Enzyme Inhibition

* Enzyme inhibitor is defined as a substance which binds with the enzyme and brings about a decrease in catalytic activity of that enzyme.
- Inhibitor may be organic or inorganic in nature.
- Enzyme Inhibition is of two types —
  1. Reversible inhibition
  2. Irreversible inhibition

1. **Reversible Inhibition** The inhibitor binds non-covalently with enzyme and the enzyme inhibition can be reversed if the inhibitor is removed.
- Extent of inhibition depends on conc. of enzyme, substrate and inhibitor.
- It is further sub-divided into three types :-
  a) Competitive inhibition
  b) Non-competitive inhibition
  c) Un-competitive inhibition

a) Competitive Inhibition

The inhibitor (I) is structural analogue of substrate (S) and hence, it competes with substrate and binds at the active site of the enzyme but does not undergo any catalysis.
- Inhibitor combines with free enzyme & give rise [EI] complex.

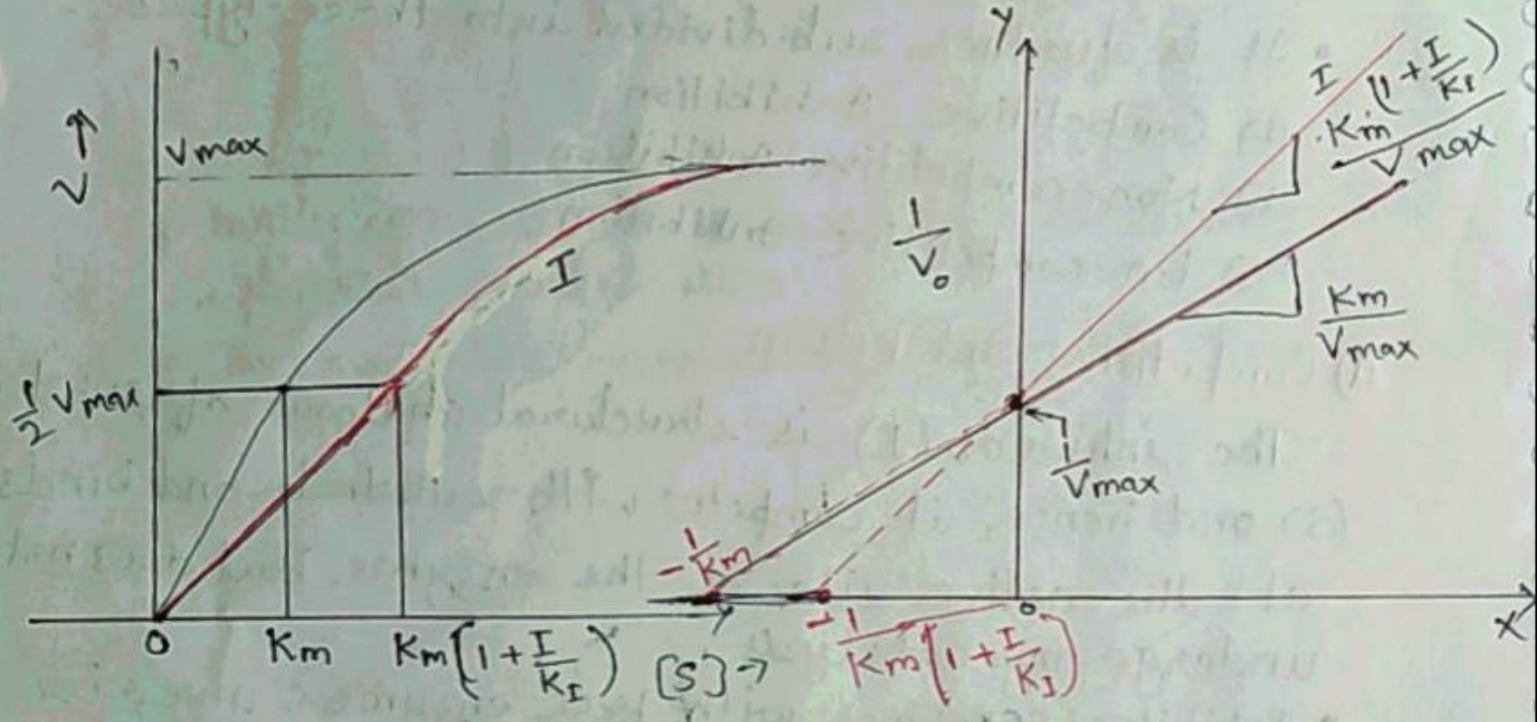
$$E + S \rightleftharpoons ES \rightarrow E + P$$
$$+$$
$$I$$
$$\uparrow\downarrow$$
$$EI$$

- The relative concentration of the substrate and inhibitor and their respective affinity with the enzyme determine the degree of competitive inhibition.
- The Inhibition could be reversed by increasing substrate concentration.
- The K_m value increases whereas V_{max} remains unchanged.

