ENZYME INHIBITION

1st YEAR MBBS

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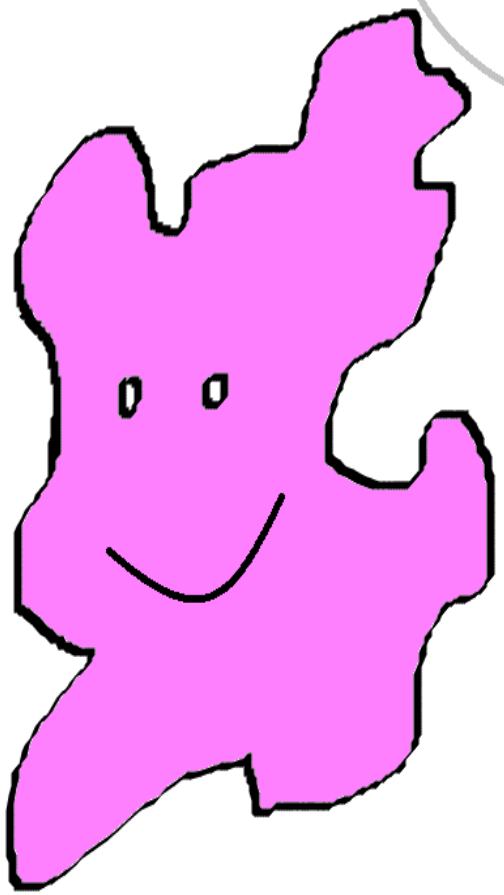
DEPTT OF BIOCHEMISTRY

KGMC

OBJECTIVES

- Definition of enzyme inhibition
- Classification of inhibitors.
- Regulatory enzymes



ohh hi there
how are you ?

*the friendly enzyme

"hello I'm new here"

*thinks to himself
i will bind to your
soul mwhahaha

*evil inhibitor

ENZYME INHIBITION

- There are certain chemical compounds that combine with enzymes and prevent the normal enzyme-substrate interaction at the active sites so that the catalysis is blocked either temporarily or permanently.
- These compounds which inhibit the enzyme activity are called the “inhibitors” and this process is called the “inhibition”

- Enzyme inhibition can also be defined as “the capacity of an inhibitor to retard or to stop the process of catalysis of an enzyme.”
- Some of the substances acting as inhibitors include drugs,antibiotics,poisons,and certain heavy metals like Hg etc

- Certain inhibitors are poisonous to the living organisms including cyanides,H2S,and CO.
- Inhibitors of the catalytic activity of enzymes provide both pharmacologic agents and research tools for study of the mechanism of action of enzymes.

- The strength of the interaction between an inhibitor and enzyme depends on the forces important in protein structure and ligand binding--------- hydrogen bonds,electrostatic interactions,hydrophobic interactions and van der Waals forces.

Classification of Enzyme inhibition

- Three types
- Reversible inhibition
- Irreversible inhibition
- Allosteric inhibition

Reversible is
Competitive

un competitive

noncompetitive.

In reversible, inhibitors binds non- covalently with the enzymes and inhibition can be reversed if enzyme is removed.

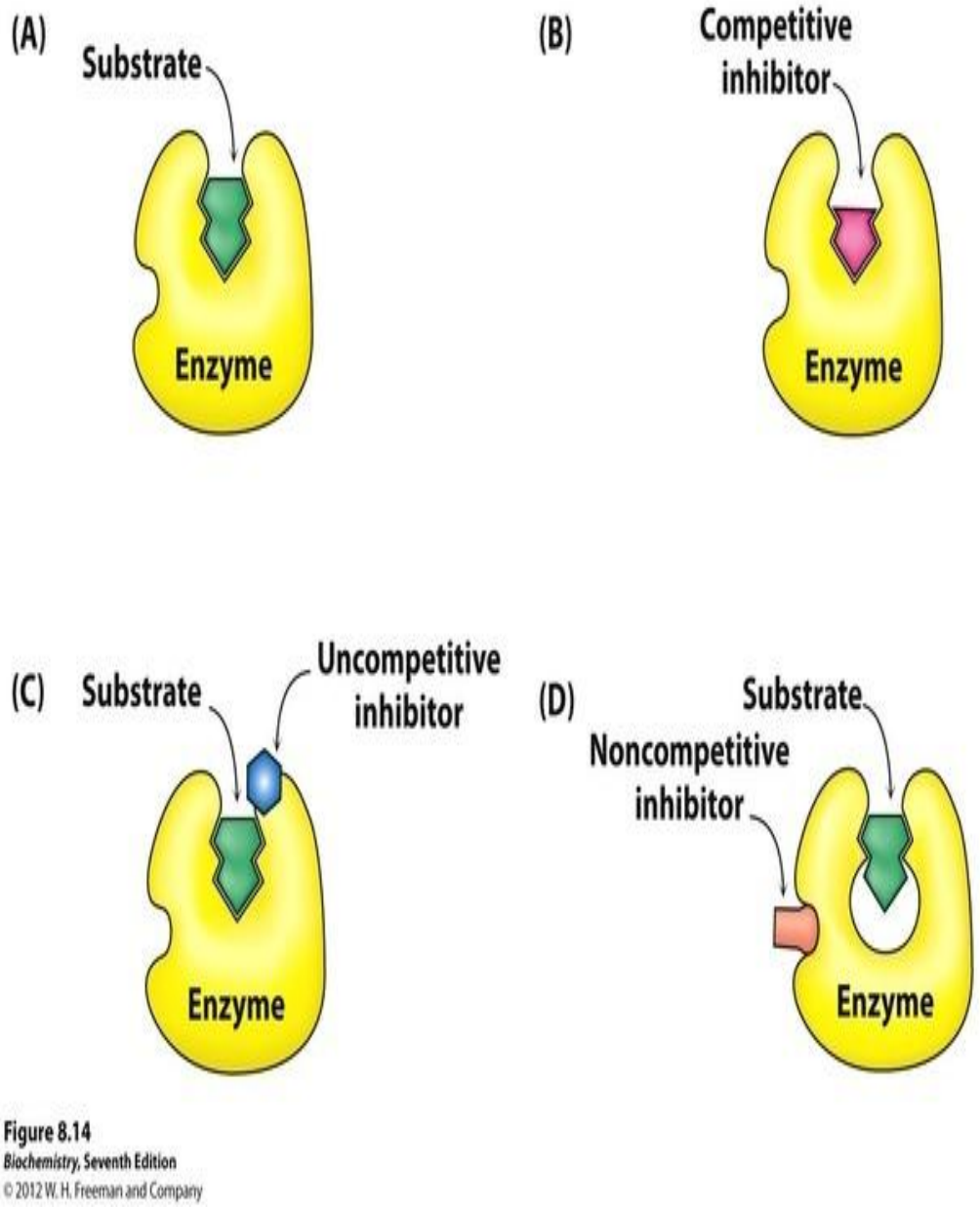
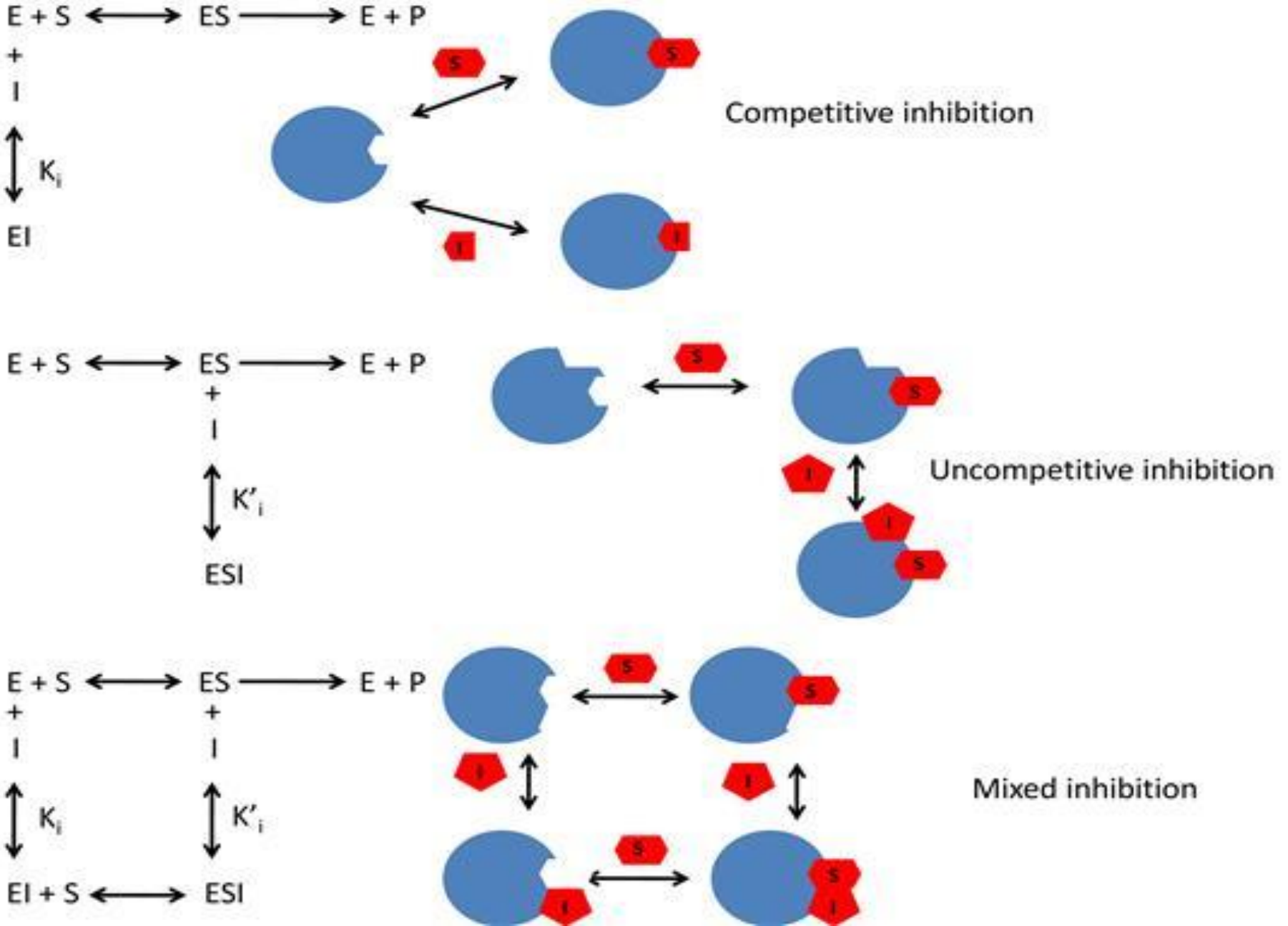


