

## Enzyme Inhibition

### A Strategy for Drug Development

#### Introduction

Early in the semester we looked at one case where enzyme inhibition was the mode of action of the drug. This was the case with sulfonamide and related antibiotics. Many antibiotics are enzyme inhibitors.

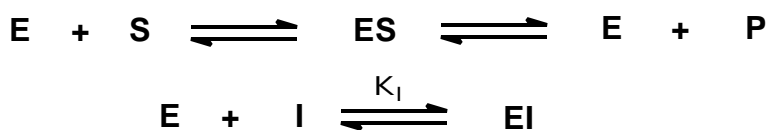
The inhibition of an enzyme involves a molecule or drug which slows or blocks its catalysis. The enzymologists recognize several classes of enzyme inhibition. These are:

1. Competitive inhibition
2. Noncompetitive inhibition
3. Uncompetitive inhibition
4. Suicide inhibition or mechanism based inactivation

#### How is Enzyme Inhibition Detected?

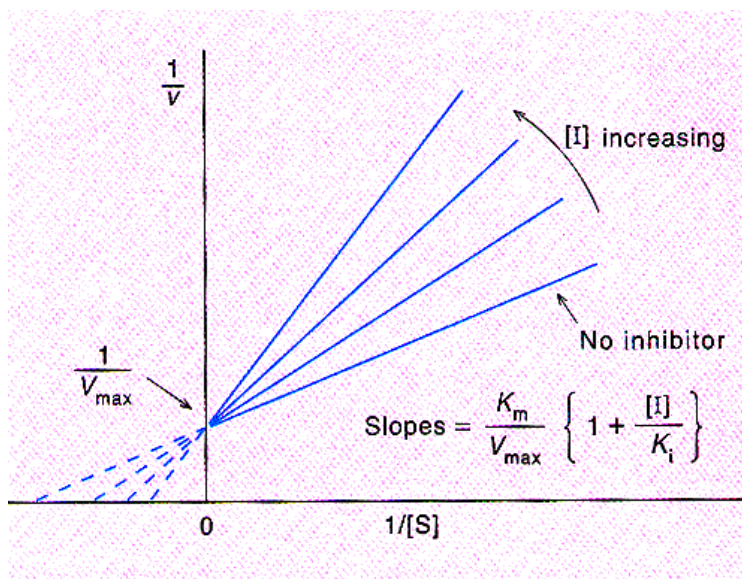
The answer is straight forward, by enzyme kinetics. Again, using initial rate measurements, a plot of  $1/v_0$  vs.  $1/[S]$  is constructed, where  $v_0$  is the initial rate, and  $[S]$  the substrate concentration. This is done at higher and higher concentrations of inhibitor  $[I]$  for each set of runs.

For Competitive Inhibition, which involves reversible competition for the active site, the equations are:

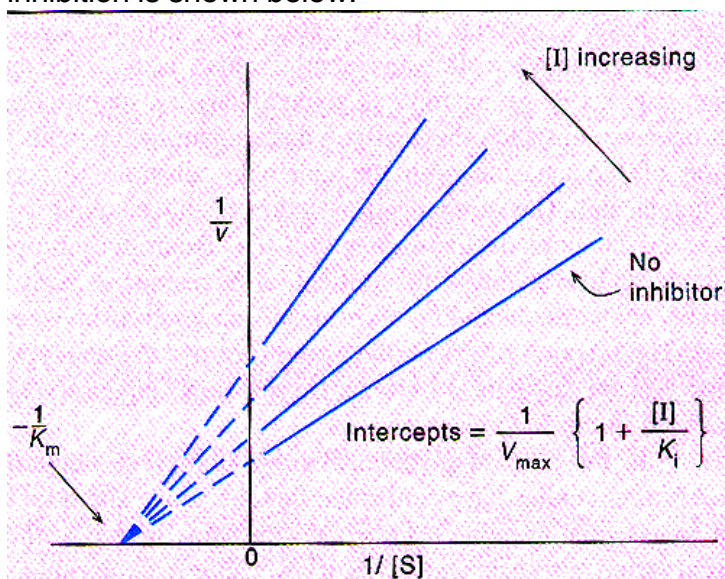


$$\frac{1}{v_0} = \frac{1}{V_{\max}} + \frac{K_m}{V_{\max}[S]} \left\{ 1 + \frac{[I]}{K_i} \right\}$$

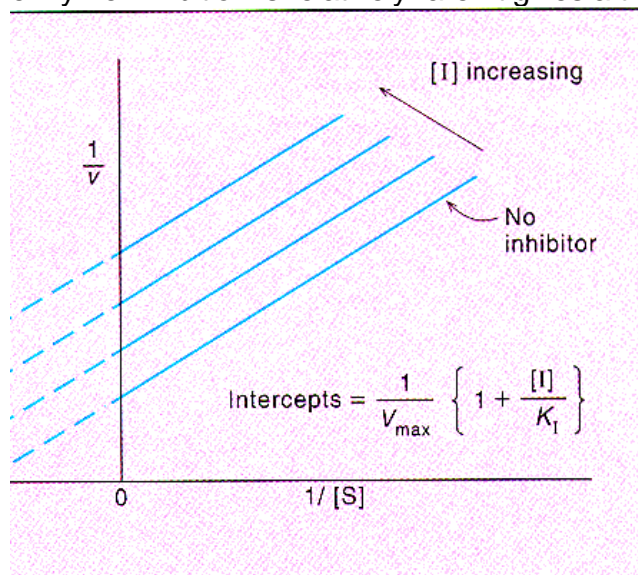
A typical plot for competitive inhibition looks as follows:



A noncompetitive inhibitor binds to site on the enzyme other than the active site and interferes with the catalytic process regardless of whether the substrate can bind. Usually this occurs by a distortion or change in the three dimensional structure of the enzyme. A typical set of plots for such inhibition is shown below.



In uncompetitive inhibition the inhibitor binds only to the enzyme-substrate complex. This type of enzyme inhibition is relatively rare. It gives a third type of plot as is shown below.



These types of inhibition can be summarized graphically in the cartoon diagram which is shown at the right.

The final type of enzyme inhibition involves mechanism based inactivation. It is detected in another way and will be discussed separately.