K_I = Dissociation constant for [EI]

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

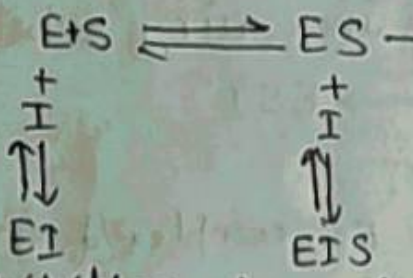
$$\frac{1}{V_o} = \frac{K_m\left[1 + \frac{I}{K_I}\right]}{V_{max}[S]} + \frac{1}{V_{max}}$$



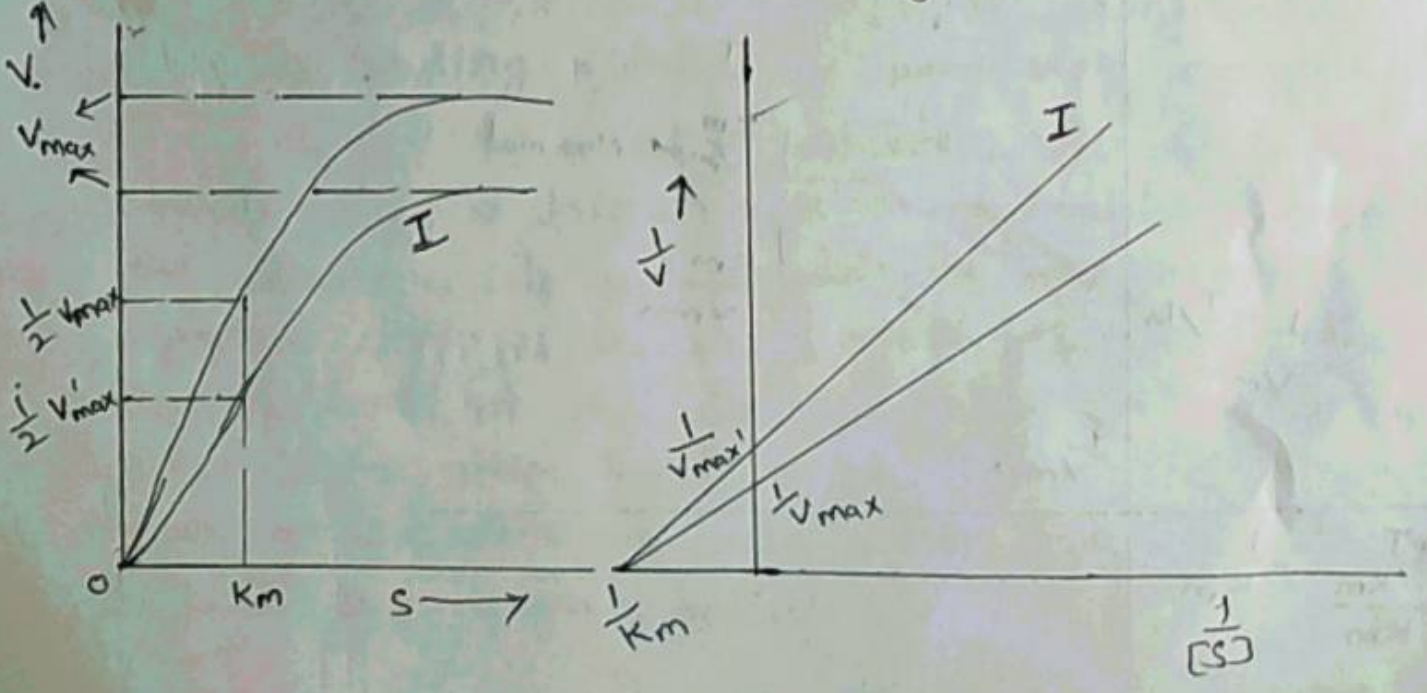
example: The compounds, namely malonic acid, glutaric acid and oxalic acid are structural analogue of succinic acid and compete with it for binding at the active site of succinic dehydrogenase (SDH)

b) Non-competitive Inhibition

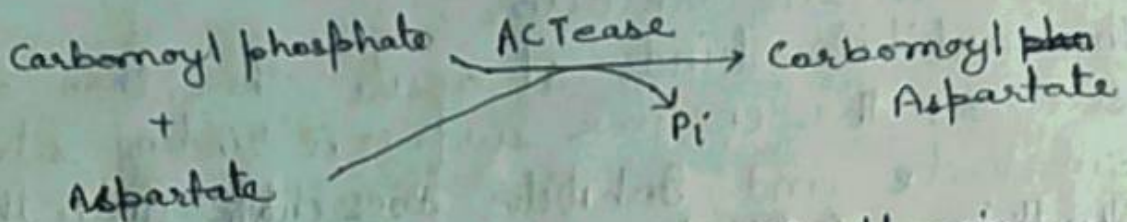
- There is no structural resemblance between substrate and inhibitor.
- The inhibitor binds at a site other than active site on the enzyme surface ie Binding site for substrate and inhibitor are different.
- Binding of inhibitor impairs the enzyme function.
- Inhibitor does not interfere with the enzyme-substrate binding but the catalysis is prevented possibly due to a distortion in the enzyme conformation.
- The inhibitor generally binds with the enzyme as well as the ES complex.



