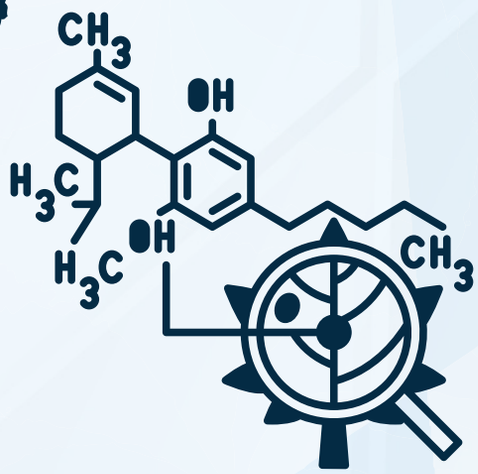
Doctor 2023
Medicine – MU



Biochemistry Sheet

Enzymology 3

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Done by :

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Enzymology- An Overview- 3 Part 1

Prof. Samir this is by far the most important lecture of enzymology topic, pay a great attention to it please 😊

Enzyme Inhibition:

- **Inhibitors are chemicals that reduce the rate of enzymatic reactions. (sometimes they may even lock enzymes activities completely).**
- **They are usually specific and they work at low concentrations.**
- **They block the enzyme but they do not usually destroy it.**
- **Many drugs (anticancer drugs [chemotherapy] stop the action of enzymes for example) and poisons are inhibitors of enzymes in the nervous system.**
- **Inhibitors of the catalytic activities of enzymes provide both pharmacologic agents and research tools for study of the mechanism of enzyme action.**

The effect of enzyme inhibition:

- **Irreversible inhibitors: (which cannot be removed and thus the enzyme cannot work) combine with the functional groups of the amino acids in the active site, irreversibly.**
- **Reversible inhibitors: there can be washed out of the solution of enzyme by dialysis and enzyme can work again normally.**

Classification: **based on:**

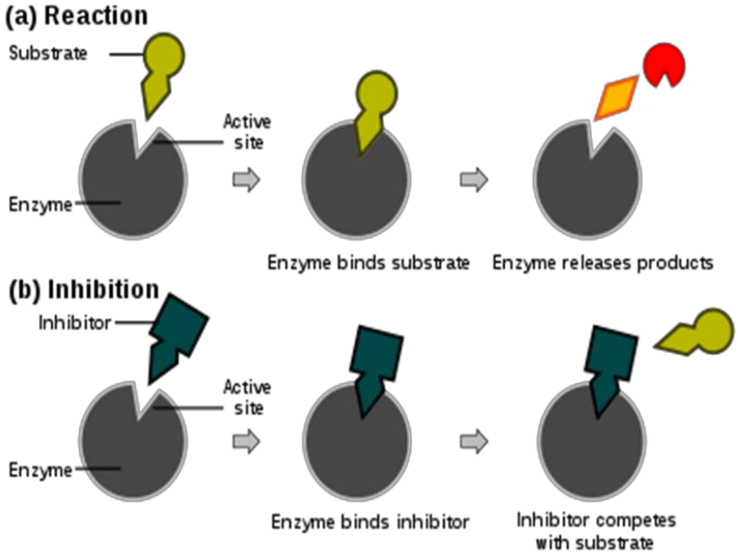
- **Their site of action on the enzyme.**
- **Whether they chemically modify the enzyme (morphological changes between the substrate and the inhibitor).**
- **The kinetic parameters they influence (Km, Vmax …)**

