

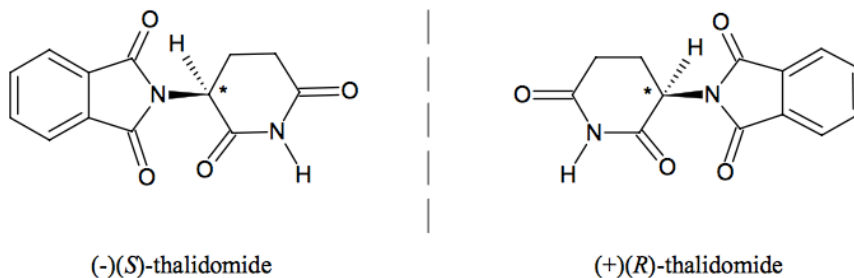
Thalidomide Case Study

(adapted from "Teaching Chemistry Through the Jigsaw Strategy" 2007 by Quality Education Fund, Hong Kong)

Part 1. Why is drug chirality important?

Enantiomers are optical isomers, which are nonsuperimposable mirror-image structures. The property of nonsuperimposability is called chirality. A molecule is chiral if and only if it is not superimposable on its mirror image. The most common chiral center is carbon. When four nonidentical atoms or groups are attached to a tetravalent carbon, the tetrahedral arrangement of the bonds in space results in two enantiomers. A mixture of equal portions (50/50) of the (+) and (-) enantiomers is called a racemic mixture.

In 1957, a pharmaceutical company in West Germany introduced a new drug to the market. It was called thalidomide with the molecular formula $C_{13}H_{10}N_2O_4$. The drug was sold in 46 countries under at least 37 brand names. Doctors prescribed it as a sedative and sleeping drug for pregnant women. There is one chiral carbon in the thalidomide molecule. The drug was made and marketed as a racemic mixture of the (+)(*R*)-thalidomide and (-)(*S*)-thalidomide.



Tragically, thalidomide was found to have serious side-effects; thousands of babies were born with missing or abnormal arms, hands, legs, or feet. It was banned by many countries in 1961. Now scientists know that it is the (-)(*S*)-thalidomide that caused the severe side-effects.

The action of drugs is usually explained using the receptor theory. Receptors are protein molecules in our body. Because protein molecules are chiral, they have different reaction with the two enantiomers of a chiral drug. In the 1950s, pharmacists and doctors did not know that the (+)(*R*)-thalidomide is an effective sedative, whereas the (-)(*S*)-thalidomide is a teratogen (a substance affecting the development of the foetus and causing structural or functional disability). Therefore, the enantiomeric composition of a chiral drug is a critically important issue in drug development. The thalidomide tragedy forced drug companies to reconsider enantiomers as separate molecules rather than just different forms of the same drug.

Not all drug molecules are chiral. Chiral drugs that are produced by chemical synthesis are usually a racemic mixture. Currently, regulatory guidelines do not prohibit the development of racemates of chiral drugs. However, drug companies should investigate the properties of each enantiomer of a new chiral drug before they introduce it to the market.

Questions

1. Why is thalidomide chiral?
2. What should drug companies consider when they develop and market new chiral drugs?

Part 2. What caused the thalidomide tragedy?

Thalidomide was first synthesized by a small drug company, Chemie Grünenthal, in West Germany in 1953. It was first recommended for the treatment of epilepsy. Trials indicated that thalidomide could not prevent convulsions, but epilepsy patients reported experiencing a good sleep.

In 1957, thalidomide was introduced to the West German market and it did not require a doctor's prescription. By 1961 thalidomide was the best-selling sleeping pill in West Germany and the UK. Thalidomide was also found to prevent nausea due to pregnancy. It was promoted by Chemie Grünenthal as a completely safe drug for pregnant women.

In 1960, harmful side effects of thalidomide were reported. Patients' nerves in their hands and feet deteriorated. Worse still, thalidomide was later found to cause severe birth defects when taken by pregnant women. Babies were born with hands and feet protruding directly from their torsos, a condition known as phocomelia. Others had limbless trunks with toes extending from their hips; others were born with just a head and a torso; still others had abnormal internal organs such as heart and kidney. It is estimated that anywhere from 8,000 to 80,000 deformed babies were born in Europe. Many died at birth due to their defects. In November 1961, thalidomide was withdrawn from the German market. The drug was not banned worldwide until 1962.

