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Review Article

A REVIEW ON ENZYME INHIBITORS

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ABSTRACT

Enzymes play very important role in living organism as biocatalyst. They play vital role like secretion, metabolism, digestion, DNA functions, reproduction, conversation of molecules and many other functions of body. By inhibiting specific enzymes, we can cure numerous pathological conditions in humans like inhibiting HMG CoA reductase, we can decrease cholesterol synthesis which is very useful in atherosclerosis and also use for heart diseases. ACE inhibitors can reduce concentration of Angiotensin II and use to reduce blood pressure. Many of them use as pesticides and herbicides in agriculture field. The history says enzyme inhibitors are use as arrow poison and use to kill animals by developing paralysis in them. Using a digital technology scientist identified number of enzymes and their functions as well as their 3D structure. We can easily design their inhibitors and use as medicine to treat pathological conditions. So, enzyme inhibitors became first choice for medicinal chemist and scientist as a target and play extremely important role in future as medicinal compounds and became a safe option compared to other available options.

KEYWORDS: Enzyme inhibitor, Reversible inhibitors, Suicide inhibitors, covalently inhibitors.

INTRODUCTION

Enzymes are the proteinous molecules that can increase the speed of chemical reactions or chemical process in body, so they are known as biocatalyst. Generally, enzymes are known to catalyze more than 5000 biochemical reaction type. In human body enzyme catalyzed all kind of chemical reaction that involved in body growth, coagulation of blood, process of healing, digestion of food, reproduction mechanism, process of DNA replication, transcription process, protein synthesis from amino acid, and process of signal transduction. In normal condition all enzymes first bind with substrate and form enzyme-substrate complex, it then converted to final product. Final product is separated from enzyme and the free enzyme ready to convert another same substrate to final product. Many naturally or artificial molecules binds with enzyme and change its speed of reaction. If molecule accelerate activity of enzyme, it's called enzyme activators and if molecule decrease activity of enzyme, so it's called enzyme inhibitors. Enzymes are classified on basis of their mechanism 1. Oxidoreductase, 2. Hydrolase, 3. Transferase, 4. Lyses, 5. Isomerase, 6. Ligase[1]

ENZYME INHIBITION AND ENZYME INHIBITORS

The term 'enzyme inhibition' itself means inhibition of enzymes. Inhibition by small molecules is often regarded as a control mechanism for various biological systems whose mechanism is exploited for many drugs discovery programs. In process of enzyme inhibition, we completely or partially inhibit the enzymes' reaction rate. We can cure number of pathological conditions by using enzyme inhibitors. Sometimes receptor blocking is not getting net effect what we want, at that stage we can inhibit target enzyme which give proper and perfect result.[2,3]

Molecule which can bind fully or partially with target enzyme and can inhibit its action called 'Enzyme Inhibitors'. Enzyme inhibitors are simple or complex molecules which is inorganic or organic in nature. They bind at place when subtract is bind or they can also cover up the side, when inhibitor is bind so subtract could not bind with enzyme which is our main goal. Enzyme inhibitors are very useful compound in our life because they are widely used in treatment of diseases in current time. In field of medicinal chemistry, pharmacology, biochemistry, and biotechnology enzyme inhibitors are active research area and their main goal is design, discovery and improvement of enzyme inhibitors. Enzyme inhibition study have contributed numerous information about many unanswered biological mechanisms such as blood coagulation (hemostasis), activation of complement system, blood clot dissolution (fibrinolysis), turnover of connective tissue and inflammatory reactions. The enzyme inhibitor is judged by its specificity and potency and their high value ensure its less side effect and toxicity. Concentration of enzyme inhibitors increased; activity of inhibitors decreased. Enzyme inhibitors are not only used for human being but also used for other purposed like control pests in farm as a 'pesticides'.[4,5]

Three types of enzyme inhibitors are available Reversible, Irreversible and Allosteric. There are different types of reversible enzyme inhibition like competitive inhibition, noncompetitive inhibition and mixed inhibition. Besides these regular types of enzyme inhibitions, allosteric, phosphorylation is some of the type of enzyme inhibition whose mechanisms are quite different then the above-mentioned inhibitions.