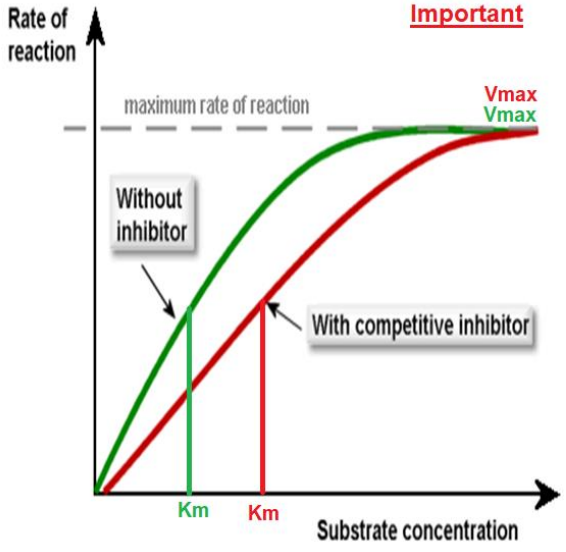
Types of enzyme inhibition:

- **Competitive inhibition.**
- **Noncompetitive inhibition.**
- **Uncompetitive inhibition.**
- **Suicidal inhibition.**
- **Allosteric inhibition.**
- **Feed back inhibition.**

1. Competitive enzyme inhibition: IMPORTANT

- **A competitive inhibitor:**
  - **Has a structure similar to substrate (structural analog)**
  - **Occupies active site**
  - **Competes with substrate for active site**
  - **Has effect reversed by increasing substrate concentration**
  - **Vmax remains same but Km is increased**
  - **So, what determines who will bind the enzyme's active site? (substrate or competitive inhibitor) it depends on their concentrations; the one with the higher concentration will bind. (i.e. when there is competitive inhibition; the inhibitor concentration is higher than the substrate concentration).**