Thalidomide was sold as the racemic mixture of enantiomers. (+)(R)-thalidomide is a sedative, but (-)(S)-thalidomide is a teratogen (i.e., a drug that can harm a fetus in the womb). (-)(S)-thalidomide inhibits new blood vessel growth. This is detrimental to a fetus because new blood vessels provide a "road map" for the growth of limbs and organs during the development of a fetus.

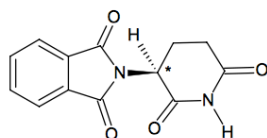
The mechanism of action of (-)(S)-thalidomide is not fully understood. More than 30 mechanisms have been proposed to explain the teratogenic action of (-)(S)-thalidomide. Some scientists have proposed that (-)(S)-thalidomide or one of its metabolites might exert its adverse effects by blocking the genes coding for some essential proteins. Thus, (-)(S)-thalidomide is the unwanted enantiomer. You might think that drug companies can simply purify the racemic mixture and give patients only the (+)(R)-thalidomide. Unfortunately, the answer is not that simple. Human liver contains an enzyme that can convert (+)(R)-thalidomide to (-)(S)-thalidomide. Therefore, even administration of enantiomerically pure (+)(R)-thalidomide results in a racemic mixture.

Questions

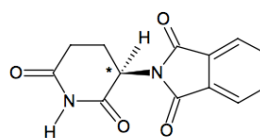
1. What are the harmful side effects of the chiral drug Thalidomide?
2. Why can thalidomide cause birth defects?
3. If doctors prescribe the pure (+)(R)-thalidomide only, could the harmful side effects of thalidomide be avoided? Why?

Thalidomide case study

- Read part 1 of the thalidomide case study
- Discuss the answers to the questions with your peers

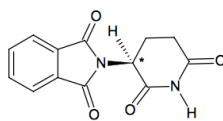


(-)(S)-thalidomide

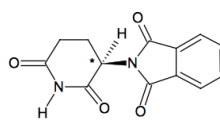


(+) (R)-thalidomide

- Why is thalidomide chiral?
 - There is 1 chiral carbon in the molecule (*)



(-)(S)-thalidomide

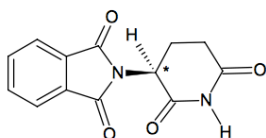


(+) (R)-thalidomide

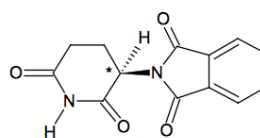
- What should drug companies consider when they develop and market new chiral drugs?
 - Will both enantiomers be safe? Will one enantiomer racemize to the other form?

Thalidomide case study

- Read part 2 of the thalidomide case study
- Discuss the answers to the questions with your peers



(-)(S)-thalidomide

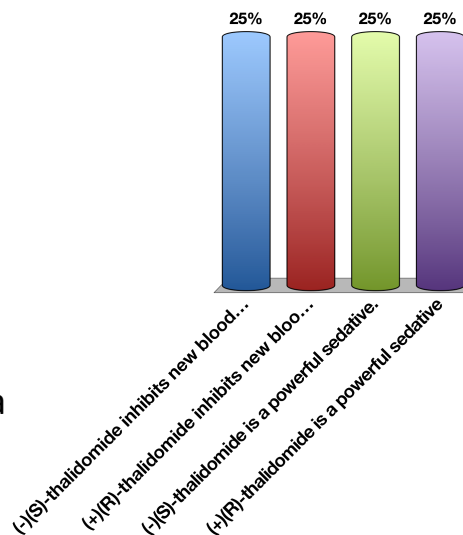


(+)(R)-thalidomide

- What are the harmful side effects of Thalidomide?
 - Deterioration of nerves, severe birth defects (which can sometimes lead to death)

Clicker question (1 point): Why can thalidomide cause birth defects?

- A. (-)(S)-thalidomide inhibits new blood vessel growth
- B. (+)(R)-thalidomide inhibits new blood vessel growth
- C. (-)(S)-thalidomide is a powerful sedative.
- D. (+)(R)-thalidomide is a powerful sedative



- If doctors prescribe the pure (+)(R)-thalidomide only, could the harmful side effect of thalidomide be avoided? Why?
 - No – the liver contains an enzyme that converts some of the (+)(R)-thalidomide to (-)(S)-thalidomide