

Teaching Chemistry Through The Jigsaw Strategy

Example 1

Topic

Thalidomide: A Controversial Chiral Drug

Subtopics

1. Why is drug chirality important?
2. What caused the thalidomide tragedy?
3. Why has thalidomide been approved for sale again?

Level

Secondary 6-7

Curriculum Links

Stereoisomerism

Enantiomerism

Chiral carbon compounds

Medium of instruction

English

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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. Why are drug molecules often chiral in order to have positive effects in humans?
3. What should drug companies consider when they develop and market new chiral drugs?

2. What caused the thalidomide tragedy?

Thalidomide, $C_{13}H_{10}N_2O_4$, was first synthesized by a small drug company, Chemie Grünenthal, in West Germany in 1953. Chemie Grünenthal patented the thalidomide molecule and began searching for a disease that it could cure. It was first recommended for the treatment of epilepsy (a disease of the nervous system causing a person to fall unconscious). 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. Actually, nothing was known about the pharmaceutical effects of thalidomide at the time of its marketing. 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. Photos of malformations caused by thalidomide are available at the following websites:

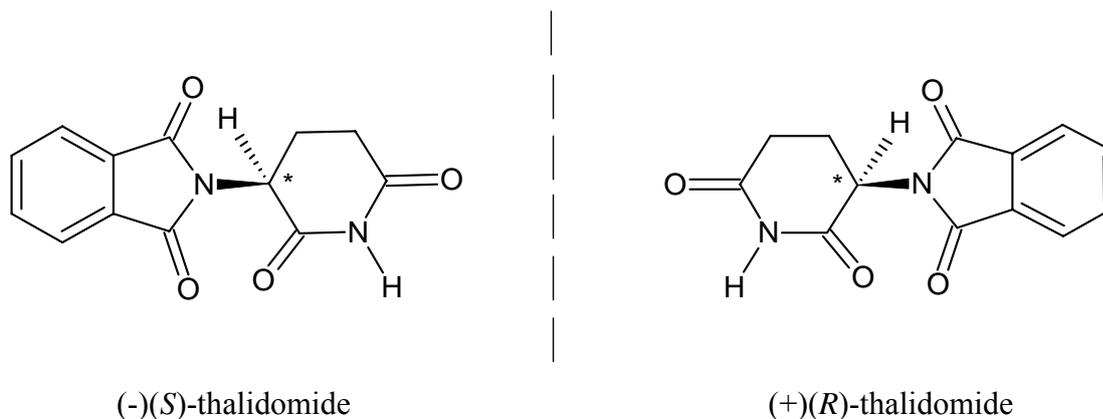
http://www.thalidomide.org/default_eng.asp?menyid=9&linkid=43

<http://www.thalidomide.ca/en/information/brochure1.html>

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

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.

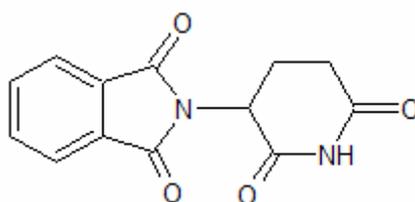
Questions

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?

3. Why has thalidomide been approved for sale again?

In the 1950s and 1960s, thousands of babies were born without arms and legs in Europe. The tragedy was caused by the side effects of a chiral drug called Thalidomide ($C_{13}H_{10}N_2O_4$) synthesized by the drug company Chemie Grünenthal in West Germany. Some babies were also born blind or deaf. Other harmful side effects of thalidomide include:

- Spinal cord defects
- Absent or abnormal external ears
- Heart, kidney, and genital abnormalities
- Abnormal formation of the digestive system



Thalidomide

Thalidomide, originally used as a sedative for pregnant women, was banned worldwide by WHO (World Health Organization) in 1962. Now doctors know that the greatest risk of thalidomide-induced birth defects is in the first 1-2 month of pregnancy, before a woman may recognize that she is pregnant. Photos of malformations caused by thalidomide are available at <http://news.bbc.co.uk/2/hi/health/202713.stm>.

However, the ban of thalidomide was lifted in 1985 by WHO. Between 1969 and 1995, 34 cases of thalidomide-induced birth defects were found in South America. Chemie Grünenthal sold 4,000 pills to Hong Kong during the years 1985 to 1992 with the brand name Poli-Gripan.