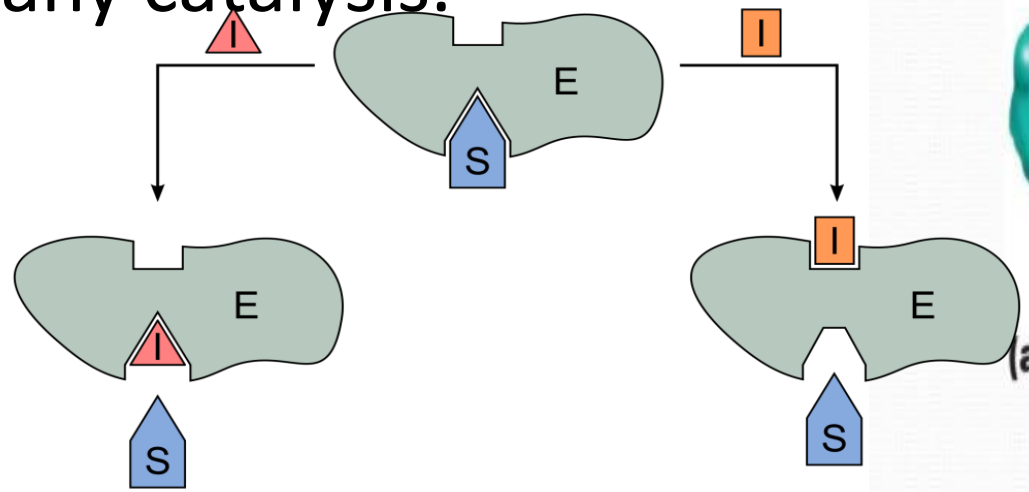
Figure 8.14
Biochemistry, Seventh Edition

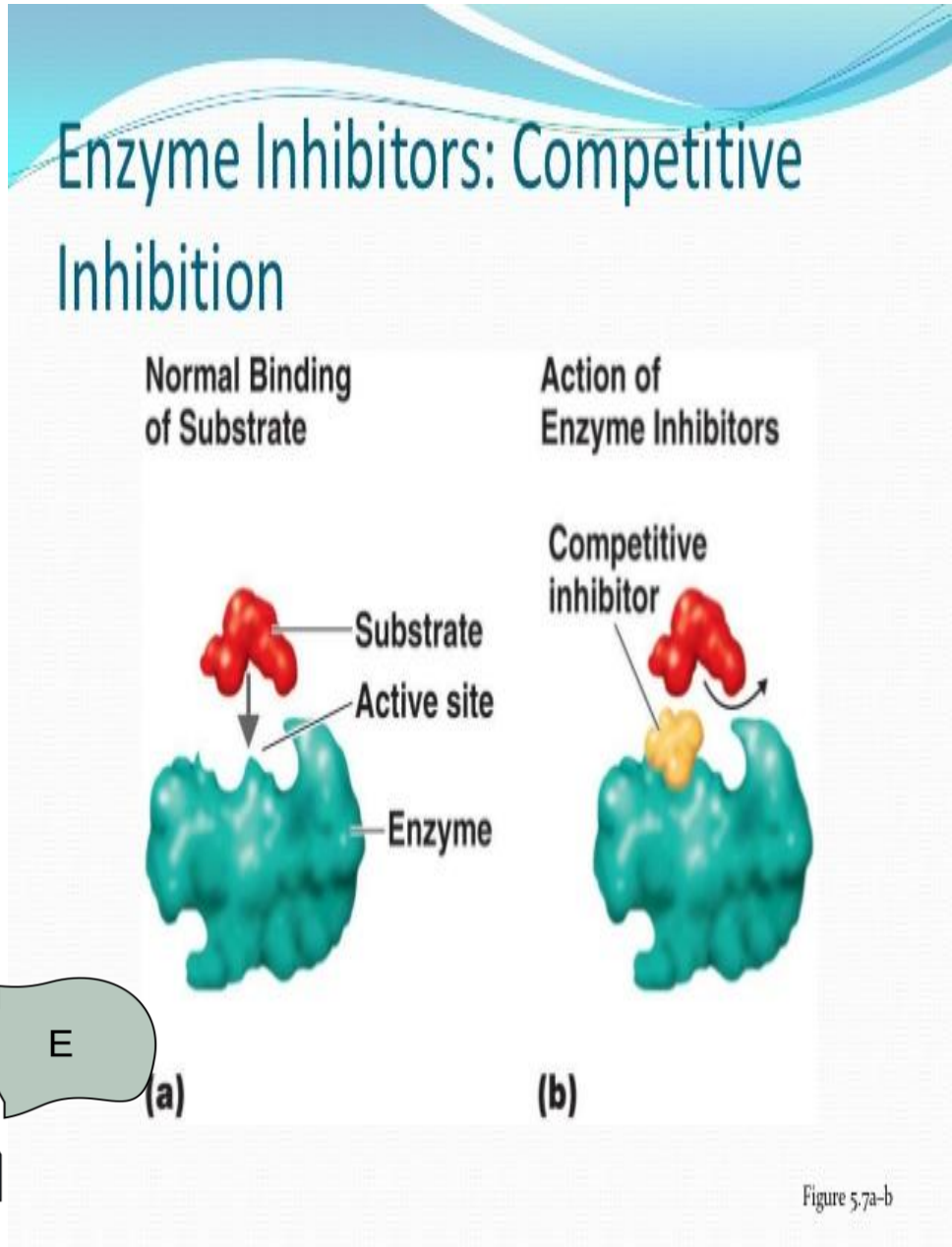
Reversible inhibition

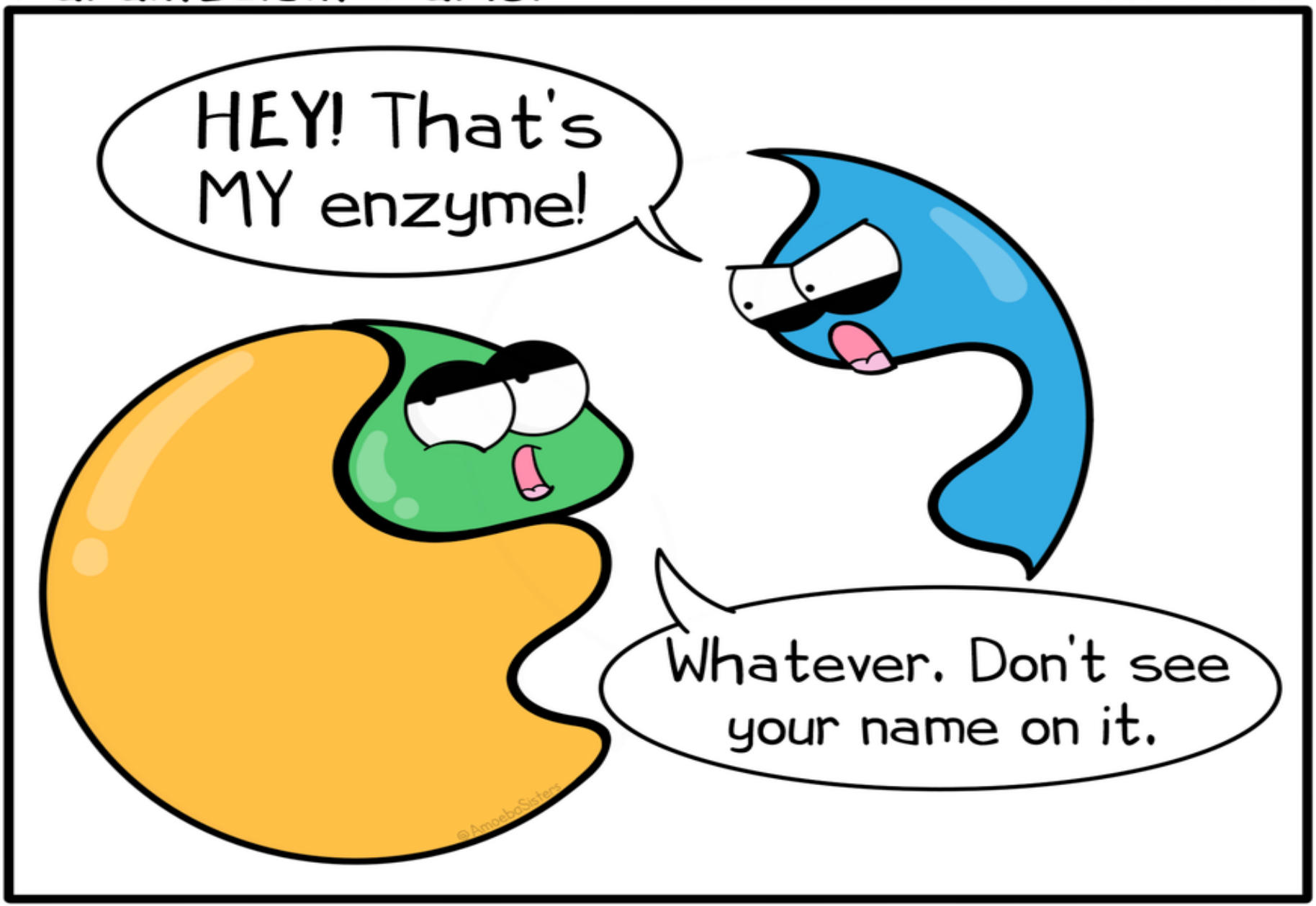


Competitive inhibition

- The inhibitors closely resemble the real substrate(structural analogue).
- the inhibitor competes with substrate and binds the active site of enzyme but does not undergo any catalysis.