TYPES OF ENZYME INHIBITION

Reversible enzyme inhibition

The name suggests that molecule which inhibit enzyme is not covalently bound with enzyme and after some time it leaves from enzyme, and we get free enzyme after limited time. Reversible enzyme inhibitors are attaching with enzyme by weak interaction like hydrogen bond, hydrophobic interactions and ionic bond which can break after limited time. Many weak interactions produce at same time and form sufficient strong binding between inhibitor and enzyme. They are good choice compared to irreversible inhibitors. Enzyme activity is regained with the help of dilution or dialysis. The inhibition is depending upon type of binding with enzyme and enzyme-substrate complex. Reversible inhibitors can classify into three classes Competitive, Non-Competitive and Uncompetitive inhibitors.[6,7,8]

Competitive inhibitors

Competitive inhibitors are the inhibitors which only binds with enzyme not enzyme-substrate complex because here affinity of substrate and enzyme have not major difference. Here inhibitor has only affinity for active side not allosteric site. Once enzyme-substrate complex is successfully produced then inhibitors cannot produce its effect. This type of inhibition can be overcome by adding high concentration of substrate. Degree of inhibition is depending on concentration of substrate and inhibitor.[9]

Some common useful drugs which show this kind of inhibition are statins like atrovastatin, which inhibit HMG CoA reductase enzyme and used for the treatment of atherosclerosis as Anti-hyperlipidemic agent. Allopurinol is Xanthine oxidase inhibitor which use in treatment of gout. Methotrexate is inhibiting Dihydro folate reductase enzyme and use in combination with sulfonamides. Angiotensin converting enzyme inhibitors like captopril, enalapril, ramipril etc. which use for cardiac and high blood pressure patients.

Non -Competitive inhibitors

Non-competitive inhibitors bind with enzyme but not at active binding site. The rate of inhibition is directly depending on concentration of inhibitor. In this mechanism enzyme-inhibitor and enzyme-inhibitor-substrate complex formation is possible. Very common examples are ethanol and narcotic drugs are non-competitively inhibit acid phosphate. Example is Pepstatin which is potent inhibitors of aspartyl proteases.[10]

Un-competitive inhibitors

Uncompetitive inhibitors are only binding to enzyme-substrate complex. It is not bind to free enzyme. They work by structural distortion of the active site, and after change in active site structure biological agonist molecule could not bind with active site. If agonist molecule not properly binds to active site, pharmacological action does not produce. In this kind of inhibition Vmax K_m both decreased.[11]

Table 1: Difference between competitive, non-competitive and un-competitive inhibitors

Competitive inhibitors	Un-competitive inhibitors	Non-competitive inhibitors
The inhibitors bind the catalytic/substrate binding site.	Substrate binding exposes the inhibitors binding site away from the catalytic/substrate binding site.	The inhibitor binds each of the free enzyme and the substrate-enzyme complex away from the catalytic/substrate binding site.
It competes with substrate for binding.	Increasing substrate concentration does not reverse the inhibition.	Increasing substrate concentration does not reverse the inhibition.
Inhibition is reversible by increasing substrate concentration.	The inhibited reaction rate parallels the normal one as reflected on decreased both $V_{max}$and $K_{m.}$	Only $V_{max\ is}$ decreased proportionately to inhibitor concentration.
V_{max} constant, the substrate concentration has to be increased as reflected on increased $K_{m.}$		$K_m$is unchanged since increasing substrate concentration is ineffective.
Therapeutic application		Toxicological application
Inhibitor does not change the shape of the active site of enzyme.		Inhibitor does change the shape of the active site of enzyme.
If substrate concentration is increased, them inhibition rate is decreased.		No effect of substrate concentration is on the inhibition rate of enzyme.

Table 2: Difference between reversible and irreversible inhibitors

Reversible inhibitors	Irreversible inhibitors
Enzymes do follow Michaelis-Menten rate equation and Lineweaver-Burk plot.	Enzymes do not follow Michaelis-Menten rate equation and Lineweaver-Burk plot.
Plot [V] versus [S] curve is Rectangular hyperbolic shape curve.	Plot [V] versus [S] curve is Sigmoidal curve.
Dissociate very rapidly from targeted enzyme because of loosely bound.	Dissociate very slowly from targeted enzyme because of tightly bound.
Classified into three categories. Competitive, non-competitive and mixed inhibitors	Classified into three categories. Group specific reagents, substrate analogs and suicide inhibitors.
Competitive inhibitors can be reversed by increasing substrate concentration.	Substrate analogs imitate enzyme substrate and irreversibly modify the active site of the enzyme.
Reversible inhibitors bind to enzyme by hydrogen bonding, hydrophobic interactions and ionic bonds.	Irreversible inhibitors bind to enzyme through covalent interactions which modify amino acid residues by reactive functional groups.
Reversing of reaction possible	Reversing of reaction not possible
Inhibitor once remove, free enzyme being to work again	Inhibitor once remove, free enzyme does not work again

