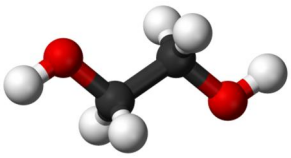
TA10 – Enzyme Inhibitors

An **enzyme** is a protein that acts as a **biological catalyst**.

For an enzyme to work, it must bind to a **substrate** molecule which is **complementary** to the enzyme's active site (binding site). The active sites are **stereospecific**, meaning that they will only be complementary to one **enantiomer** of a substrate. They bind to form an **enzyme-substrate complex**.

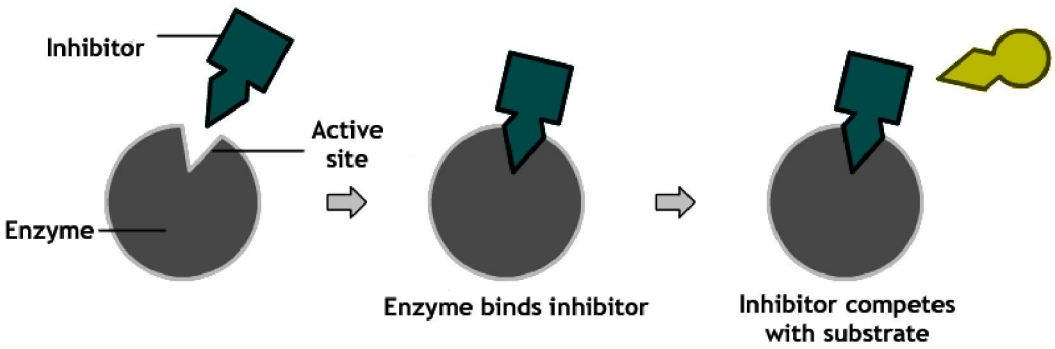
An **enzyme inhibitor** is a substance which has a similar shape to a substrate molecule and can inhibit an enzyme, slowing down or preventing a particular chemical reaction from occurring by binding to an enzyme and **decreasing its activity**. Blocking an active site can stop particular reactions occurring.



There are **two** types of enzyme inhibitors;

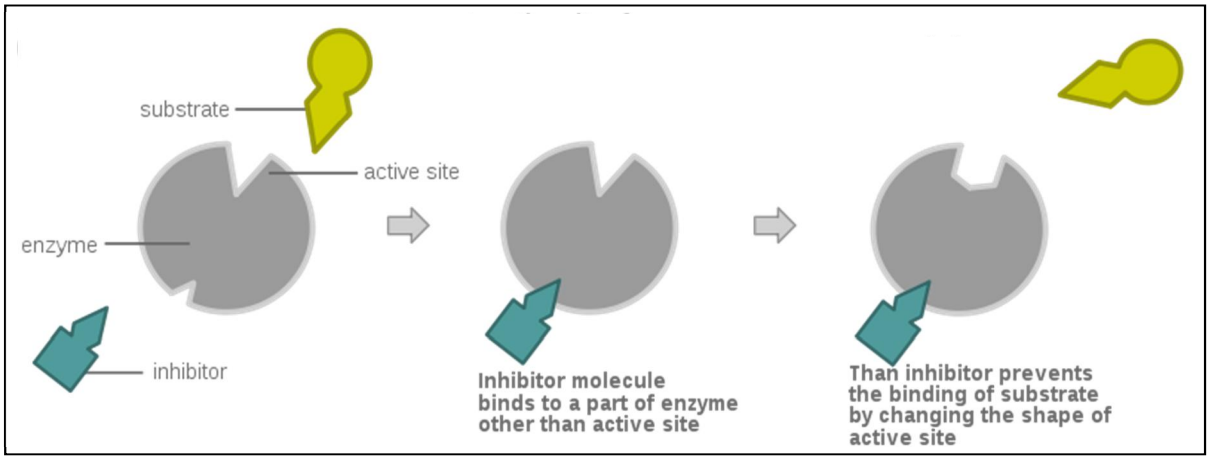
Competitive Inhibitors

A competitive inhibitor is a compound which has a similar chemical structure to that of a **substrate** molecule. This allows the inhibitor to bind to the active site of the **complementary** enzyme and therefore compete with the substrate molecules. The inhibitor **'blocks'** the active site for the substrate molecules and reduces the rate of reaction. The complex created, and shown in the image below, cannot react to form the desired products – but its formation is still **reversible** unlike a non-competitive binding.