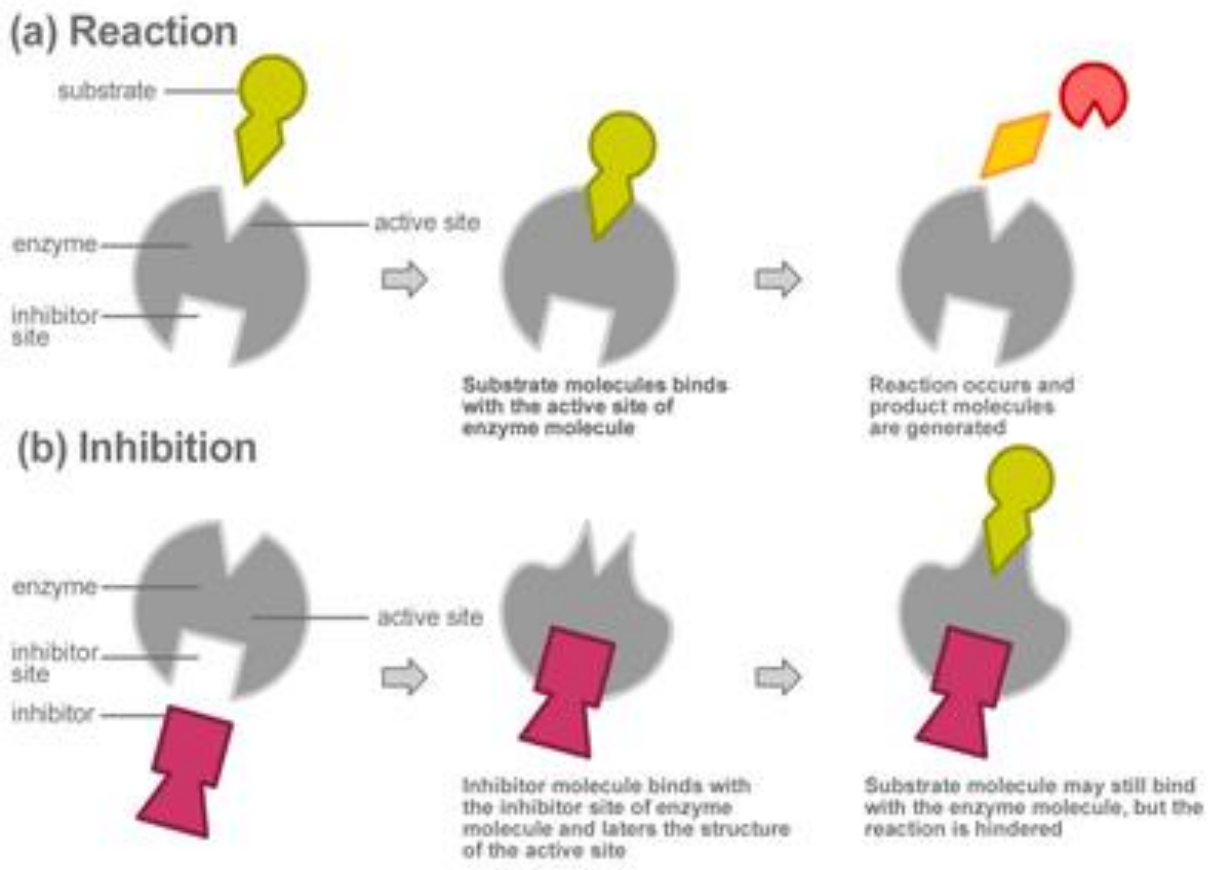


Clinical Significance of competitive enzyme inhibitors:

Drug	Enzyme Inhibited	Clinical Use
Dicoumarol	Vitamin K Epoxide Reductase	Anticoagulant
Sulphonamide	Pteroid Synthetase	Antibiotic
Trimethoprim	Dihydrofolate reductase	Antibiotic
Pyrimethamine	Dihydrofolate reductase	Antimalarial
Methotrexate	Dihydrofolate reductase	Anticancer
Lovastatin	HMG CoA Reductase	Cholesterol Lowering drug
Alpha Methyl Dopa	Dopa decarboxylase	Antihypertensive
Neostigmine	Acetyl Cholinesterase	Myasthenia Gravis

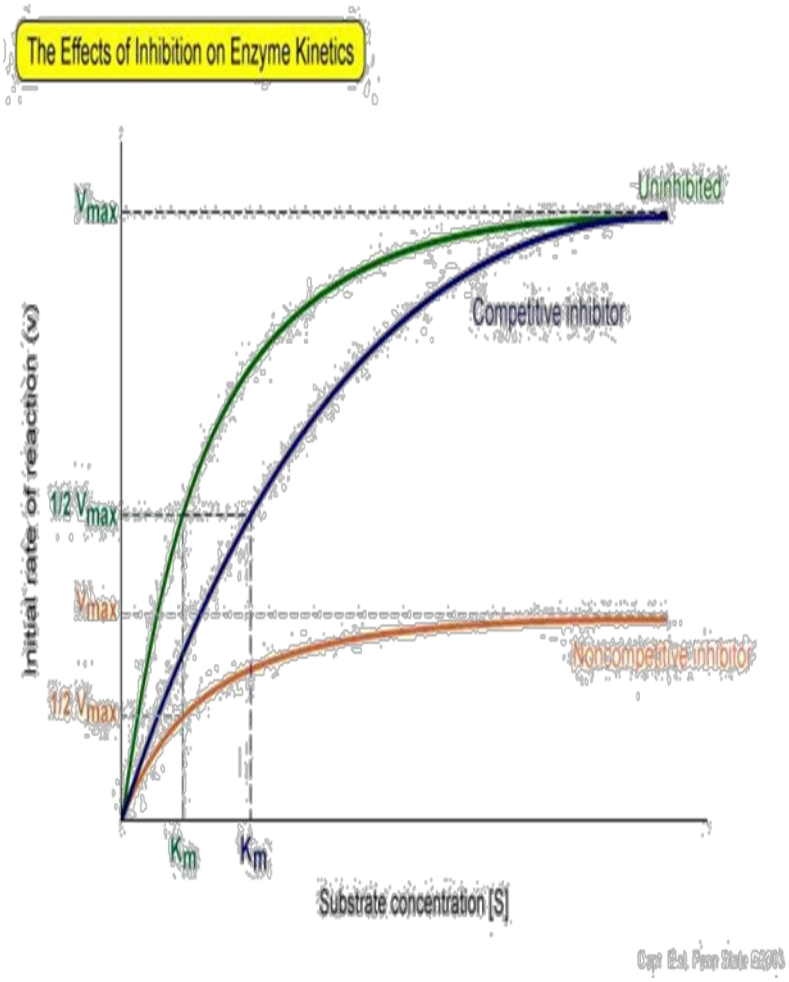
2. Non-competitive enzyme inhibition:

