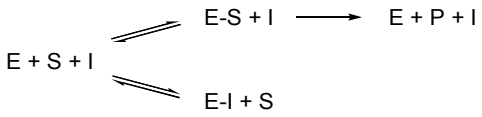
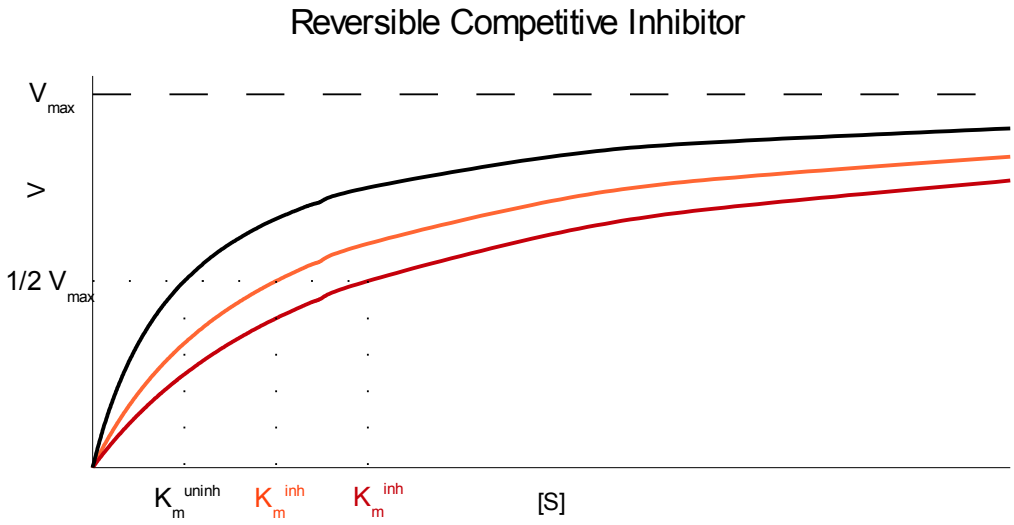
DavidsonX – D001x – Medicinal Chemistry
Chapter 4 – Enzymes
Part 2 – Enzyme Inhibition
Video Clip – Reversible Inhibitors

From a drug discovery standpoint, enzymes are very interesting, but only in as much as they can serve as drug targets. Drugs that interfere in an enzyme's function are called **inhibitors**. Inhibitors are classified as being reversible or irreversible. Among the reversible inhibitors are three different types: **competitive**, **noncompetitive**, and **uncompetitive**. All inhibitors, when bound to an enzyme, prevent the conversion of substrate to a product.

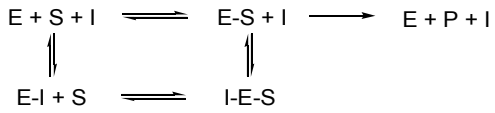
Competitive inhibitors bind an enzyme just like a substrate does – at the **active site**. The active site is the binding pocket in which a substrate is converted to a product. By trying to occupy the active site, the inhibitor *competes* with the substrate for the enzyme.



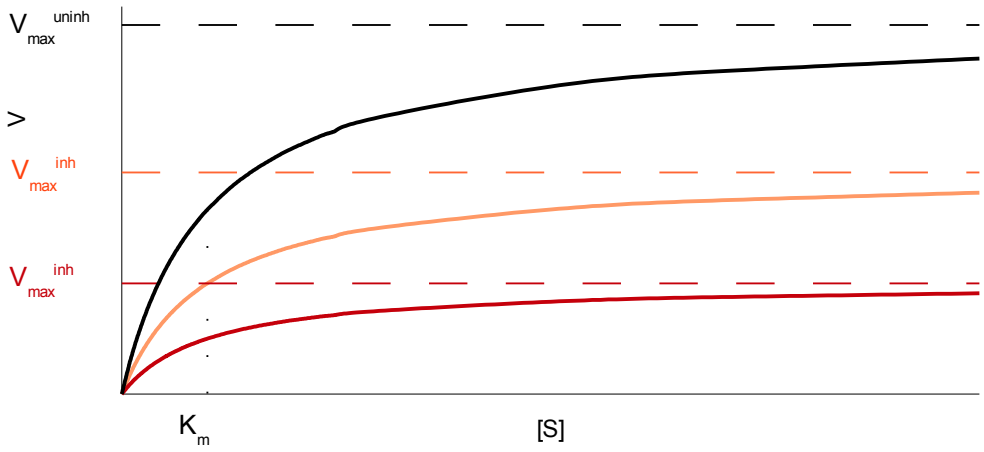
Mathematically, the effect of a competitive inhibitor on an enzyme is to decrease the affinity of an enzyme for a substrate. The affinity is measured by K_m, the Michaelis constant, and a lower affinity appears as a higher value for K_m in the presence of the inhibitor. V_{max}, however, is unchanged, but it does require a higher substrate concentration to approach V_{max} if an inhibitor is present. Visually, these changes are apparent in the graph below.