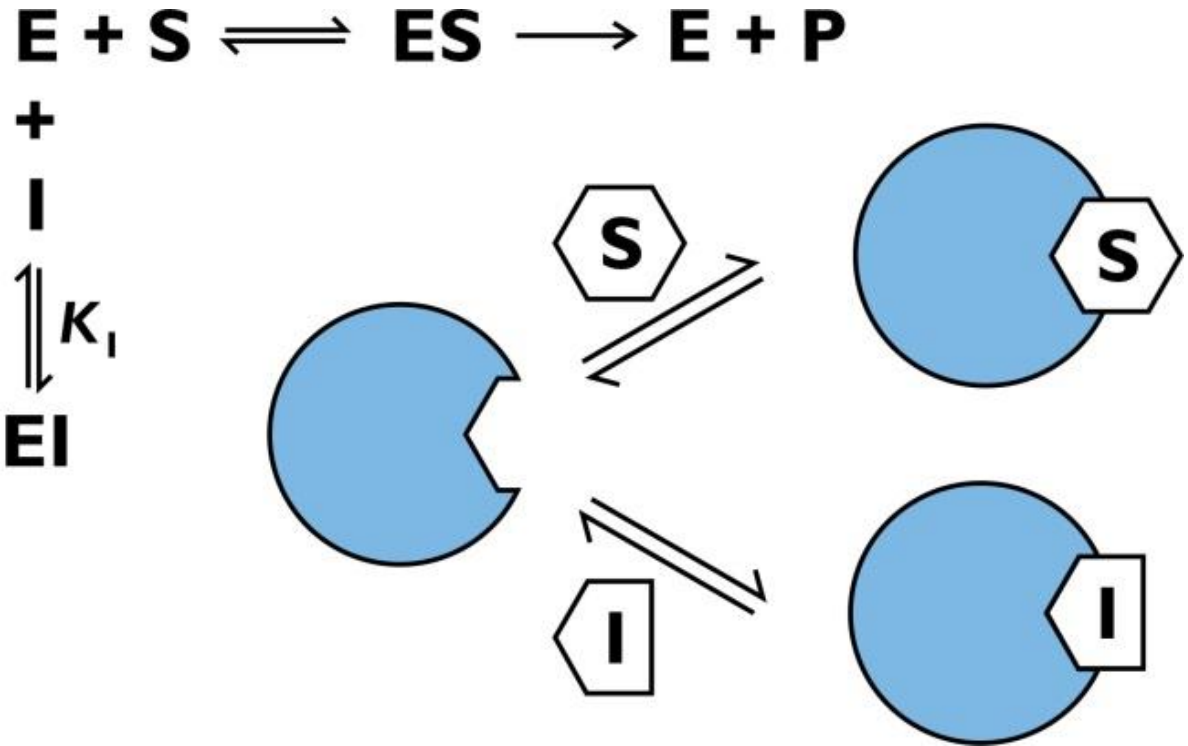




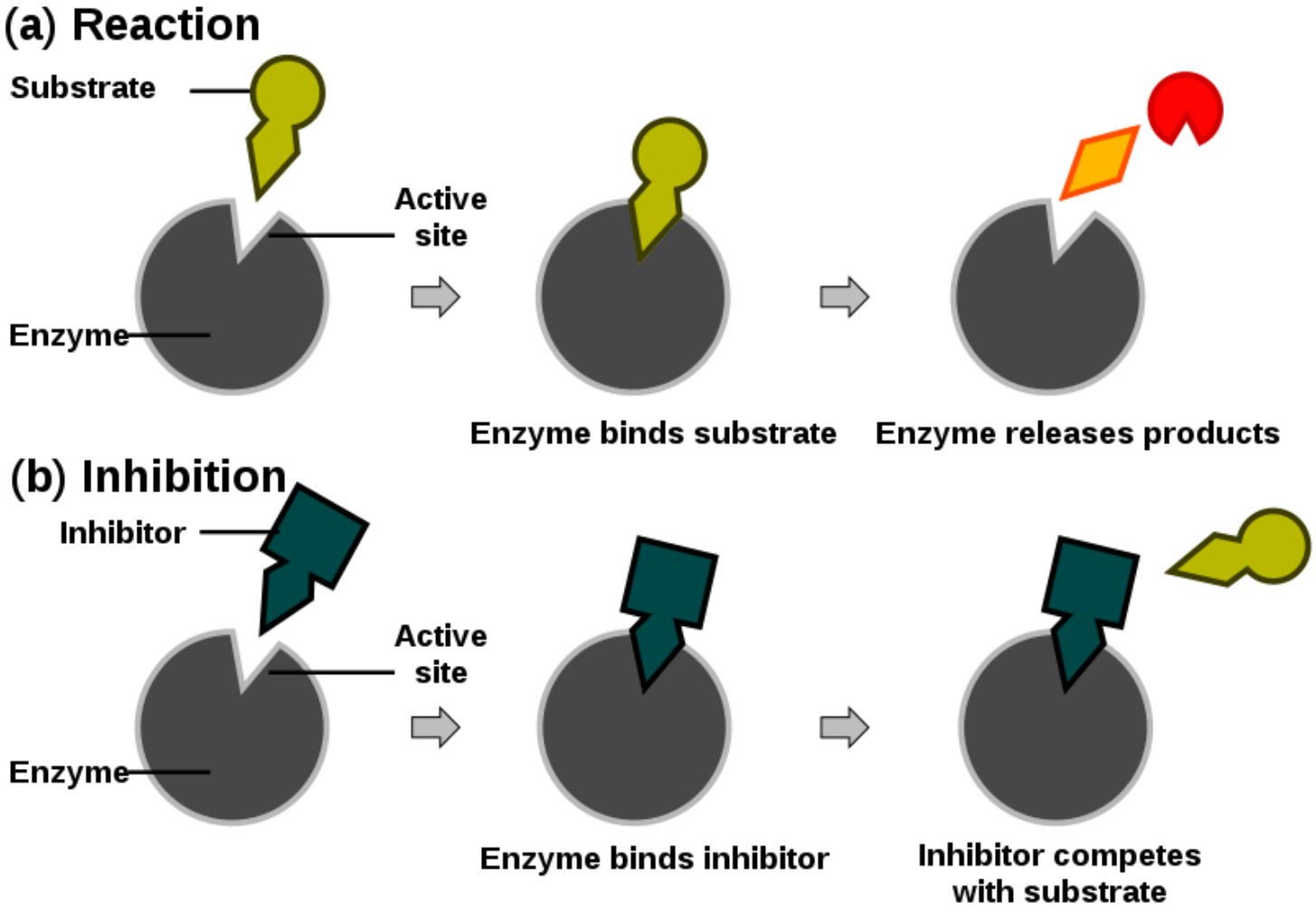
Competitive Inhibitors: If it fits, it sits.

- In such inhibition both the ES & EI complexes are formed during the reaction.
- The amount of formation of EI & ES complexes will depend upon:

1. Affinity b/w ENZYME & SUBSTRATE / INHIBITOR.
2. Concentration of substrate and inhibitor present.

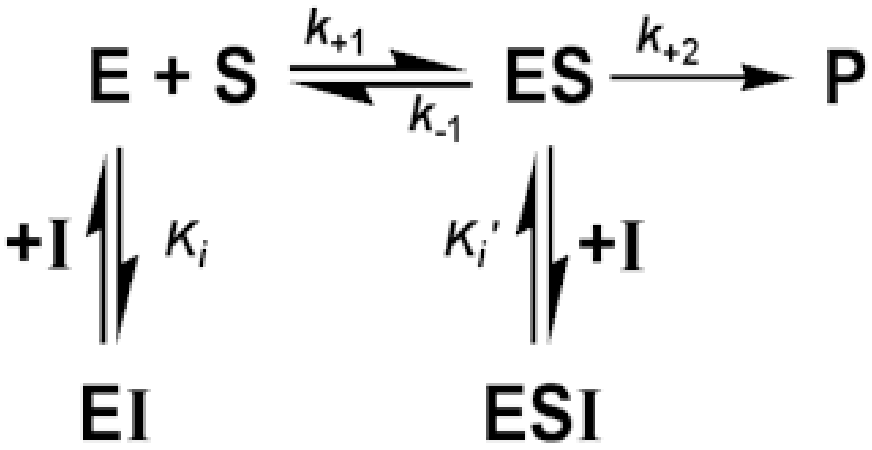


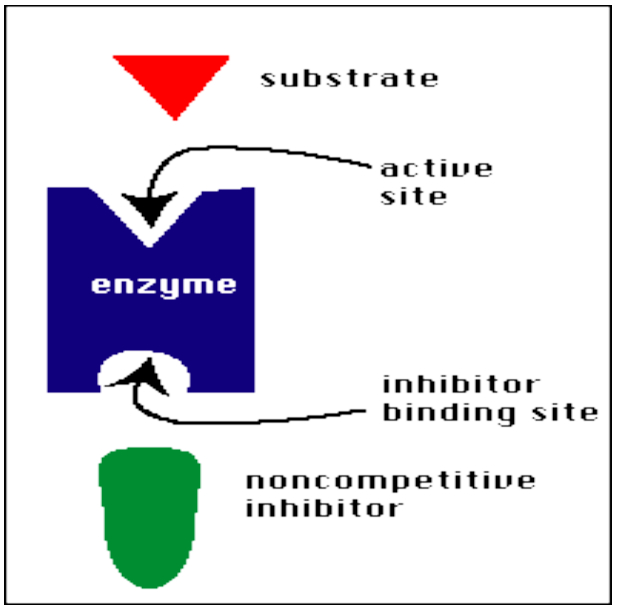
- Competitive inhibitor acts by decreasing the number of free molecules available to bind with the substrate to form ES & thus to form product.



