THE PAINS OF PAINKILLERS

By Dragos Bora

In the fall of 1960, Canadian pharmacologist and physician Frances Oldham Kelsey was one of the Food and Drug Administration's latest recruits. As such, Kelsey was assigned what was thought to be an easy review. A new drug application from the US company Merrell to sell a drug called Thalidomide. At the time, this sedative was already used in dozens of countries to treat insomnia and stress. Pregnant women with morning sickness were also prescribed Thalidomide thanks to its anti-nausea properties.

Reviewing the data on Thalidomide's absorption and toxicity, Kelsey found it insufficient. Merrell, like many other drug companies of the time, had not tested its drug on pregnant animals. In 1960, many experts believed that the placental barrier shielded foetuses from harm. Kelsey's earlier studies with pregnant animals proved the opposite.

Kelsey rejected Merrell's application. Merrell was hoping to quickly launch Thalidomide in the US for the holiday season, one of the most stressful times of the year. Rather than resubmitting applications with new research, Merrell tried to convince Kelsey to approve the drug through calls and visits. When these attempts failed to influence her decision, Merrell insisted Kelsey was the problem not Thalidomide. The FDA supported Kelsey and Merrell was forced to submit several more applications all of which were rejected.

As Kelsey reviewed and rejected each new submission, news of the horror of Thalidomide's effects on newborns slowly began to surface. Throughout Europe and Canada, thousands of babies died in utero and tens of thousands were born with malformed limbs, or no limbs at all. In the fall of 1961, Thalidomide was pulled from the West German market. Merrell continued trying to get the drug approved in the US for several more months before finally withdrawing its 6th application.

The source of Thalidomide's negative effects on newborns was later discovered to be the geometry of the drug. Much to the surprise of Merrell, the drug they had marketed was a racemic mixture. While the D enantiomer helped alleviate morning sickness in pregnant women, the L enantiomer caused severe birth defects and premature death in foetuses.

For her part in preventing a tragedy from ensuing, Kelsey slowly became famous. In 1962 President John F. Kennedy presented her with the President's Award for Distinguished Federal Civilian Service. She continued to help the FDA in various capacities well into her 90s and returned to Canada where she was named to the Order of Canada. She died at age 101.

Note: When referring to enantiomers, L and S are used synonymously, and D and R are also used synonymously.

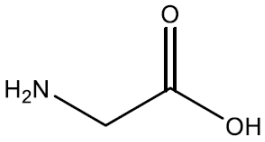
On account of your world-renowned organic synthesis skills, the pharmaceutical company *Kurall* recruited you several months ago to synthesize a new alleviative to treat osteoarthritis. After many sleepless nights, you created the perfect compound. This new drug falls under the category of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), a class which also includes acetylsalicylic acid (Aspirin), ibuprofen (Advil), and naproxen (Aleve). When initially tested in laboratory rats, your new drug was shown to have substantially increased potency and fewer side effects than any known NSAID. Last week, the first large scale synthesis of the drug was completed by the process chemists at *Kurall*. When tested again in lab animals, the compound exhibited only half the potency that was observed from your original samples. This made no sense to you! The predicted chemical properties of the drug and its effects on the target enzyme were inconsistent. Similar to ibuprofen and naproxen, your new drug contains a chiral center. As with all NSAIDs, the biological target is the enzyme cyclo-oxygenase, which is known to be affected primarily by enantiomers of the L-stereoconfiguration.

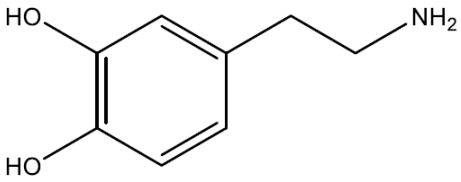
You sent a sample of the compound from the large-scale synthesis to be analyzed by the department of analytical chemistry and the results have arrived. High resolution nuclear magnetic resonance spectroscopy and mass spectrometry indicate the presence of two species in the sample of the same molecular weight. It is up to you to determine what has gone wrong in the large-scale production of your new drug.

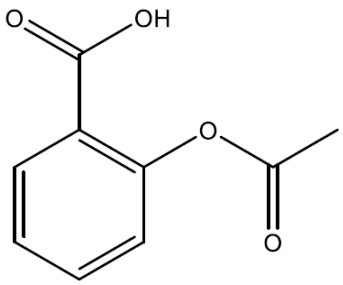
Questions

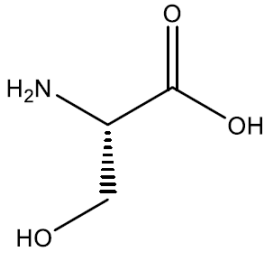
1) Identify the functional groups for each molecule and match the commercial/common names and IUPAC names with the structures on the page.

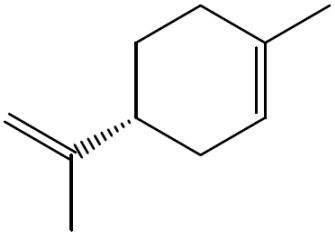
IUPAC Name	Common Name
2-Acetoxybenzoic acid	Aspirin
(*S*)-4-Isopropenyl-1-methyl-1-cyclohexene	S-limonene
2-Aminoethanoic acid	Glycine
L-2-Amino-3-hydroxypropanoic acid	L-Serine
4-(2-Aminoethyl)benzene-1,2-diol	Dopamine
(*R*)-4-Isopropenyl-1-methyl-1-cyclohexene	R-limonene

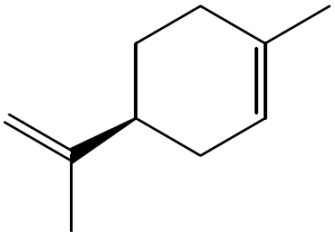












2) Which of these molecules contain a chiral center? How might you experimentally determine this from a sample?
3) When a sample of the large-scale synthesis of your drug was testing using a polarimeter, it exhibited no rotation. What is a polarimeter? How does it work, and what property does it measure?
4) Use the materials provided to construct your own polarimeter and analyze the provided samples of *R-limonene* and *S-limonene*. What do you observe when you measure mixtures of the two? What may have happened to cause the reduced potency of your drug?

Available Materials:

1) 100mL beaker.
2) 2” PVC pipe with 7cm length.
3) 2” PVC pipe with 1cm length.
4) Protractor face with 4” diameter.
5) Scissors.
6) Linear polarized film.
7) Glue.
8) Chiral samples.
9) A light source such as a lamp or overhead projector.