COMPARISON OF INHIBITION MECHANISMS

Competitive inhibition

I binds only to free E - prohibits binding of substrate. Binding of I and S to E are mutually exclusive.

\[ E + I \quad \text{Ki} \quad I + E \quad E + S \quad K_s \quad ES \quad k_2 \quad E + P \]

I does not affect \( V_{\text{max}} \), but does affect the apparent \( K_M \) - it removes E from the enzyme-substrate equilibrium. Reciprocal plots indicate that this statement is true:
Noncompetitive Inhibition

I binds equally well to E or ES - it does not affect the binding of S (and S does not affect the binding of I):

Reciprocal plots - the slope of the line and the intercept of the lines are affected equally, but the $K_M$ is not affected - the result is a set of lines intersecting on the $1/[S]$ axis.

Noncompetitive Inhibition
**Uncompetitive Inhibition**

I binds only to ES - this affects $K_M$ by removing ES from the enzyme-substrate equilibrium. It also affects $V_{max}$, since some enzyme is removed from possible catalysis by binding to I.

Reciprocal plots - the slope is unaffected, since the $V_{max}$ and $K_M$ are affected equally. The $1/V_{max_{app}}$ intercept is affected - the result is a set of parallel lines dependent upon the concentration of [I].

\[
\begin{align*}
E + S & \quad \xrightarrow{K_S} \quad ES \quad \xrightarrow{} \quad E + P \\
I & \quad \uparrow \quad \rightarrow \quad ESI \quad \rightarrow \quad x
\end{align*}
\]
Mixed Inhibition

Noncompetitive inhibition is a special case of mixed inhibition. In a more general description of mixed inhibition, the following equilibria describe the binding of inhibitor to different states of the enzyme:

\[
E + S \xrightarrow{K_S} ES \xrightarrow{} E + P
\]

\[
K_I \quad I \quad K'_I \quad I
\]

\[
EI + S \xrightarrow{} ESI \quad x
\]

In this more general case, \( I \) binds to \( E \) and \( ES \) with different affinity, as indicated by different values for the \( K_I \).

As you can see from the double reciprocal relationship, both the slope of the line and the Y-axis intercept are affected by the mixed inhibitor, as in the
case of the noncompetitive inhibitor, but that the apparent $K_M$ may be different. With mixed inhibition, you will observe in the Lineweaver-Burk plot a series of lines intersecting between the Y axis intercept and the X-axis intercept. When the two different $K_i$'s are the same, mixed inhibition reduced to noncompetitive inhibition.

Table 14-2 summarizes the effect of different types of inhibitors on the constants in the Michaelis-Menton analysis.

<table>
<thead>
<tr>
<th>Type of Inhibition</th>
<th>$V_{\text{app}}$</th>
<th>$K_{\text{app}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>$V_{\text{max}}$</td>
<td>$K_M$</td>
</tr>
<tr>
<td>Competitive</td>
<td>$V_{\text{max}}$</td>
<td>$\alpha K_M$</td>
</tr>
<tr>
<td>Uncompetitive</td>
<td>$V_{\text{max}/\alpha'}$</td>
<td>$K_M / \alpha'$</td>
</tr>
<tr>
<td>Mixed</td>
<td>$V_{\text{max}/\alpha'}$</td>
<td>$\alpha K_M / \alpha'$</td>
</tr>
</tbody>
</table>

$\alpha = 1 + \frac{[I]}{K_i}$ and $\alpha' = 1 + \frac{[I]}{K_i'}$