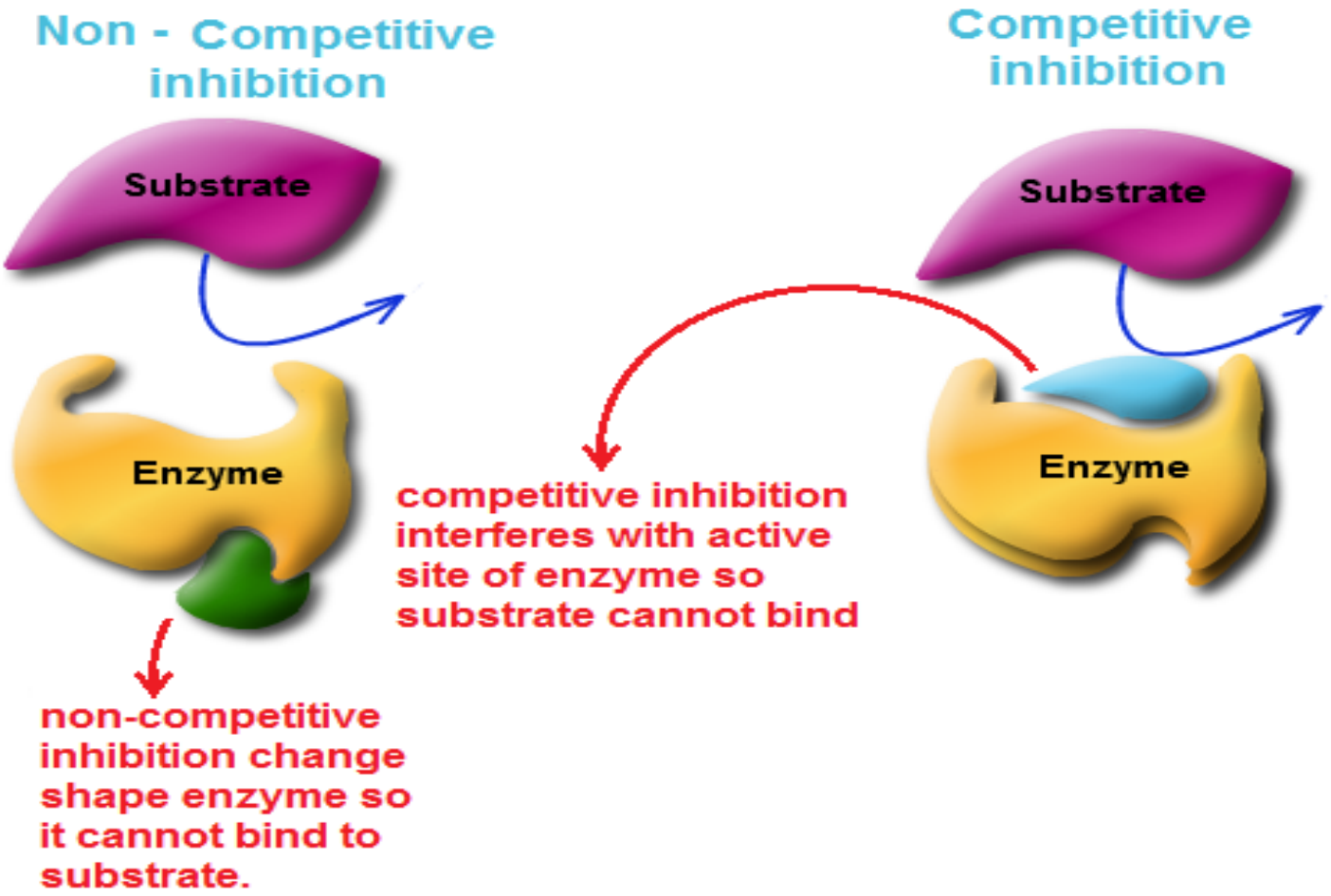
NON COMPETITIVE INHIBITOR

- In non comp. inhibition binding of the inhibitor does not affect the binding of substrate therefore formation of EI & EIS complex is possible.