- **Noncompetitive inhibitors bind enzymes at sites distinct from the substrate- binding site (not in the active site).**
- **Generally, bear little or no structural resemblance to the substrate (not similar to substrate).**
- **Binding of the inhibitor does not affect binding of substrate.**
- **Formation of both EI (Enzyme- inhibitor) and EIS (enzyme- inhibitor- substrate) complexes is therefore possible.**
- **The enzyme- inhibitor complex can still bind substrate, its efficiency at transforming substrate to product, reflected by V_{max}, is decreased, while K_m will be constant.**
- **In this type of inhibition, substrate binds the enzyme after the inhibitor bind its site.**
- **This type of inhibitions reduces the efficiency of the reactants in yielding products.**



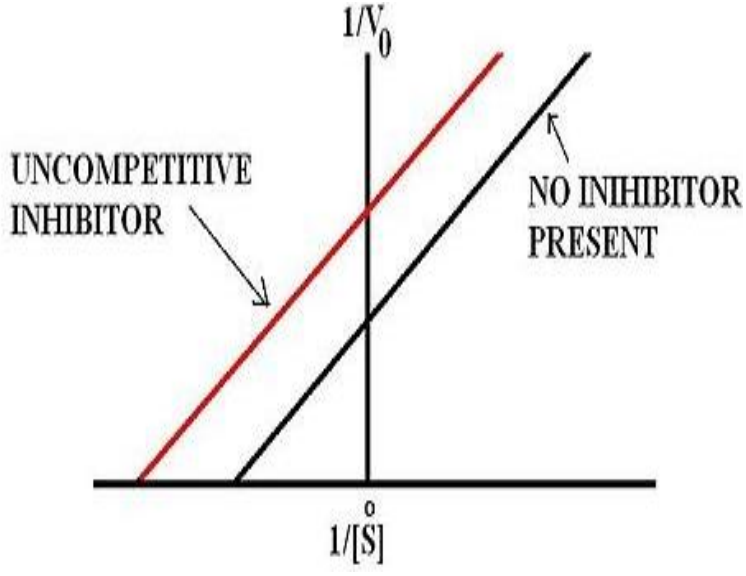
Examples of non- competitive enzyme inhibitors:

