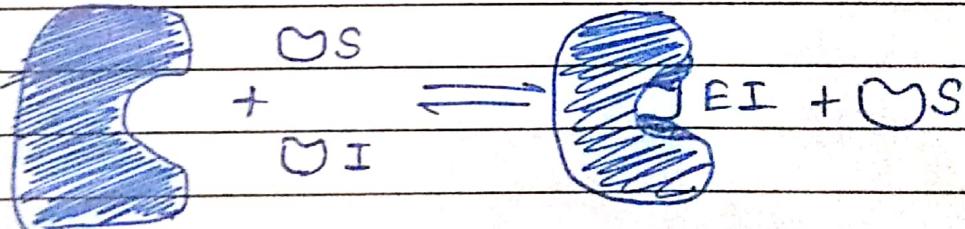


→ Enzyme Inhibition:

i) In order to function effectively, the biological systems must be able to regulate the activity of enzymes. Special agents called inhibitors can bind onto enzymes & block or inhibit their activity.

• Reversible Inhibition: The defining property of reversible inhibition is the ease with which the inhibitor can dissociate from the enzyme under certain cond's

ii) Competitive Inhibition: In this inhibition, the inhibitor molecule typically resembles the substrate & can therefore bind directly to the enzyme. Once bound, the inhibitor prevents the substrate from occupying the active site.

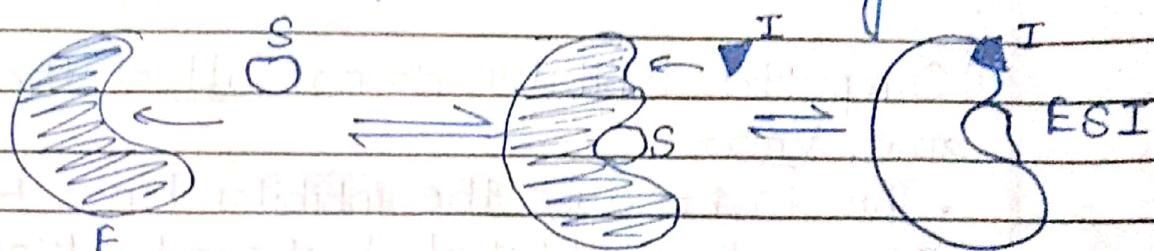


• Competitive inhibitor typically have a much higher affinity for active site than the natural substrate. However, if we inc the conc' of substrate, -Hence the additional substrate can outcompete the inhibitor for the active site. Thus, inc. the substrate concn can remove the effect of competitive inhibitor.

② Uncompetitive Inhibition: In some instances,

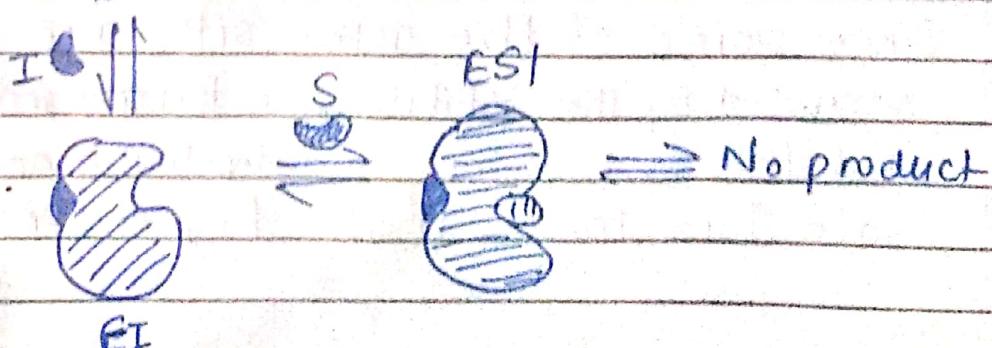
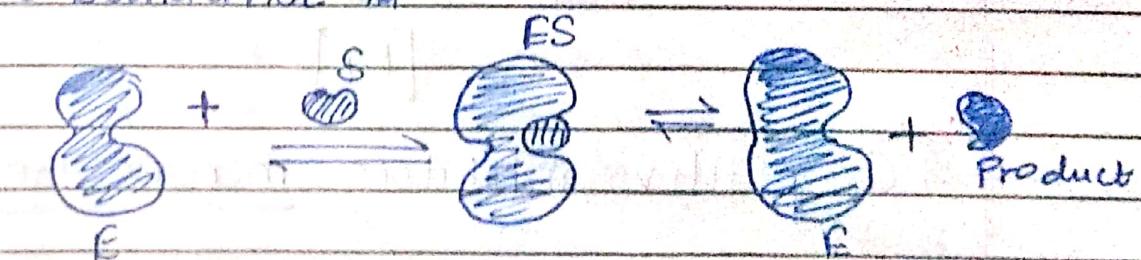
the binding of substrate to the active site changes the conformation of the enzyme & creates an allosteric site that wasn't previously there.