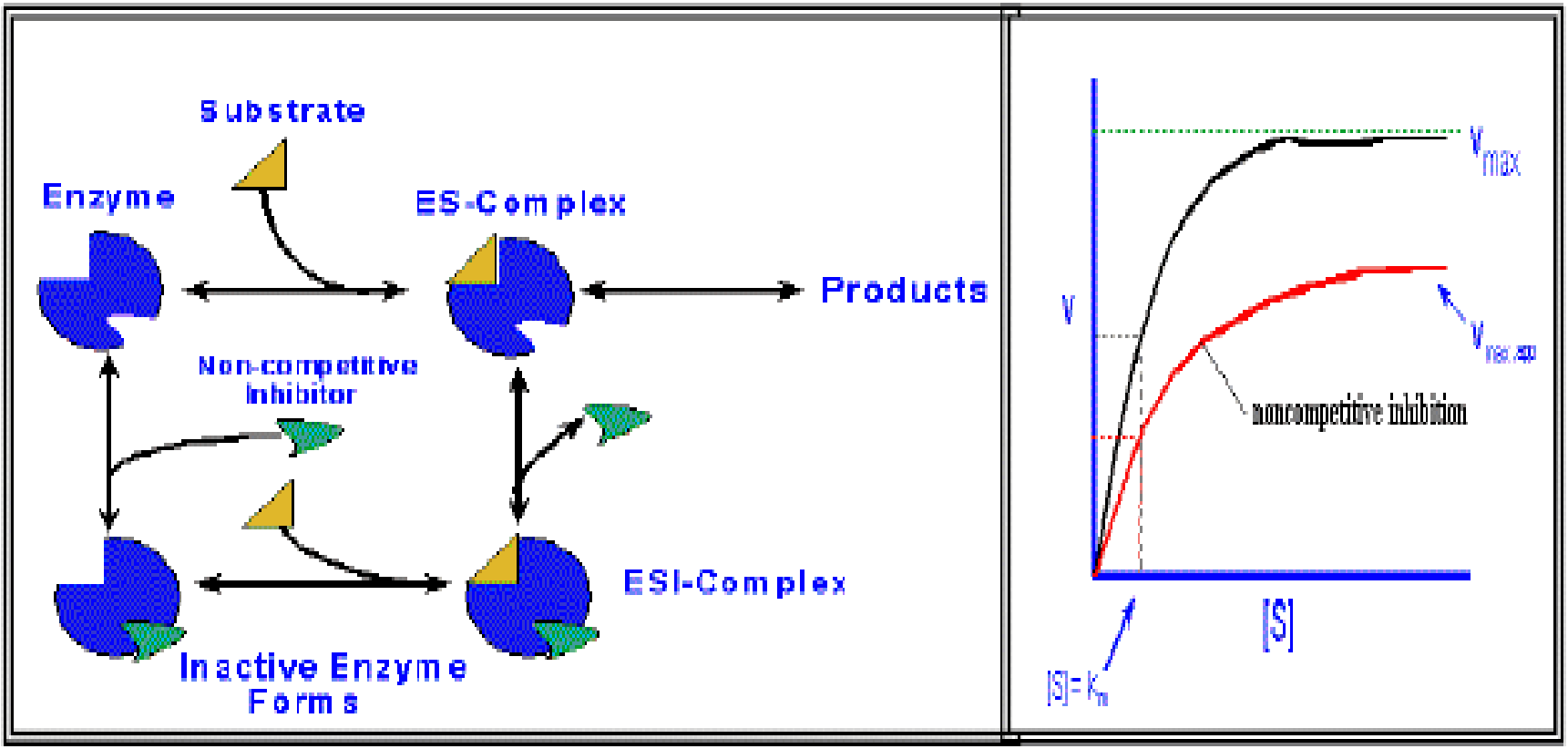




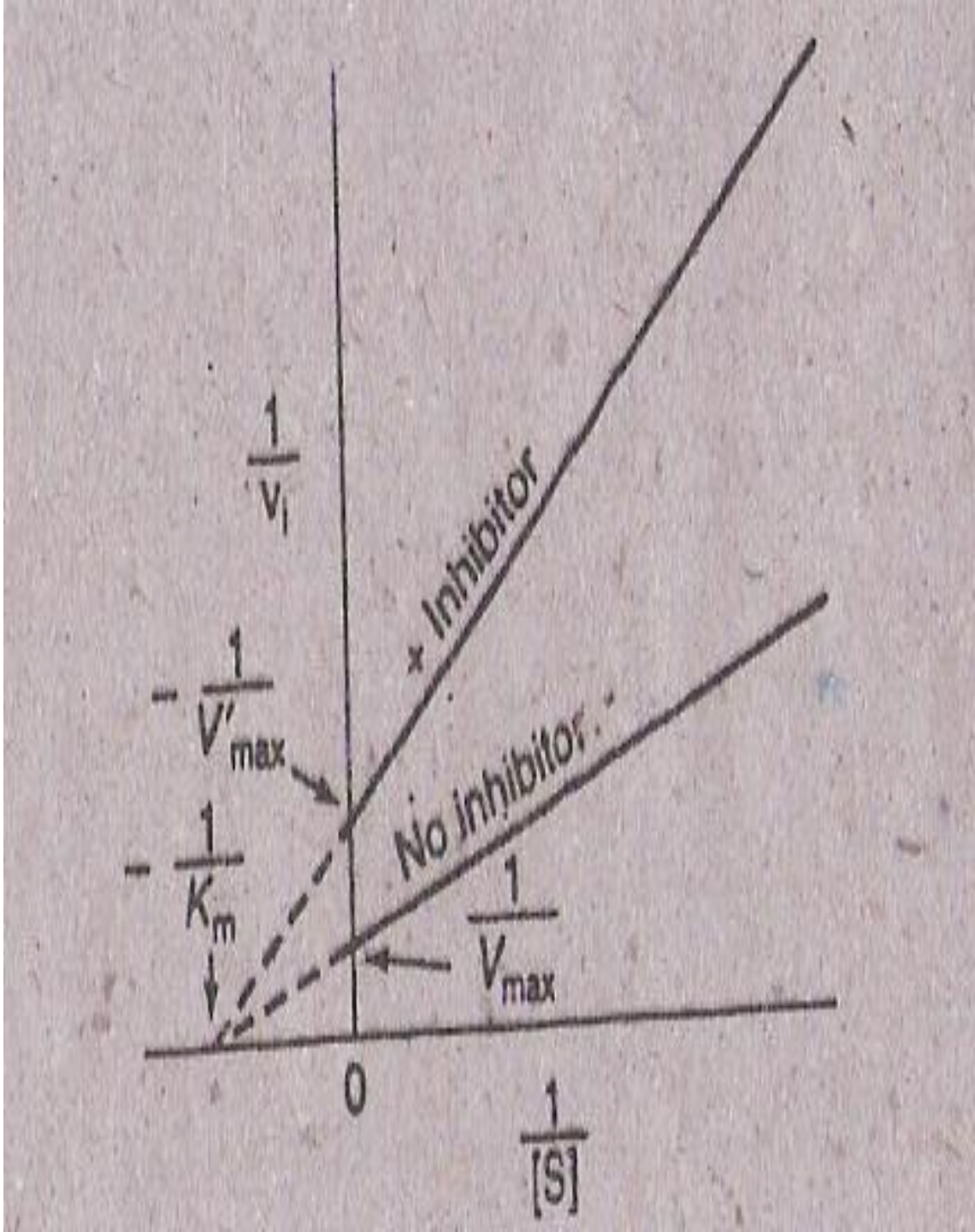
- Non-competitive inhibitors bind enzymes at sites distant from the substrate binding site & generally bear little or no resemblance to the substrate.



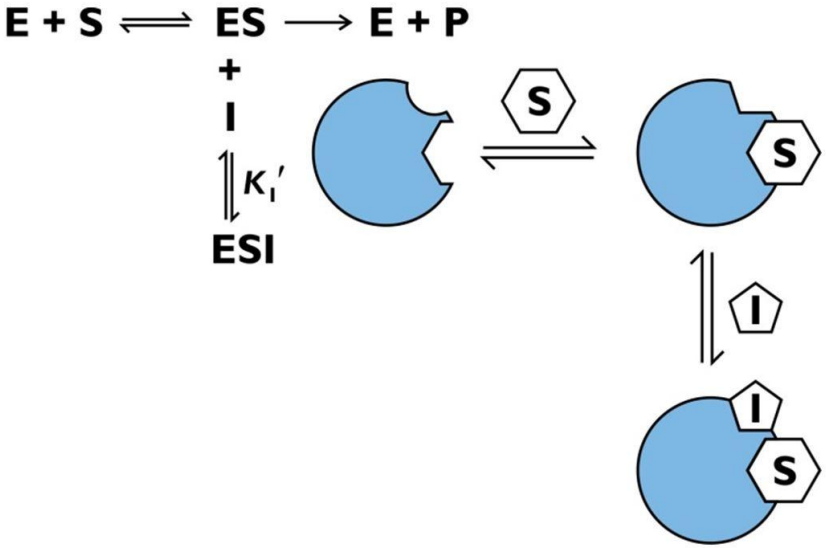
- Even after binding of inhibitor substrate can still bind to EI complex.

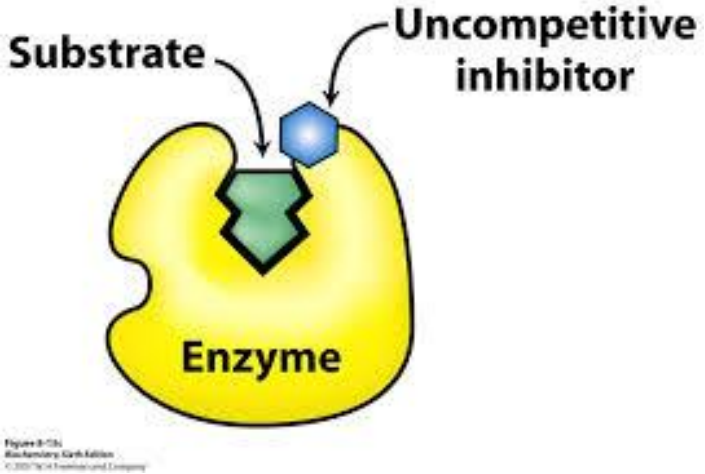


Km value is unchanged ,V max is lowered



Uncompetitive inhibition





- Inhibitor can only bind to the enzyme substrate complex.
- The binding site is created only on interaction of enzyme and substrate.
- This inhibition can not be overcome by increasing the conc of substrate.

In uncompetitive inhibition, the inhibitor can bind only to the enzymesubstrate complex.Uncompetitive inhibition occurs with multisubstrate enzymes that bind substrates and inhibitors in an obligatory order.

Uncompetitive inhibitors decrease both the $V_{max,app}$ and the $K_{m,app}$ of the enzyme

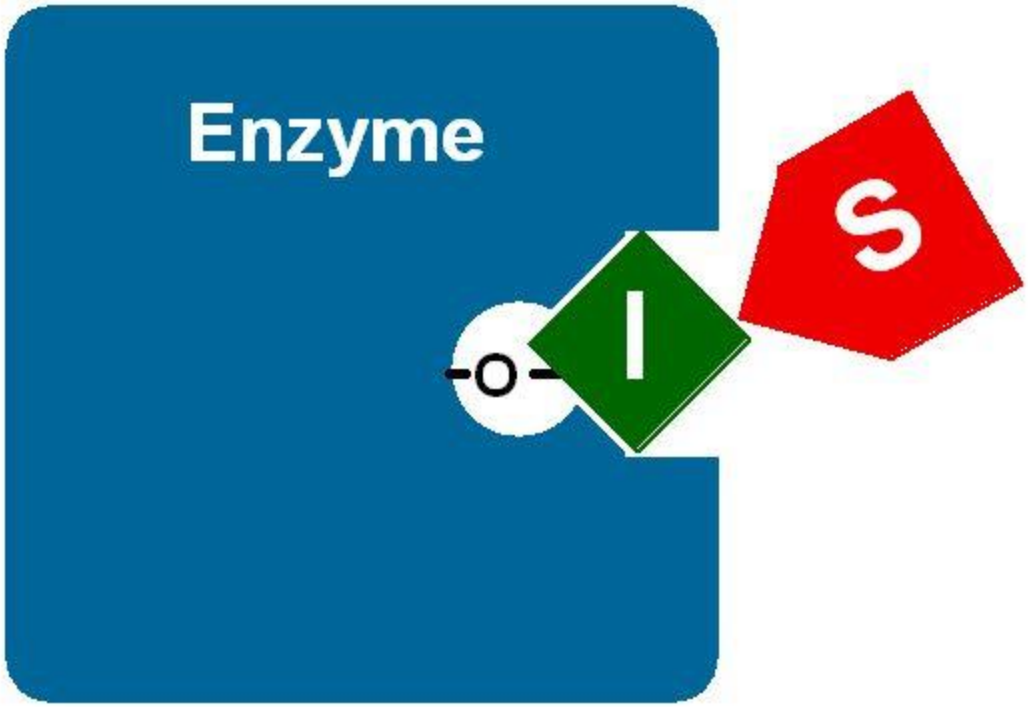
$$E + S \rightleftharpoons ES \rightarrow E + P$$

$$+ \; I \; \updownarrow$$

$$ESI$$

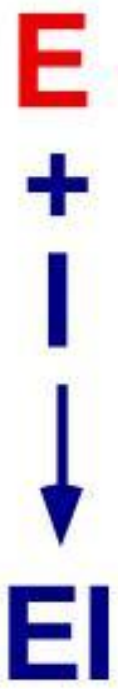
Notice that uncompetitive inhibitors don't bind to the free enzyme, so there is no EI complex in the reaction mechanism

Irreversible Inhibition



In irreversible inhibition, the inhibitor binds to the enzyme irreversibly through formation of a covalent bond with the enzyme , permanently inactivating the enzyme

Irreversible Inhibition - Reaction Mechanism



In irreversible inhibition, the inhibitor permanently inactivates the enzyme. The net effect is to remove enzyme from the reaction.

