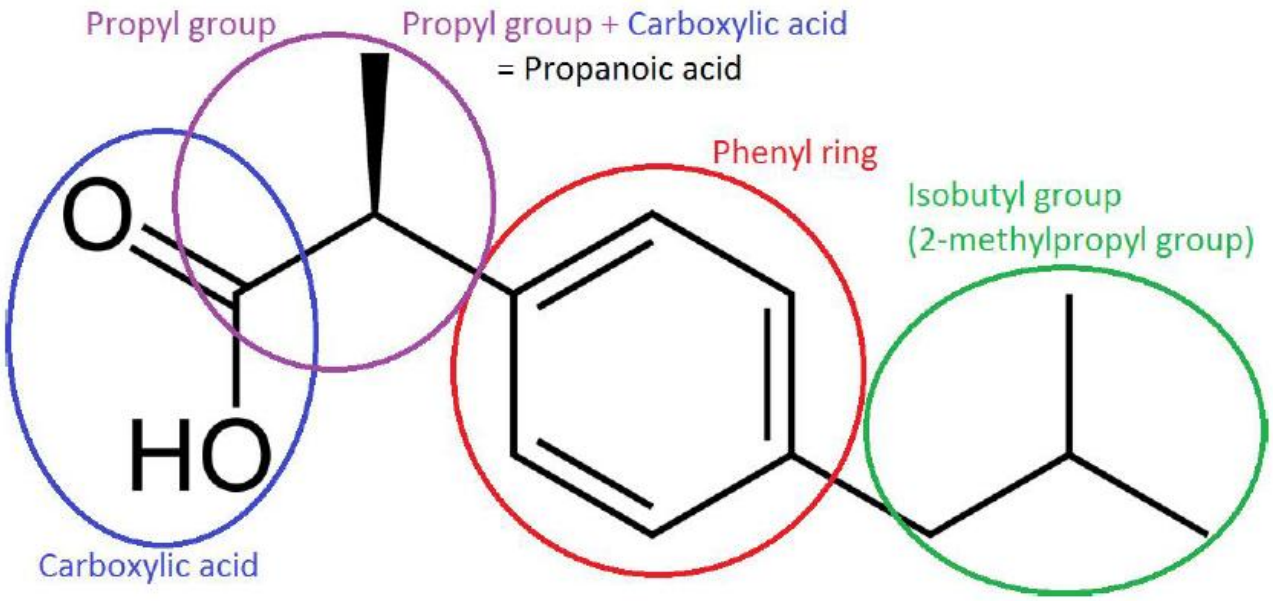
Ibuprofen Stereochemistry

- Ibuprofen has just one chiral atom and so exists as two enantiomers.
- It is an optically active compound with both S and R-isomers, of which the S (dextrorotatory) isomer is the more biologically active; this isomer has also been isolated and used medically.
- Ibuprofen is produced industrially as a racemate.

Optical Isomers structure of Ibuprofen

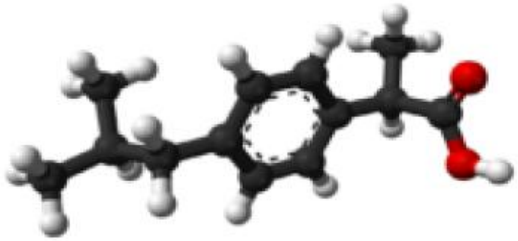


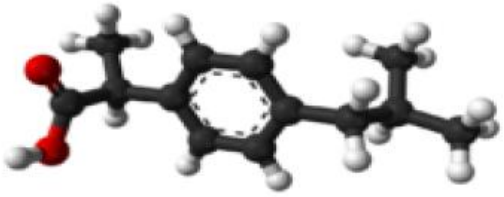
2D Structure of Ibuprofen, and Functional Groups



3D Structure of Ibuprofen

(R)-ibuprofen	(S)-ibuprofen





Ibuprofen biological effects:

- **Mirror Image of Ibuprofen (pain killer drug) has no side effect**
- (S) enantiomer, effective in reducing fever and pain relief
- (R) enantiomer has no side effect
- Most drugs in racemic mix equal (R) and (S)