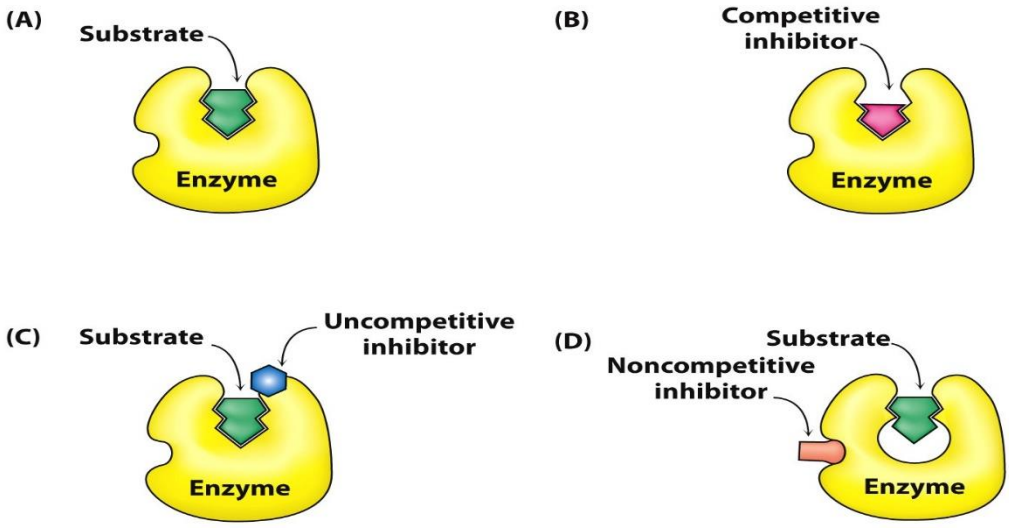
- **Cyanide inhibits cytochrome oxidase (important in electron transport chain, ETC for ATP production).**
- **Fluoride inhibits enolase and hence glycolysis (ATP production in both aerobic and anaerobic conditions).**
- **Iodoacetate inhibits enzymes having SH groups in their active sites.**
- **BAL (British Anti Lewisite, dimercaprol) is used as an antidote for heavy metal poisoning.**
- **Heavy metals act as enzyme poisons by reacting with the SH groups, BAL has several SH groups with which the heavy meal ions bind and thereby their poisonous effects are reduced. (i.e. Heavy metals are the non-competitive inhibitors, BAL has many SH groups that will attract the heavy metals to bind them instead of the enzyme; thus, preventing their inhibitory activity).**



3. Uncompetitive enzyme inhibition:

- **Inhibitor binds to enzyme- substrate complex (the substrate will bind the active site and close it then the inhibitor will bind the complex).**
- **Both Vmax and Km are decrease.**
- **Such as; inhibition of placental alkaline phosphatase (Regan isoenzyme) by phenylalanine.**
- **Substrate will never leave its place in the active site.**
- **One more time, substrate binding happens before the inhibitor.**