V_{max} decreases

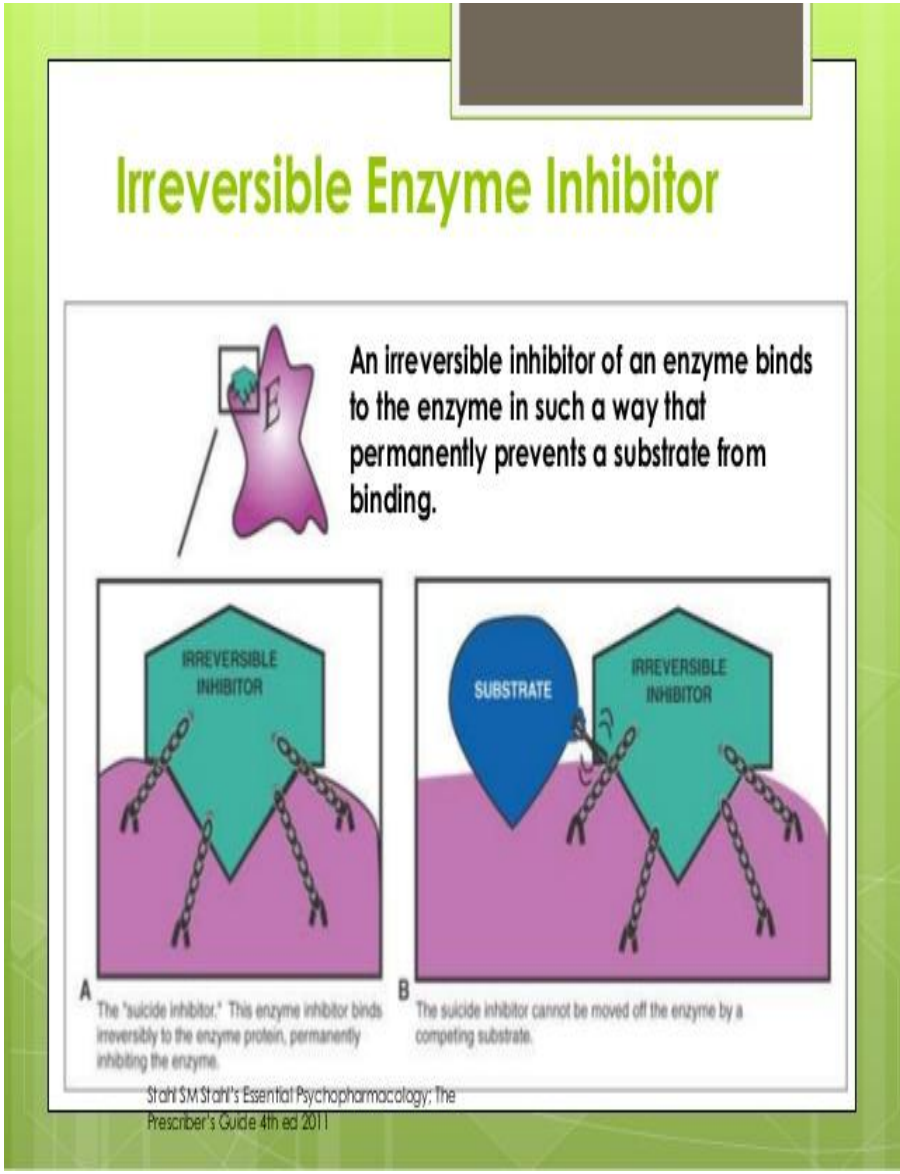
No effect on K_m

Irreversible inhibition

- Inhibitor binds covalently with the enzyme and inactivate them these are usually toxic substances that poison enzyme.

- Iodoacetate is an irreversible inhibitor of the enzymes like papain and glyceraldehyde 3-phosphate dehydrogenase.

- Iodoacetate combines with sulfhydryl(SH) groups at active site and make them inactive.

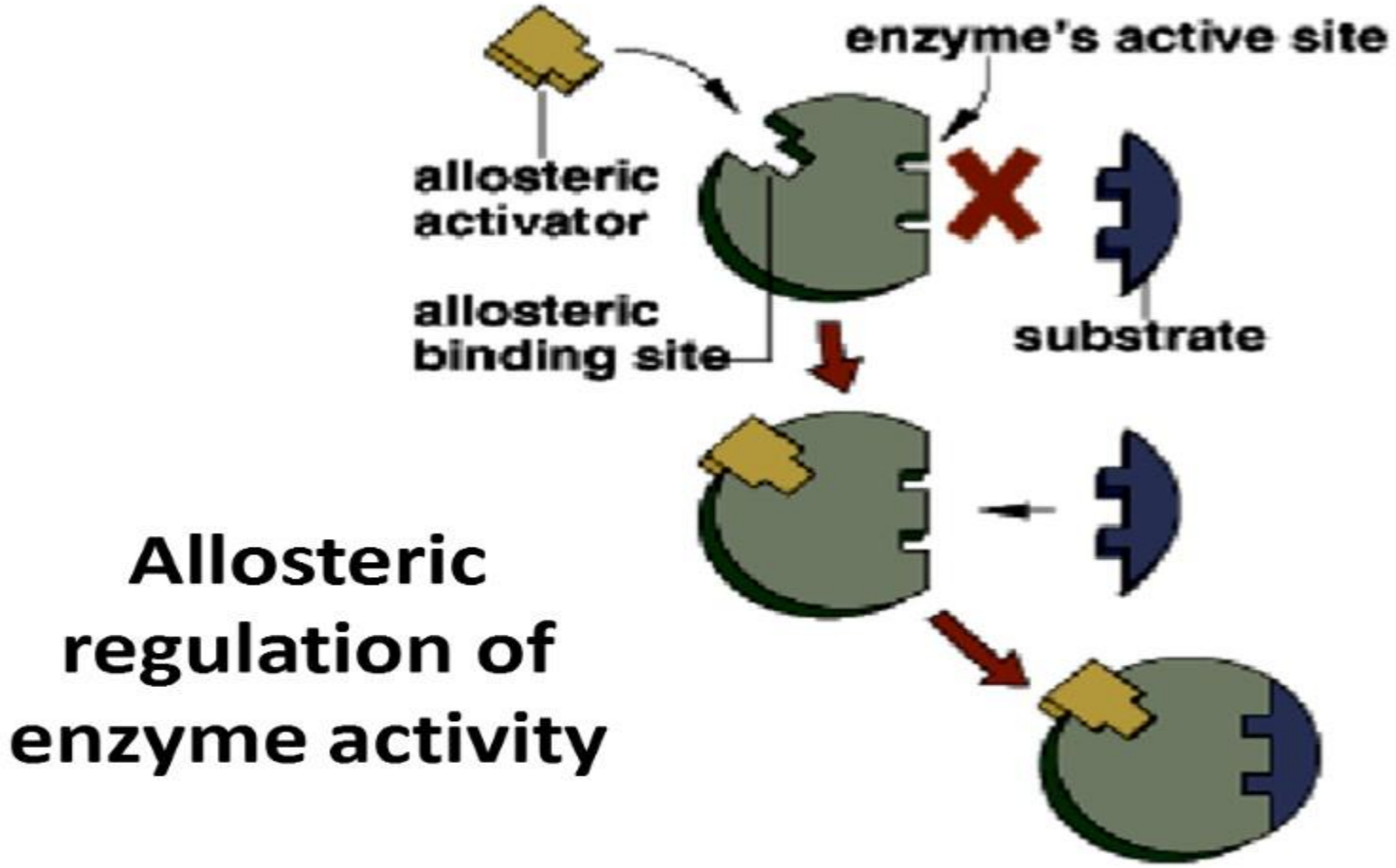


Suicide inhibition

- Specialized form of irreversible inhibition.
- Original inhibitor (structural analogue) is converted to more potent form by the same enzyme that ought to be inhibited. This form binds irreversibly with enzyme.
- Example is Allopurinol ,an inhibitor of xanthine oxidase ,converted to alloxanthine ,which is more effective inhibitor.