IRREVERSIBLE INHIBITION

Irreversible inhibitors bind with enzyme and change enzyme chemically by formation of covalent bond with it. In enzyme structure some key amino acids are present which is essential for activity, irreversible inhibitors tightly bind with enzyme. Inhibitors binds covalently (strongly) with enzyme irreversibly. So, it can't dissociate from enzyme. Enzyme's activity is not regained by dialysis or increasing concentration. They are also called suicide inhibitors because they attach to enzyme for long

time and not easily detach from binding site, that's why toxicity can create, and it will become reason for death. [12]

Best examples of irreversible inhibitors are 1. Disulfiram which is alcohol dehydrogenase inhibitor. Disulfiram is used to treat alcoholism.2. Malathion, an acetylcholine esterase inhibitor which is used as organophosphorus insecticides.

ALLOSTERIC INHIBITION

It is the type of enzyme inhibition where reactions in a pathway are catalyzed by different enzymes in sequence and the final end-product produced may be responsible for inhibiting the activity of the first enzyme of the series. There is a complete change in structural features of the inhibition caused by the final end product from the substrate molecule. Such an inhibition is known as allosteric inhibition and the enzyme involved is known as allosteric enzyme. Some Enzymes have addition site other than active site called allosteric site which is very important target for medicinal chemist and research associates. It has a unique site on protein molecule. There are two types of it, positive allosteric in which enzyme activity is increased and Negative allosteric in which enzyme activity is decreased.[13] When an inhibitor binds to allosteric site, the configuration of catalytic site is modified such that substrate cannot bind properly and if substrate does not bind properly so enzyme is not giving action and as the result enzyme action is inhibited.

If we see the kinetics of this kind of inhibition, Km is increased, and Vmax is decreased. The allosteric enzymes are modulated by non-covalent binding of some specific metabolite. They usually catalyze the first or the most important reaction of a multi-enzyme sequence and are generally inhibited by the end product of the sequence which binds to a specific regulatory or allosteric site on the enzyme molecule. Allosteric enzymes are usually irreversible under intracellular condition. They are usually much larger in molecular weight and more complex in configuration. Some of them are unstable at zero degree but stable at room/body temperature.[14,15]

Allosteric enzymes having a single modulator are called monovalent and having multi modulators are called polyvalent. Allosteric enzymes show two different types of control – heterotropic and homotropic. Heterotropic enzymes are stimulated/inhibited by an effector (modulator) molecule other their substrate. Homotropic enzymes are modulated by their substrate itself. However, a large number of allosteric enzymes are of mixed homo-heterotropic type. One special kind of allosteric inhibition is negative feedback/end product inhibition in this required to control metabolic pathways for efficient cellular functions. End product of the metabolic pathway is produced in large amount and inhibits first and regulatory enzymes.[16]

Properties of Allosteric enzymes

1. Allosteric enzymes do not follow the Michaelis-Menten Kinetics as they have multiple active sites. All these active sites exhibit the cooperatively property in the enzyme. Binding of one active site influences the affinity of other active sites on the enzyme.

2. Allosteric Enzymes are regulated by some other agents. This is noticed in the condition, the molecules 2, 3-BPG, pH, and CO2 modulates the binding affinity of hemoglobin to oxygen. 2, 3-BPG reduces the binding affinity of O2 to hemoglobin by stabilizing the T- state. In this Lowering the pH from physiological pH=7.4 to 7.2 (pH in the muscles and tissues) helps in the release of O2. Hemoglobin often releases oxygen in CO2 rich areas in the body.[17]

PHOSPHORYLATION

Phosphorylation is an important enzyme inhibition by which the activity of proteins can be altered after they are formed. A phosphate group is added to a protein by specific enzymes called kinases. This phosphate group is usually provided by ATP, the energy carrier of the cell. Phosphorylation is the chemical addition of a phosphoryl group (PO3-) to an organic molecule. The removal of a phosphoryl group is called dephosphorylation. Both phosphorylation and dephosphorylation are carried out by enzymes (e.g., kinases, phosphotransferases). Phosphorylation is important in the fields of biochemistry and molecular biology because it's a key reaction in protein and enzyme function, sugar metabolism, and energy storage and release.

