Medicinal Chemistry & Drug Discovery
Section 2.2.1 – Enzymes & Inhibitors

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Learning goals

- describe enzyme catalytic activity
- interpret enzyme inhibition data
- correlate substrate and inhibitor structure

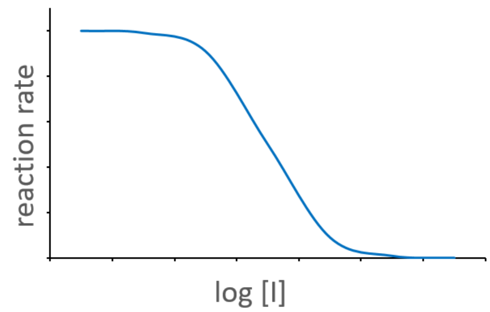
Vocabulary

- enzyme
- substrate
- product
- active site
- inhibitor
- IC_{50}
- competitive inhibitor

Enzymes are proteins that facilitate or catalyze the conversion of one molecule into another. The starting molecule is called the **substrate** – "S". The product is called a **product** – "P". Enzymes (E) bind a molecule of substrate at the **active site** of the enzyme to make an enzyme-substrate complex. A reaction forms the product, which is immediately released from the enzyme. The enzyme can then find another substrate molecule and repeat the process.

E	+	S	$\rightleftarrows$	E-S	$\longrightarrow$	E	+	P
enzyme		substrate		enzyme-substrate complex				product

Drugs that act on enzymes are **inhibitors** – "I". A drug or potential drug binds the enzyme and prevents product formation. How do we measure whether a molecule is acting as an inhibitor? Here is a graph that plots the rate of an enzyme-catalyzed reaction against the concentration (or the logarithm of the concentration of an added inhibitor). At very low inhibitor concentration, the rate of the reaction is high – about 100%. At high inhibitor concentration, the rate is low – about 0%. In between these extremes, the curve of rate vs. log[I] follows a sigmoidal curve. The inflection point of this curve occurs at the log[I] value at which the rate is reduced to 50%. The x-axis value is log IC_{50}. The concentration at this point is the IC_{50}. Determining the IC_{50} of an inhibitor requires multiple experiments to get data points that can generate this curve.



Inhibitors are often designed based on the structure of the substrate. If the substate binds the active site, then molecules similar to the substrate should also bind the active site.

Xanthine oxidase is an enzyme. It catalyzes the conversion of xanthine (the substrate) into uric acid (the product). An inhibitor of xanthine oxidase should have a similar structure to xanthine so that the inhibitor will bind at the active site. The inhibitor should be different so it won't undergo the chemical reaction. A known inhibitor of xanthine oxidase is allopurinol. Allopurinol resembles xanthine but lacks a carbon atom for the oxidation step. Allopurinol is called a **competitive inhibitor** because it competes with the substrate for the active site. Knowing the structure of the substrate is very helpful for the design of an enzyme inhibitor.