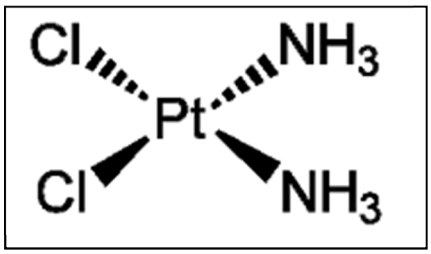


Non-competitive Inhibitors

A non-competitive inhibitor is a compound which interacts with an enzyme **elsewhere** from the active site. When it binds to the enzyme, a non-competitive inhibitor will cause a change in shape of the enzyme, and therefore the active site. This means that the substrate molecule will no longer be complementary to the active site. This is an **irreversible** reaction as once the inhibitor is bound, the active site cannot go back to its original structure and will no longer be a functioning enzyme. As you can see in the image below, the inhibitor prevents the binding of a substrate molecule as the active site has been changed to a **non-complementary** structure.



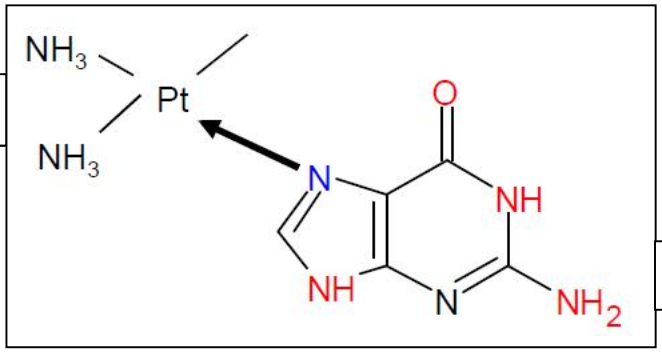
Cisplatin



Anticancer drugs act as enzyme inhibitors to prevent the replication of cancer cells.

Cisplatin is used as an **anticancer drug**. Its role is to stop the cancerous cells from spreading throughout the body, causing further damage. It does this by preventing DNA replication in cancer cells by a **ligand** replacement reaction with DNA. This forms a direct **dative covalent bond** between the platinum atom in cisplatin and a nitrogen atom on the nitrogenous base guanine, found in a DNA strand. By doing this, guanine is then unable to bind to its complementary base, cytosine, and so stops the two strands of DNA from replicating.

Cisplatin



Guanine

Factors Affecting:

Substrate concentration:

- **Competitive inhibition**: if the substrate concentration is increased then the effect of the inhibitor is decreased. This is because the inhibitor-enzyme complex is reversible so substrate molecules can still bind to the enzyme and compete with the inhibitor.
- **Non-competitive inhibition**: an increase in substrate concentration will have no effect on the inhibitor. This is because the substrate and inhibitor are not competing, the inhibitor is changing the shape of the active site.

Temperature:

- For both types of inhibition, an increase in temperature will increase the rate of reaction and the amount of enzyme-substrate complexes formed in a shorter amount of time. The molecules will have a larger amount of kinetic energy, increasing the speed at which they move and so there will be a higher chance of successful collisions occurring. However, increasing the temperature too much will give the enzyme too much energy. This will cause the enzyme to denature, as the bonds holding the tertiary structure in place will be broken.

Inhibitor concentration:

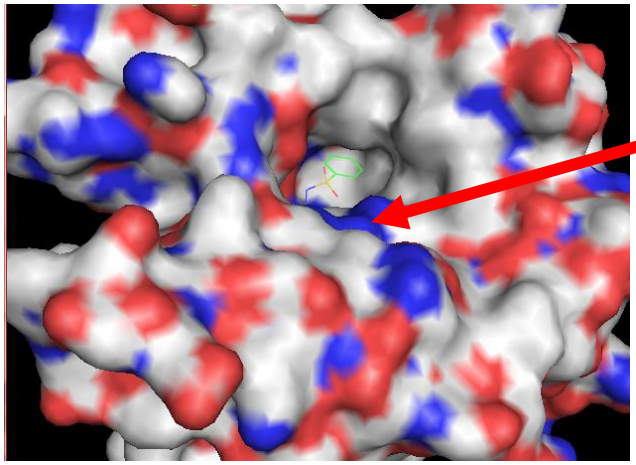
- For both types of inhibition, an increase in inhibitor concentration would increase the effect of the inhibitor as there will be a higher chance of successful collisions between inhibitor and enzyme. This will reduce the amount of enzyme-substrate complexes formed and so reduces the rate of reaction.

For a cartoon visual of the factors effecting enzyme inhibition visit:

http://www.kscience.co.uk/animations/enzyme_model.htm

PDBe:

To understand the structure and function of enzyme inhibitors further, use the Protein Date Bank in Europe to research different enzyme inhibitors. You can then use the 4-character code given to you on the PDBe to look at the 3D structure of the enzyme inhibitor.



A good example is carbonic anhydrase and its inhibitor:

4yx4

Recall Questions:

1. What is an enzyme inhibitor?
2. Describe how anticancer drugs act as inhibitors.
3. Explain the difference between a competitive & non-competitive inhibitor.