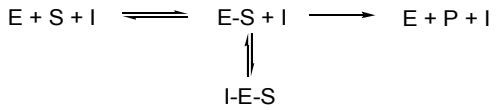
Noncompetitive inhibitors can bind both the enzyme and the enzyme-substrate complex. The inhibitor binds at a site other than the active site. The other site is called an **allosteric site**. Noncompetitive inhibitors reduce V_{max} but give no change in K_m.



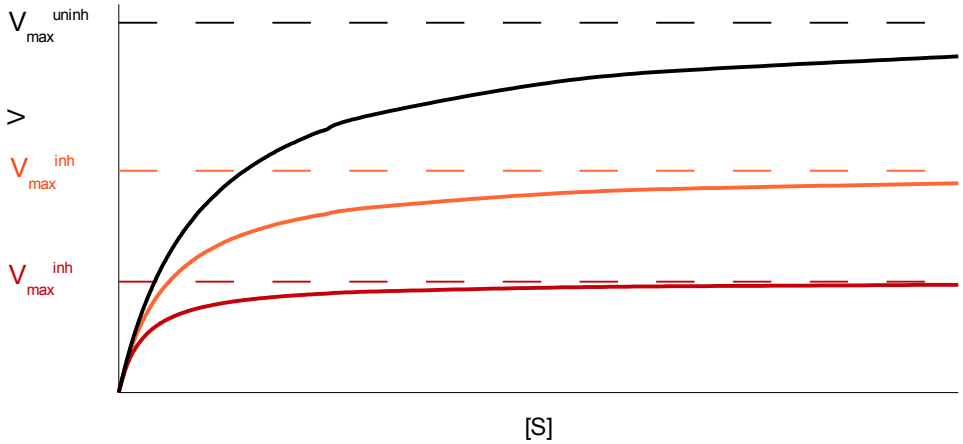
Reversible Noncompetitive Inhibitor



Uncompetitive inhibitors bind only the enzyme-substrate complex. This binding decreases *V*max *and* decreases *K*m. The net effect is that the inhibited *V* vs. [S] lines tightly follow the uninhibited line and then rapidly plateau toward V_{max}. In extreme cases, the inhibited lines can actually shift left of the uninhibited line before quickly moving to the right with a lower V_{max} value. This "crossing" of the lines is found with some, but not all, uncompetitive inhibitors.



Reversible Uncompetitive Inhibitor



Of the three types of reversible inhibitors, we will focus most on competitive inhibitors. Competitive inhibitors are very common in medicinal chemistry. The reason is because if you know the natural substrate of an enzyme, then you also know the same of a molecule that binds the enzyme's active site. That knowledge is very helpful in the design of other molecules, such as competitive inhibitors, that will also bind the active site.

We have avoided irreversible inhibitors because drug programs also generally avoid irreversible inhibitors. Irreversible inhibitors act by chemically reacting with the enzyme. The altered enzyme is then ineffective for converting a substrate to a product. Irreversible

inhibitors therefore are somewhat chemically unstable and at risk for reacting elsewhere in the body and not just at the desired enzyme. In the past five years, however, medicinal chemistry has enjoyed a resurgence in irreversible inhibitors. This new interest is irreversible inhibitors is most common in cancer treatments, an area in which the potential benefits outweigh the serious risks. Regardless, competitive reversible inhibitors are still more common than all other types of enyzme inhibitors.