Now, a certain inhibitor can bind to the enzyme substrate complex & block its activity.



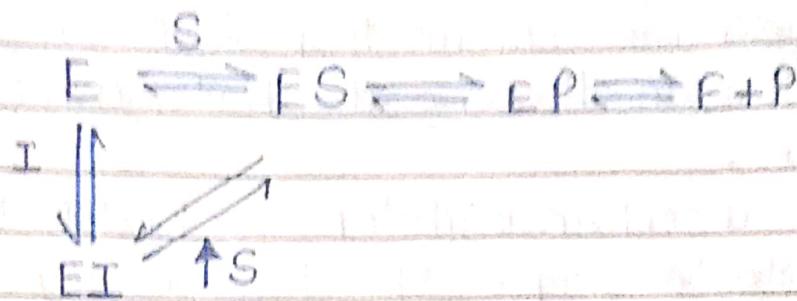
Note: It cannot be overcome by ↑ conc of subst.

③ Non-competitive Inhibition: Some enzymes have a permanent allosteric site to which an inhibitor can bind. These inhibitors, called non-competitive inhibitors do not compete for the active site & can bind to the enzyme regardless of whether the substrate is bound or not.



→ Effect of Inhibitors on Enzyme Kinetics:

1. Competitive Inhibition:



i) Competitive Inhibitors do not affect the maximal rate, V_{max} .

• This is because the inhibitor binds to the same site of substrate & it can be kicked out, by increasing the conc' of substrate. Therefore, at high concentration of substrate, virtually all the active sites are filled & V_{max} is unchanged.

2) Competitive inhibitors do not affect the turnover no (K_{cat}).

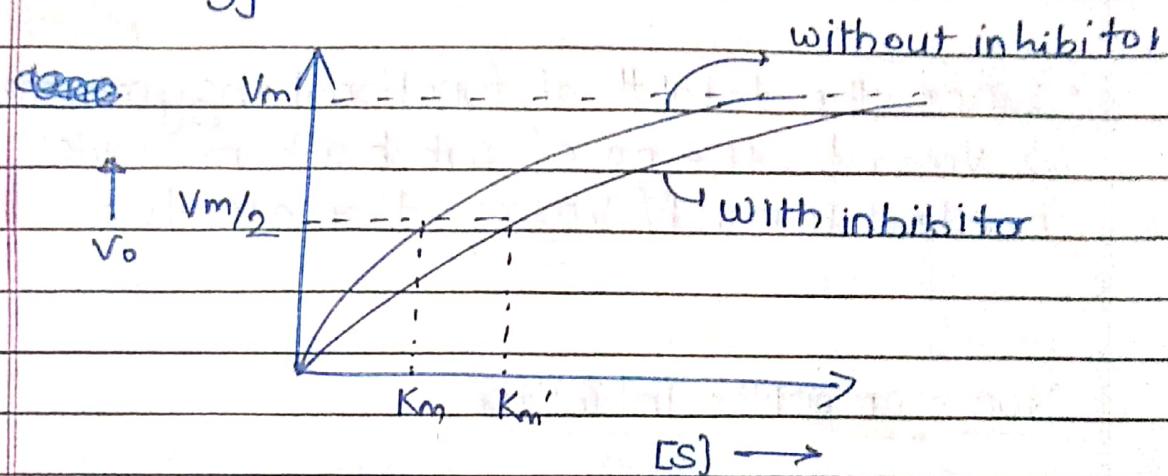
$$K_{cat} = \frac{V_{max}}{[E_t]}$$

3) Competitive inhibitors increase the K_m.

