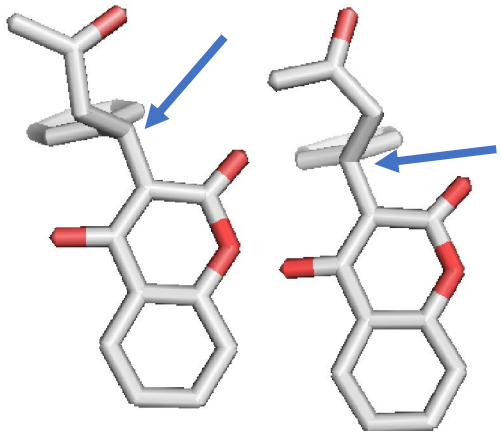
TC4 – Stereospecificity and Computational Biochemistry

STEREOSPECIFICITY AND ENANTIOMERS

One of the most important features of an active site is its **stereospecificity**. Many drugs have chiral centres, and therefore can exist as a pair of **enantiomers**, labelled D- or L- (sometimes R/S). This is important because each enantiomer can have different effects on the body, based on the interactions of the enantiomers with enzymes in the body. The active site of an enzyme has a very specific structure and shape which affects the **enzyme-substrate interactions**. Even though one enantiomer may bind very well to an enzyme, the other enantiomer is a mirror image, and may not be able to bind effectively. Either because the drug **cannot fit well into the active site**, or if it can, then the drug **may not be able to interact as effectively.**



The two enantiomers of warfarin. The chiral centre is indicated.

COMPUTATIONAL MEDICINAL CHEMISTRY

Traditionally, there were two main approaches to developing drugs. The first is the **ethnopharmacological approach**, which uses folklore to find possible drugs. Aspirin was discovered through this, as the bark and leaves of the willow tree was used for centuries to reduce pain, inflammation and fevers. Aspirin was isolated as the active compound in the 19th century, and ever since it has been produced in laboratories across the world as one of the most common drugs.

Another approach is **reverse** pharmacology, to take the target compound, and attack it with a barrage of possible drugs. Once the target protein has been found, such as an enzyme which you want to inhibit, then you can test the target against a library of known drugs. This allows you to find promising leads, which you can further develop and study. However, this can be very time consuming, and very costly.

A modern approach involves **computational chemistry**. This combines the chemical knowledge of scientists with the computational power of modern day computer software. There are many factors which need to be considered when designing a drug. Such as its solubility, acidity, and other drug-drug interactions. If the target enzyme is known, then the active site can be found. Once the active site is known, it is possible to screen potential drugs using computer software. This makes it clear to see if a drug is too large, or too small to interact with an active site. It also allows other interactions to be considered, such as if the drug is the right shape and size to interact, but may have the wrong chemical groups to interact well. This can save considerable time and money from laboratory-based investigations. Computational chemistry also allows the properties of a drug to be calculated. For example, the solubility of a drug is vital, and even if it appears to be the perfect drug to interact with the target, if it doesn't dissolve, then it's not going to be able to travel in the body, through the bloodstream and cell membranes to interact!

Produced by Adam Stubbs at Newcastle University as part of a summer outreach project.