Three kinds of phosphorylation occur in body. Glucose phosphorylation, oxidative phosphorylation, protein phosphorylation. In Glucose phosphorylation the phosphorylation of glucose can be enhanced by the binding of Fructose-6-phosphate and lessened by the binding fructose-1-phosphate. Allosteric activation by glucose 6 phosphate, which acts as an effector, stimulates glycogen synthase, and glucose 6 phosphate may inhibit the phosphorylation of glycogen synthase by cyclic AMP-stimulated protein kinase.[18]

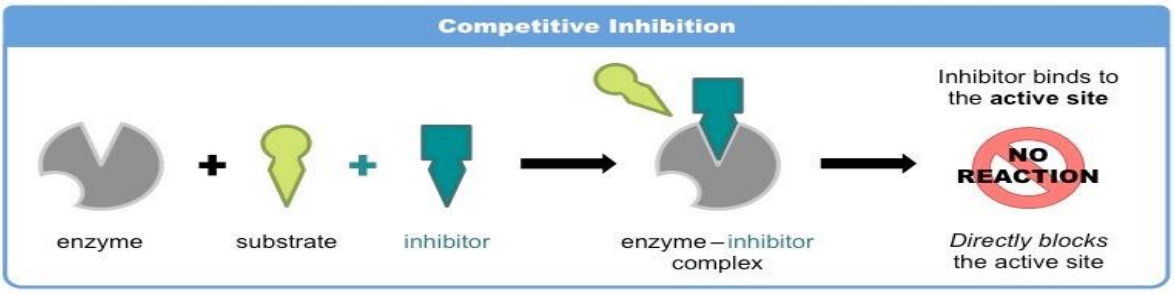

Fig 1: Mechanism of competitive inhibition

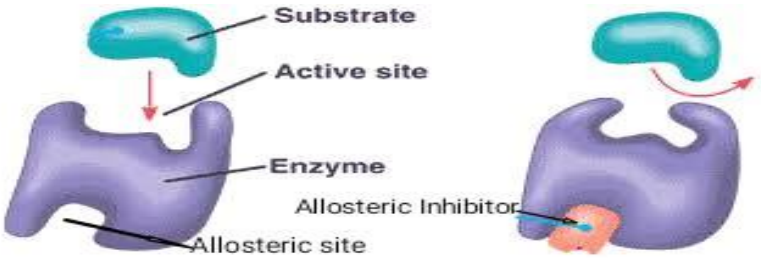

Fig 2: Mechanism of Allosteric inhibition

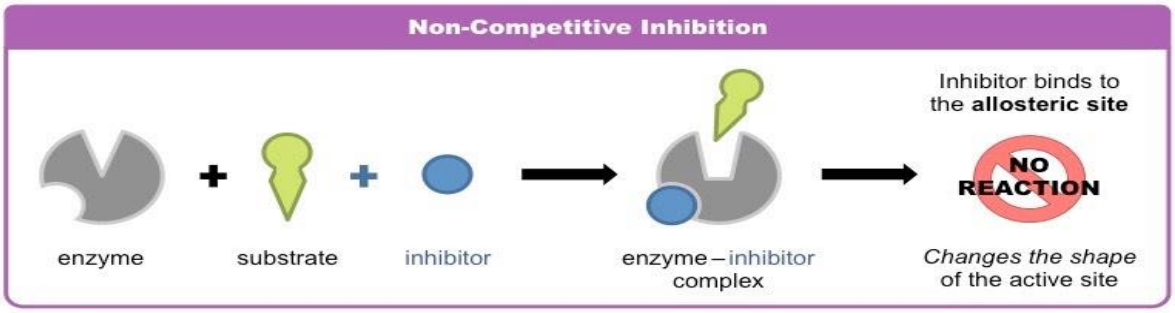

Fig 3: Non-Competitive inhibition

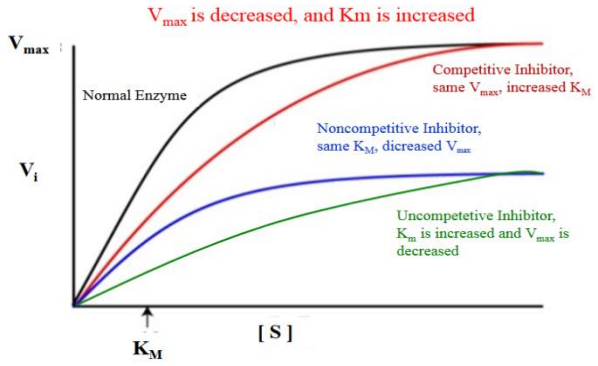

Fig 4: Kinetic curve of enzyme inhibitors

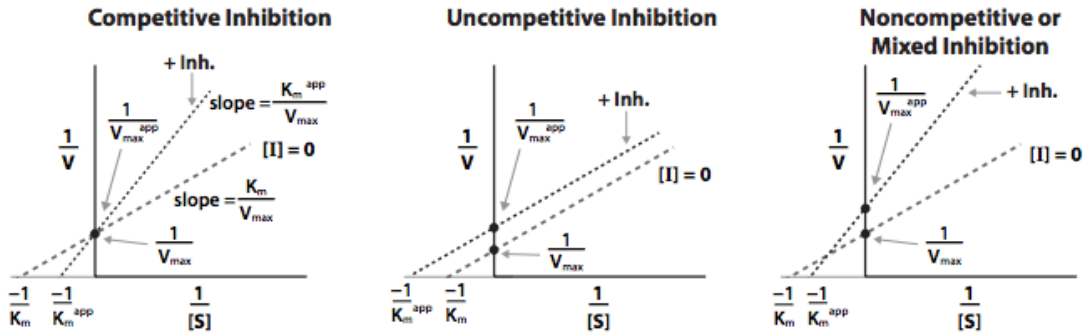

Fig 5: Kinetics of Enzyme Inhibitors

MECHANISM OF INHIBITION

Competitive inhibition

The structural resemblance of the competitor matches of the substrate and therefore binds to the active site competitively. But when competitive inhibitor's concentration exceeds that of the substrate, competitive inhibitor binds to the active binding site to form enzyme inhibitor complex (EI) and finally no product is formed. It is complete ambiguous information that inhibitors lash out the substrate from the enzyme. Rather, the fact is that the inhibitor would bind to the Enzyme substrate complex and would compel the substrate to dissociate from the enzyme through a thermodynamic principle where the binding between the substrate/inhibitor and the enzyme is governed by the concentration and affinity of the former and the later.

In a normal enzymatic activity, Vmax is the maximum velocity of the reaction while Km (or Michaelis-Menten constant) is the substrate concentration which is halfway to Vmax. Km is a suitable measuring unit to measure the rate of reaction with