Since some of the active sites are now occupied by the inhibitor, a larger amt of substrate is needed to activ. the same enzyme rate. This means that a higher conc'

is needed to reach $\left(\frac{V_{max}}{2}\right)$.

This also means that affinity of the substrate for enzyme decreases.



→ Uncompetitive Inhibition:



ESI → No rxn!

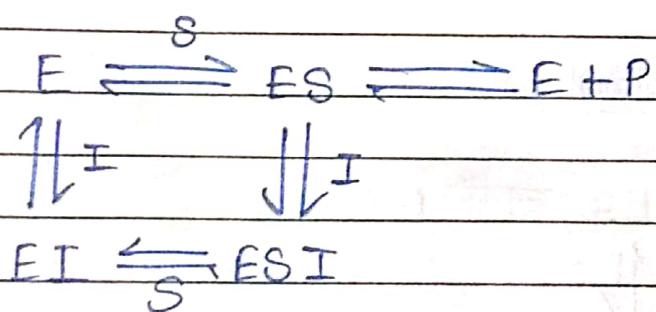
i) Uncompetitive inhibitors lower the V_{max} , because it binds to ES & decrease the total no of functional enzymes.

$$V_{max} = K_{cat} [ES] = K_{cat} [E]_{\text{Total}}$$

2) Uncompetitive inhibitors decrease the K_m .

- When the inhibitor binds to the ES complex & forms ESI, it basically prevents the substrate from leaving the active site. Hence, the affinity of the enzyme for substrate increases.
- Since the total # of functional enzyme dec. & $V_{max} \downarrow$, the no of substrate molecules needed to reach $(\frac{V_{max}}{2})$ decreases too.

Non-competitive inhibition :



① V_{max} is lowered.

• Since some no of inhibitors are bound to the enzyme at any moment, less func. enzyme is present & so $V_{max} \downarrow$

② K_{cat} is lowered.

• When the enzyme binds to the inhibitor, the inhibitor changes shape of the active site

& hence, the active site is no longer complementary to substrate & therefore the efficiency of the active site to convert substrate to product is decreased.

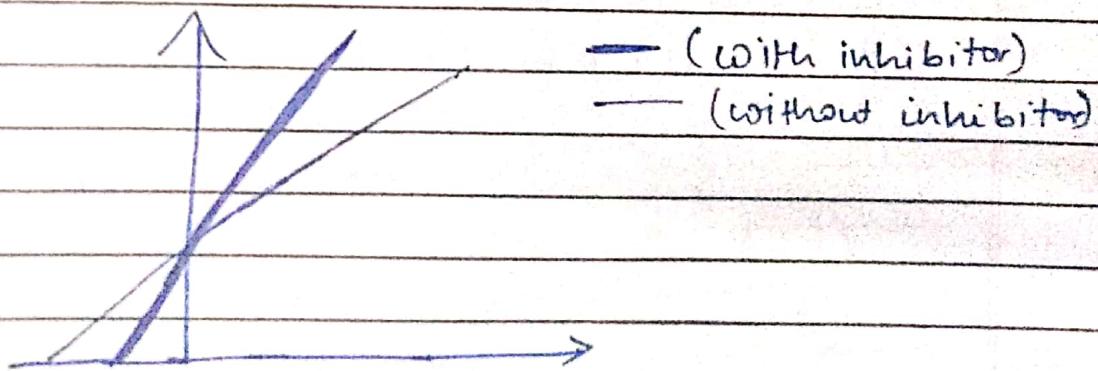
③ K_m remains constant

- Michaelis constant describes the ability of the substrate to bind to the active site. The substrate can bind or dissociate from the enzyme regardless of whether or not the inhibitor is bound.

→ Lineweaver Burk plot & reversible inhibition:

- The double reciprocal plot can be used to diff b/w 3 types of reversible inhibitors.