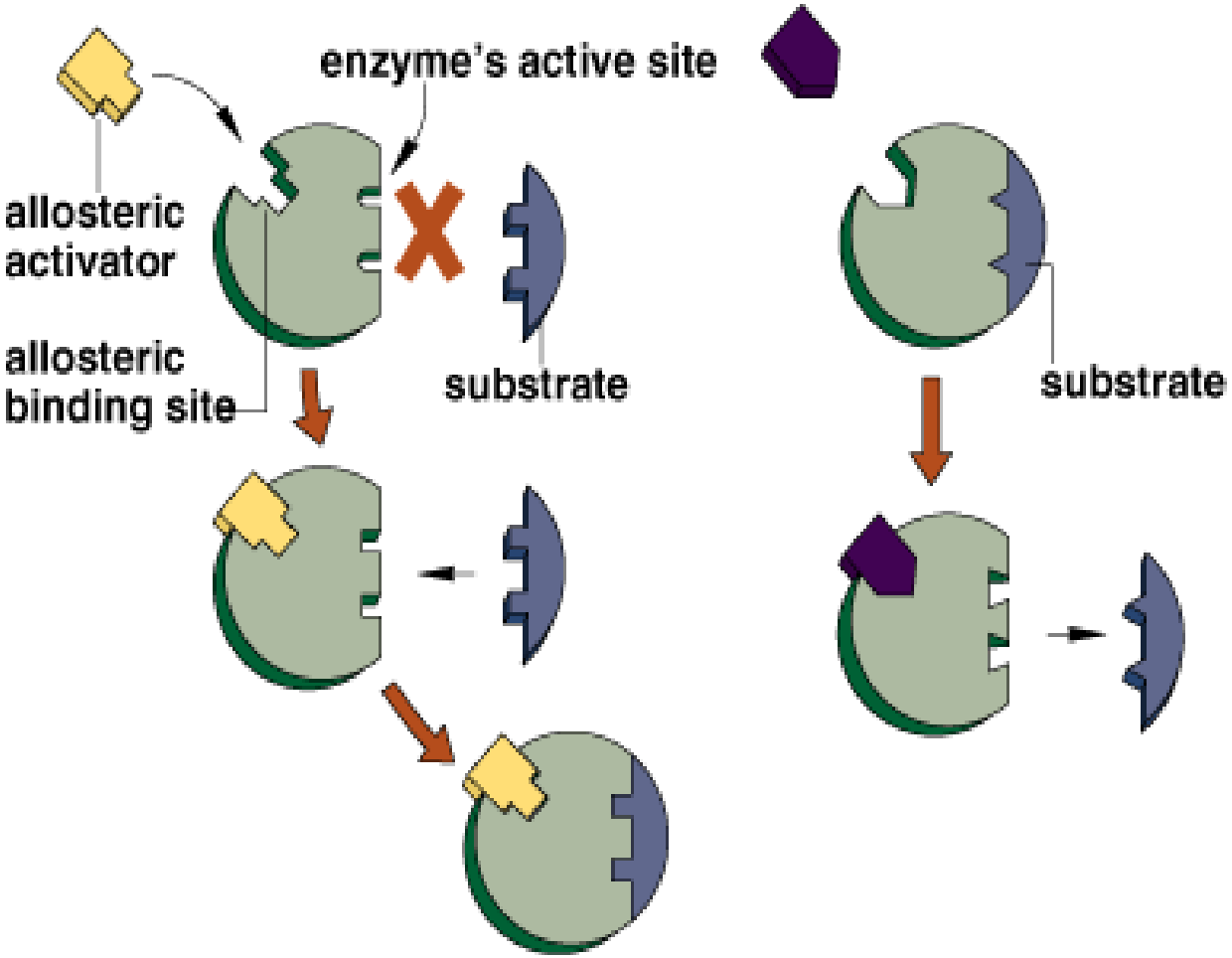
ALLOSTERIC INHIBITION

- The inhibitor binds to the enzyme at a site other than the active site but on a different region in the enzyme molecule, called the ALLOSTERIC SITE

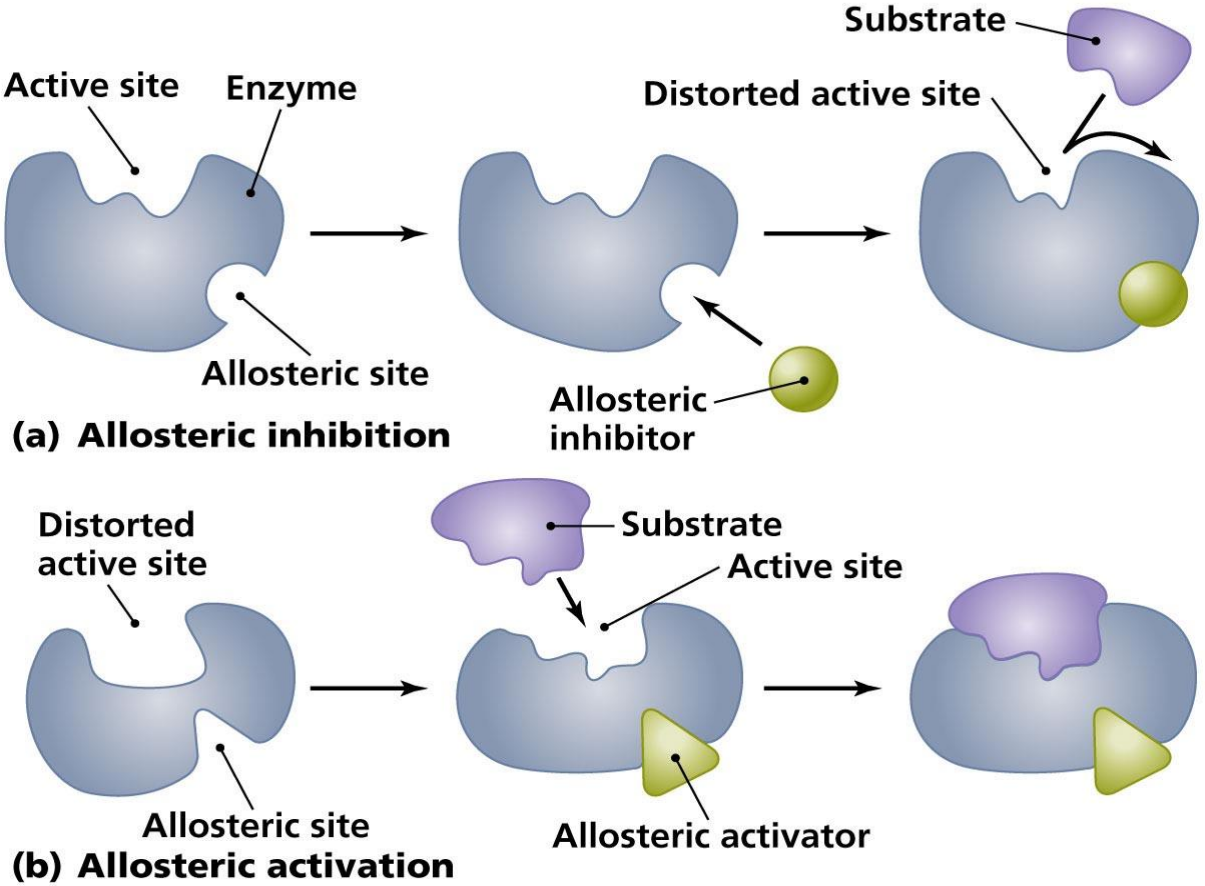


Allosteric inhibition

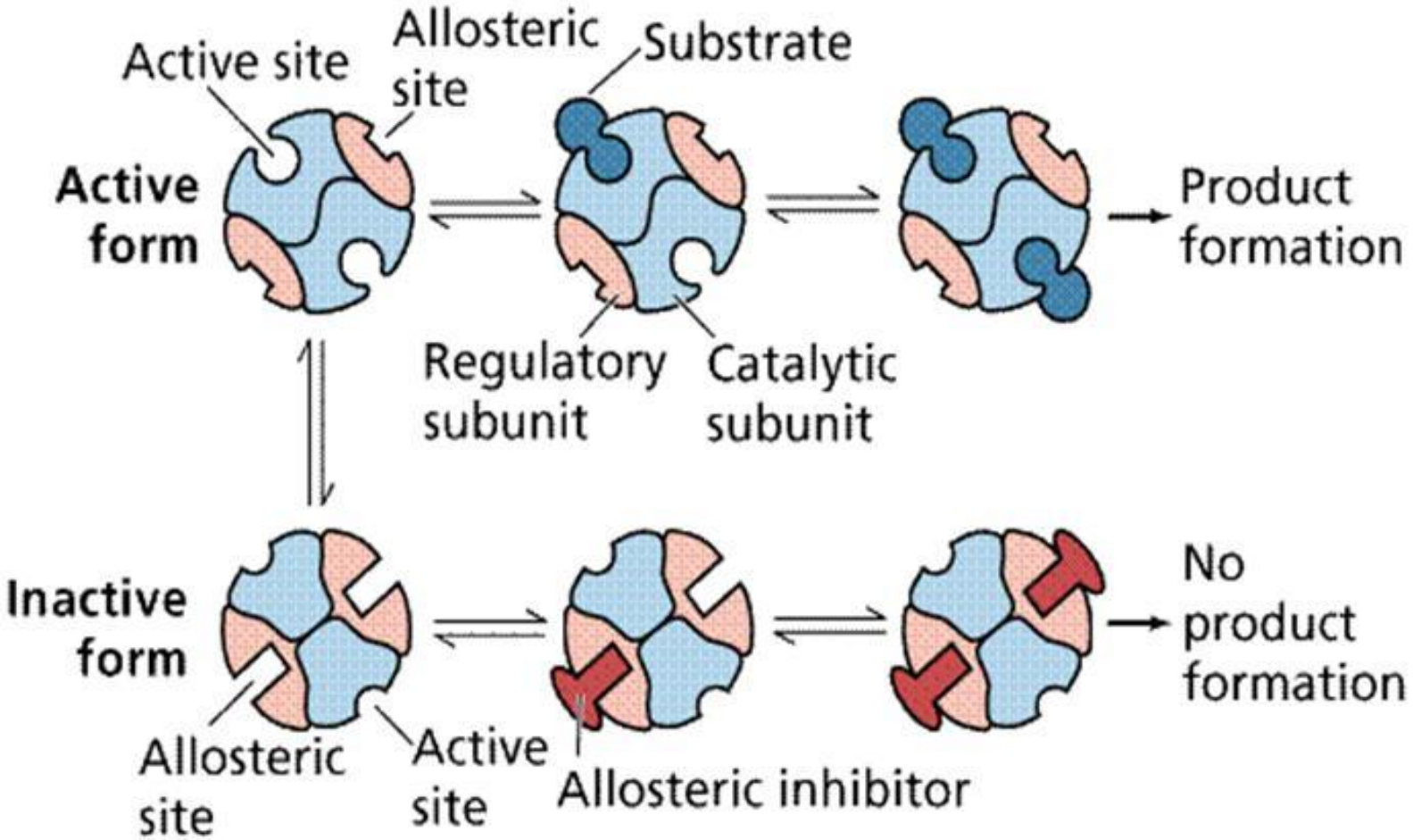
- Certain substances referred to as allosteric modulators(effectors) bind at allosteric site and regulate the enzyme activity.



- Enzyme activity increase when a positive (+) allosteric effector binds at the allosteric site known as activator site.



- Negative (-) allosteric effector binds at the allosteric site called inhibitor site and inhibit the enzyme activity.