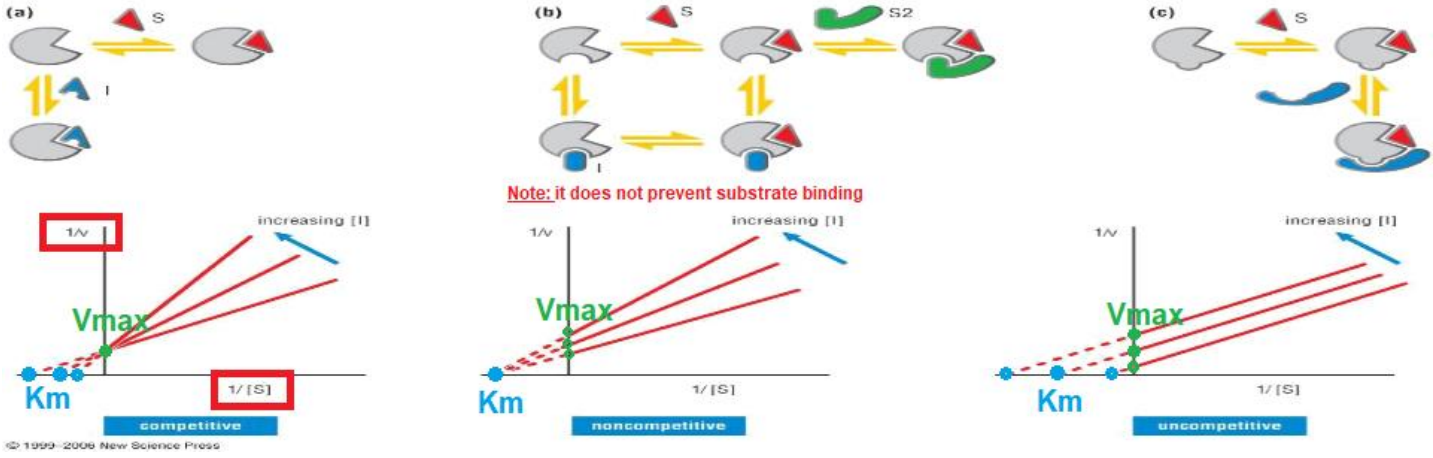


Competitive V/S Non competitive V/S Uncompetitive Enzyme Inhibition

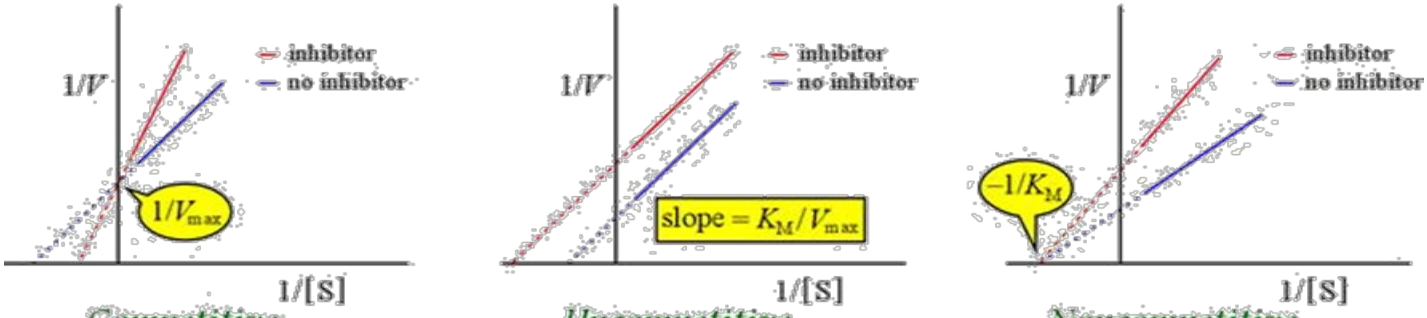
Figures here are very important:

From **Protein Structure and Function 2005-2006 Online Update**
by Gregory A Petsko and Dagmar Ringe

IMPORTANT



The Lineweaver-Burk plots for inhibition



Competitive inhibition
K_M increased
V_{max} unaffected

Uncompetitive inhibition
K_M reduced
V_{max} reduced

Noncompetitive inhibition
K_M unaffected
V_{max} reduced

4. Suicidal inhibition:

- **Irreversible inhibition (once it happens cells have to synthesize new enzyme molecules).**
- **Here, the enzyme makes an inhibitor to inhibit itself.**
- **Structural analog of the substrate is converted to more effective inhibitor with the help of enzyme to be inhibited (it is weak by itself but the enzyme makes stronger and convert it to be effective).**
- **The new product irreversibly binds to the enzyme and inhibits further reaction.**
- **Such as;**
  - **Ornithine decarboxylase: is irreversibly inhibited by difluoromethyl ornithine (non-proteinogenic amino acid), as a result multiplication of parasite is arrested. It is used against trypanosome in sleeping sickness.**
  - **Allopurinol (trade name is Zyloric) is oxidized by xanthine oxidase to alloxanthin which is a strong inhibitor of xanthine oxidase (Allopurinol is used to treat gout).**
  - **Aspirin (for headache) has an action that is based on suicide inhibition: acetylates a serine residue in the active center of cyclo-oxygenase. Thus, PG (prostaglandins) synthesis is inhibited so inflammation subsides.**
  - **Disulfiram: used in treatment of alcoholism (the active substance of alcohols is ethyl alcohol). This drug irreversibly inhibits the enzyme aldehyde dehydrogenase preventing further oxidation of acetaldehyde (oxidation of acetaldehyde produces acetic acid which has effects on central nervous system) which (accumulated acetaldehyde) produces sickening effects leading to aversion (strong dislike) to alcohol.**

سَبَقَ المُفَرِّدُونَ!
قالوا: وَما المُفَرِّدُونَ يا رَسولَ اللّه؟
قالَ: الذّاكِرُونَ اللّهَ كَثيرًا وَالذّاكِراتُ🌻

– صحيح مسلم.