• Competitive Inhibitors

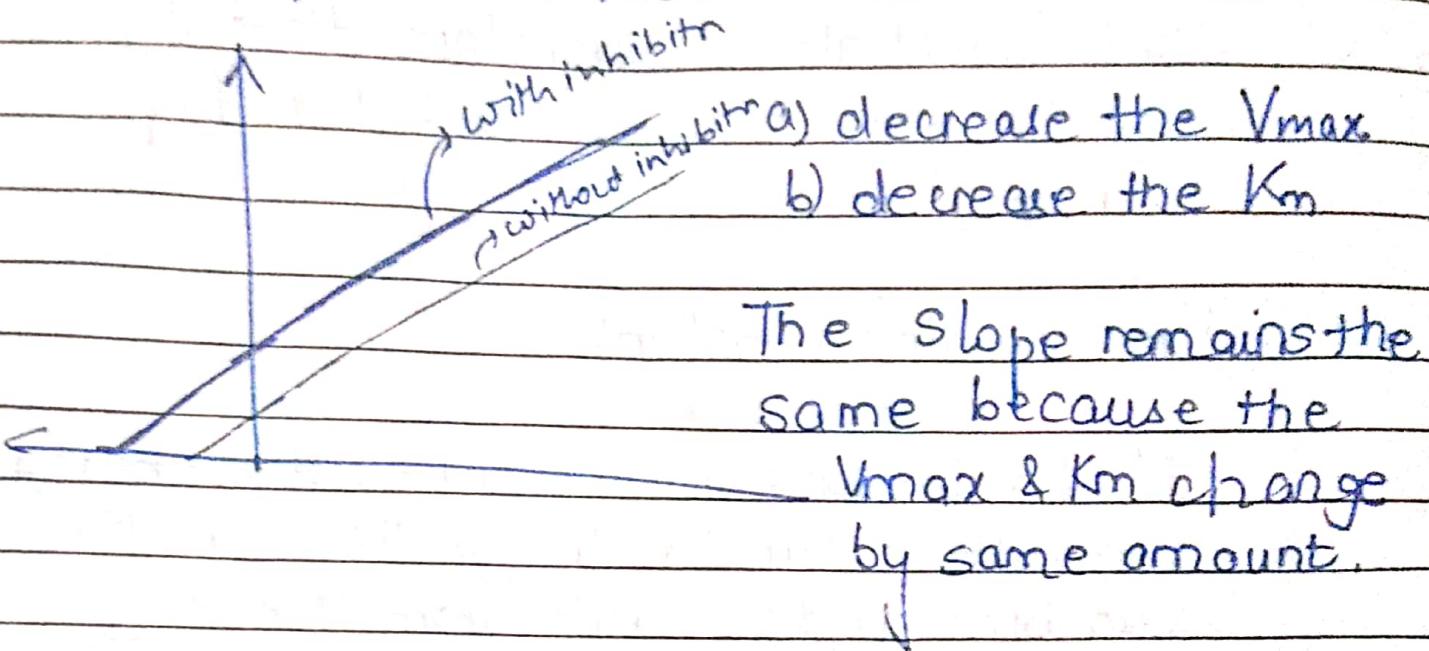


In a competitive inhibitor: i) V_{max} doesn't change

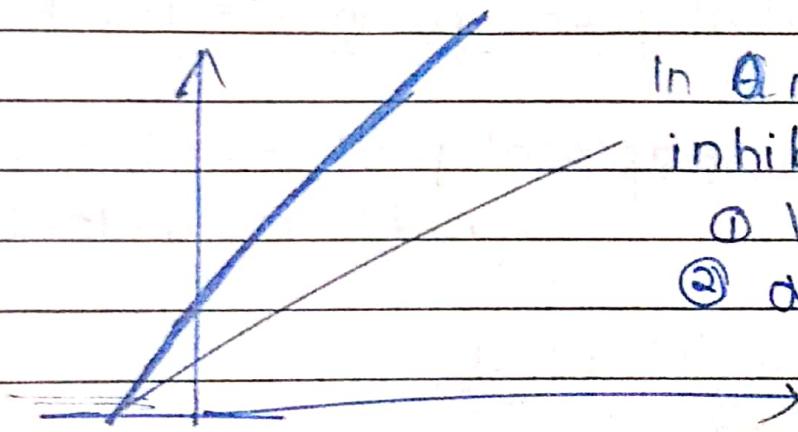
ii) increase K_m

∴ y intercept remains constant, but the slope & x intercept changes

② Uncompetitive inhibitor



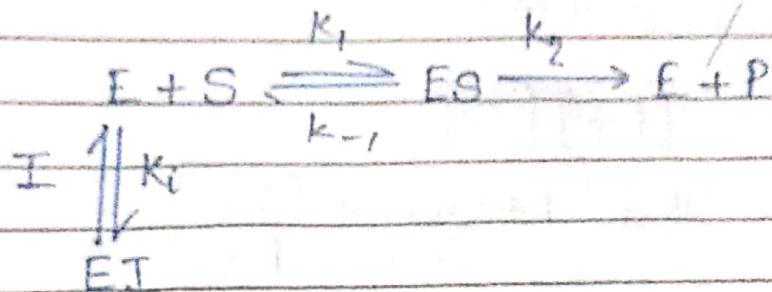
③ Non-competitive Inhibitor:



In a non competitive inhibitor :-

- ① V_{max} dec.
- ② doesn't affect K_m .

→ Competitive Inhibition (Derivation)



$$* K_m = \frac{[E][S]}{[ES]}$$

$$* K_i = \frac{[E][I]}{[EI]}$$

$$\boxed{[E_T] = [E] + [ES] + [EI]}$$

$$\Rightarrow [E_T] = [E] + \frac{[E][S]}{K_m} + \frac{[E][I]}{K_i}$$

$$\cancel{[E_T] = [E] \left(\frac{[S]}{K_m} + \frac{[I]}{K_i} \right)}$$

$$\Rightarrow [E_T] = [E] \left(1 + \frac{[S]}{K_m} + \frac{[I]}{K_i} \right)$$

$$\Rightarrow [E] = \frac{[E_T]}{1 + \frac{[S]}{K_m} + \frac{[I]}{K_i}}$$

$$[ES] = \frac{[E] [S]}{K_m}$$

$$[ES] = \frac{[E_T] [S]}{K_m \left(1 + \frac{[S]}{K_m} + \frac{[I]}{K_i} \right)}$$