Classes of allosteric enzymes

K-class

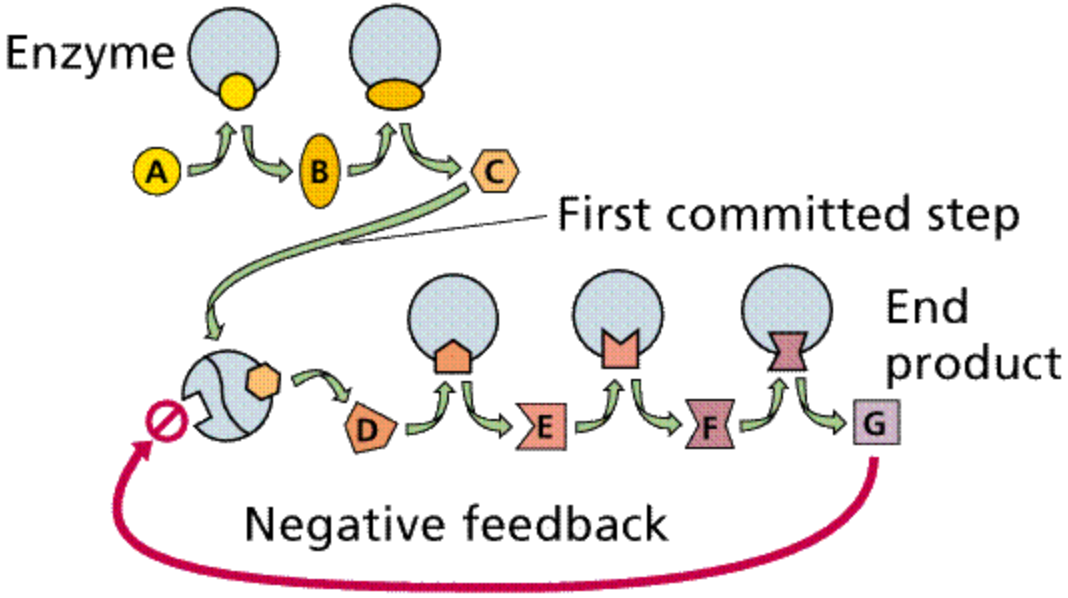
The effectors change the Km not the V max.
Double reciprocal plots ,similar to competitive inhibition,
e.g phosphofructokinase

V-class

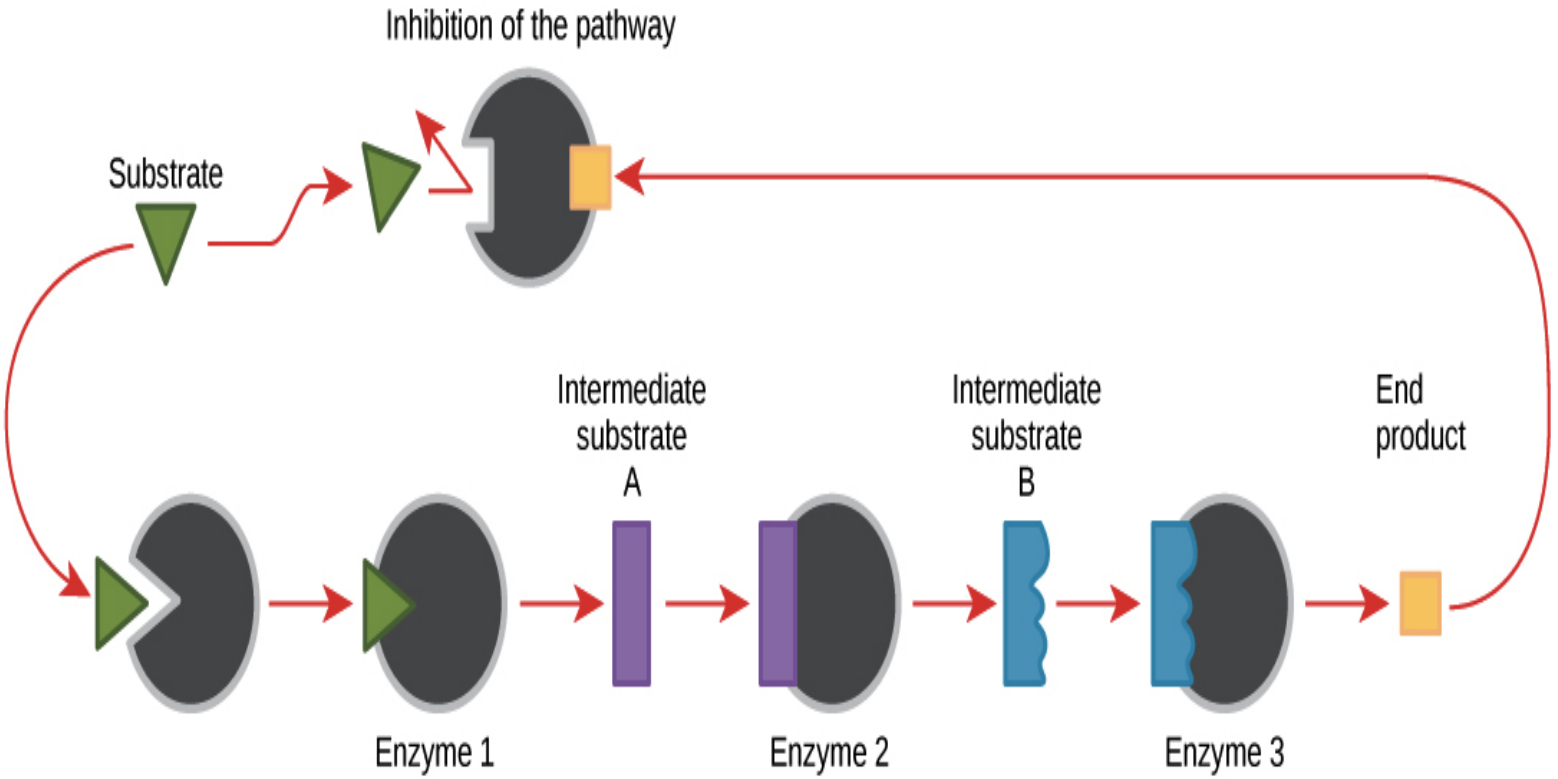
- The effector alters the V-max and not the Km .
- Double reciprocal plots resemble that of non competitive inhibition eg, acetyl CoA carboxylase.

FEEDBACK INHIBITION

- Feedback inhibition is the phenomenon where the output of a process is used as an input to control the behavior of the process itself,

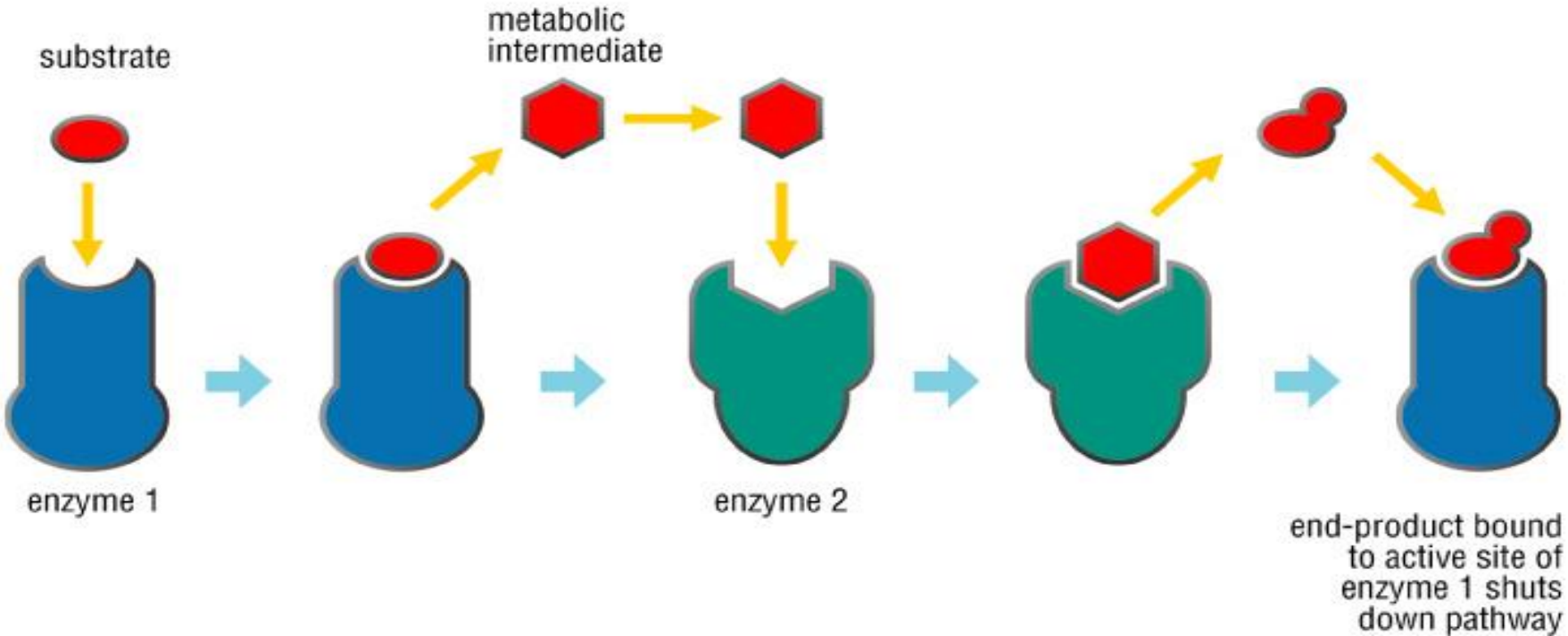


- Many enzyme catalyzed reactions are carried out through a biochemical pathway. In these pathways, the product of one reaction becomes the substrate for the next reaction.



- At the end of the pathway, a desired product is synthesized. In order to tightly regulate the concentration of that product, the biochemical pathway needs to be shut down. This is done through feedback inhibition.

From **Protein Structure and Function** by Gregory A Petsko and Dagmar Ringe



- The higher the concentration of the final product, the more likely that product will bind to the allosteric site of the enzyme, shutting down that pathway.


GOOD NEWS!