In July, 1998, the Food and Drug Administration in the USA approved it for the treatment of erythema nodosum leprosum (ENL, an inflammatory complication of leprosy). The drug does not kill the bacteria that cause leprosy, but it does change the body's immunological response to those bacteria. Thalidomide can decrease the level of TNF- α (tumour necrosis factor alpha) in ENL patients. TNF- α is responsible for the tissue inflammation in ENL patients. WHO does not recommend the use of thalidomide to treat ENL because there are other drugs that work just as well as thalidomide but do not cause birth defects. However, thalidomide is easy

to produce at a very low cost. This is the main reason why it is often used in the treatment of ENL in many countries.

In May, 2006, the US Food and Drug Administration also granted approval for thalidomide in combination with another drug called dexamethasone for the treatment of multiple myeloma (a bone marrow cancer). It was approved under accelerated approval regulations which require further clinical trials to demonstrate thalidomide's benefit in the treatment of multiple myeloma.

The Chemie Grünenthal patent on thalidomide has expired. Today it is legal for anyone to synthesize thalidomide. In the USA, Celgene Corporation sells thalidomide under the trade name "Thalomid". Celgene is allowed to market it only under a special restricted distribution program approved by the US Food and Drug Administration. It is called the "System for Thalidomide Education and Prescribing Safety (STEPS)." Only prescribers and pharmacists registered with the STEPS program are allowed to prescribe and dispense Thalomid. Patients must be advised of, agree to, and comply with the requirements of the STEP program to receive Thalomid.

Today, thalidomide is used experimentally in all continents to treat various cancers and inflammatory diseases. They are particularly interested in the following three properties of thalidomide:

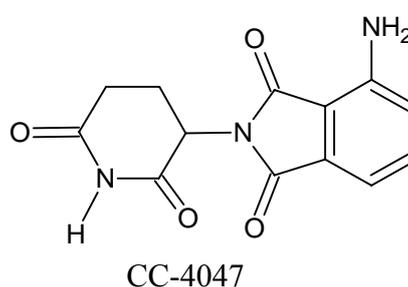
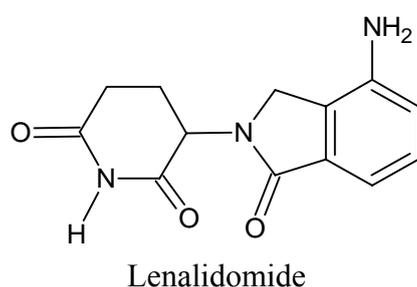
- Inhibition of the growth of new blood vessels
- Activation of human immune system
- Anti-inflammatory effects

For example, some drug manufacturers are conducting trials to see if thalidomide can cure breast, prostate, brain, lung and pancreatic cancer. Because thalidomide can inhibit new blood vessels forming in and around tumors, doctors hope that the drug can kill tumors directly by shutting down the blood supply to them. Also, thalidomide is being investigated as a treatment for AIDS (acquired immune deficiency syndrome). More than a million people a year die from AIDS as a result of infection with HIV (human immunodeficiency virus). Some AIDS sufferers cannot eat due to painful ulcers in the mouth and esophagus. Clinical trials indicated that thalidomide may help AIDS patients by reducing their ulcers.

However, thalidomide victims are very concerned about the return of this drug. One of the reasons is that the control of the intake of thalidomide during early pregnancy is very difficult because most pregnancies are unintended. Taking even one thalidomide pill (e.g., one capsule

of 50 mg) can cause birth defects. Another reason is that thalidomide not only adversely affects pregnant women but also men and children. A common harmful effect is permanent nerve damage (called peripheral neuropathy). Thalidomide victims believe that it is impossible to avoid misuse of thalidomide. They have suggested that the drug should always be called “Thalidomide” and not sold under a brand name.

Thalidomide victims hope that pharmaceutical companies could discover an analogue with the positive clinical effects of thalidomide but without its harmful side effects. One class of thalidomide analogues is called immunomodulatory drugs. Examples are lenalidomide and CC-4047.



In 1999, scientists found that lenalidomide and CC-4047 can inhibit TNF- α and are 2,000 and 20,000 times more potent than thalidomide respectively. Lenalidomide and CC-4047 also stimulate T cells, which are a type of white blood cell involved in a variety of immune reactions. In 2000, analogues of thalidomide were found to have the ability to kill multiple myeloma cells.

Questions

1. Why was thalidomide banned in 1962?
2. Why did the US Food and Drug Administration approve the use of thalidomide in 1998?
3. Thalidomide victims have expressed a lot of concerns about the return of thalidomide to the market. What are their major concerns? What are their recommendations?