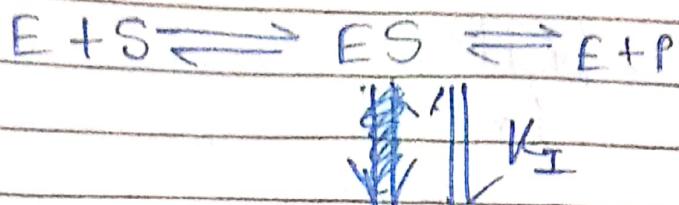
$$[ES] = \frac{[E_T] [S]}{K_m \left(1 + \frac{[I]}{K_i} \right) + [S]}$$

$$\therefore V_o = k_2 [ES]$$

$$= \frac{k_2 [E_T] [S]}{K_m \left(1 + \frac{[I]}{K_i} \right) + [S]}$$

$$V_o = \frac{V_m [S]}{K_m \left(1 + \frac{[I]}{K_i} \right) + [S]}$$

→ Uncompetitive Inhibition



$ESI \rightarrow \text{No rxn}$

$$K_m = \frac{[E][S]}{[ES]}$$

$$K_I = \frac{[ES][I]}{[ESI]}$$

$$[E_T] = [E] + [ES] + [ESI]$$

$$\Rightarrow [E_T] = [E] + \frac{[E][S]}{K_m} + \frac{[ES][I]}{K_I}$$

$$\Rightarrow [E_T] = [E] + \frac{[E][S]}{K_m} + \frac{[E][S][I]}{K_m K_I}$$

$$\Rightarrow [E_T] = [E] \left(1 + \frac{[S]}{K_m} + \frac{[I]}{K_m K_I} \right)$$

$$[E] = \frac{[E_T]}{\left(1 + \frac{[S]}{K_m} + \frac{[S][I]}{K_m K_I} \right)}$$

$$V_o = k_2 [ES]$$

$$V_o = \frac{k_2 [E][S]}{K_m}$$

$$V_o = \frac{k_2 [E_T][S]}{K_m \left(1 + \frac{[S]}{K_m} + \frac{[S][I]}{K_m k_i} \right)}$$

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