- Inhibition is not reversed by increasing the substrate concentration.
- The Km value remains unchanged while Vmax is lowered



example:- Inhibition of acetylcholine esterase by tertiary amine (R_3N).



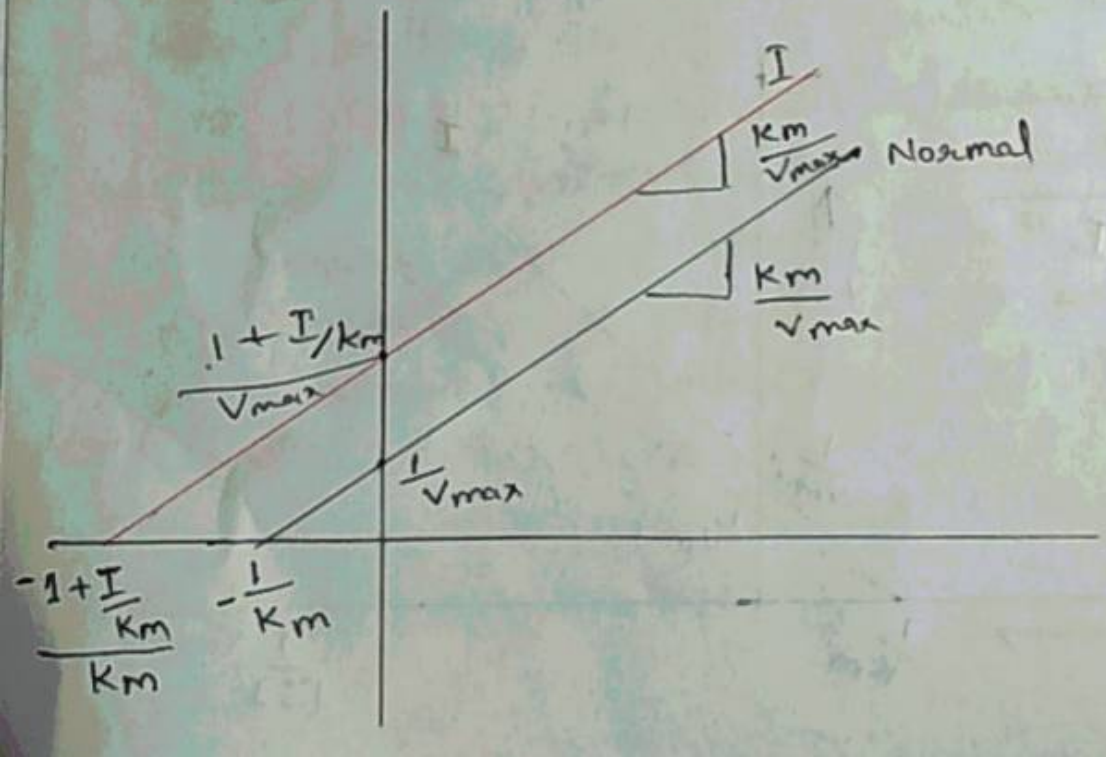
- Inhibition of Gyrase(A) by Ciprofloxacin.

Un-Competitive Inhibition

- In Un-competitive Inhibition, Inhibitor does not bind to free Enzyme that means inhibitor interact with the [ES] complex.
- The binding of Inhibitor is dependent on the binding of substrate.
- Inhibition is not reversed by increasing substrate conc.

$$E + S \rightleftharpoons ES + I \longrightarrow ESI$$

- Km and Vmax decreases.
- Km decrease favours more ES complex formation that means more inhibition.
- binding site of substrate and Inhibitor are different



e.g. • L-phenylalanine inhibit the gut intestinal alkaline phosphatase.
• Inhibition of aryl sulphatase by hydrazine.

2. Irreversible Inhibition

The inhibitors bind covalently with the enzymes and inactivate them, which is irreversible. These inhibitors are usually toxic substances which may be present naturally or man-made.

e.g. Iodoacetate is an irreversible inhibitor of the enzymes like papain and glyceraldehyde-3-phosphate dehydrogenase. Idoacetate combines with sulfhydryl (-SH) group at the active site of these enzymes and make them inactive.