increasing concentration of substrate. Lower the Km, higher is the affinity for the substrate (dissociation constant increases KI) and vice-versa. A plateau occurs in the graph because all the enzyme molecules are saturated with available substrates and no enzymes other than substrates left for further binding. That means, the extra available substrates left out is due to unavailability of enzymes which may be a rate limiting factor for the rate of the reaction. But in competitive inhibition, Vmax remain unchanged, or the reaction reaches its normal Vmax but to reach that point, higher concentration of Km is required.[19] (Fig 1)

Allosteric inhibition

Allosteric inhibition occurs due to the presence of allosteric site on the surface of the allosteric enzyme. This site is totally far from the active site of the enzyme. The accumulated final end-product perfectly fits to the allosteric site. It brings a structural change of the enzyme in such a way that the active site of the enzyme is unable to fit for making complex with its substrate. The allosteric inhibition is a reversible phenomenon. When the concentration of the final end product in the cell decreases, it leaves the allosteric site. Then the activity of the allosteric enzyme is restored in cells. (Fig 2)

Non-competitive inhibition

In non-competitive inhibition, there is no similarity between the structure of the substrate and the inhibitor. The inhibitors bind with the enzyme at sites other than the substrate binding site leading to the formation of both enzyme-inhibitor (EI) and enzyme-inhibitor-substrate (EIS)complexes. The inhibitor forms non-covalent bonding with the enzyme and so the enzyme inhibition can be reversed by simply removing the inhibitor. In simple non-competitive inhibition, both enzyme and enzyme inhibitor complexes have similar affinity for the substrate whereas the enzyme-inhibitor-substrate complex produces product in a very small amount. More complex non-competitive inhibition occurs when inhibitor binding affects the apparent affinity of the enzyme for substrate.

The inhibitor binds to some other site located in the same enzyme and changes the total shape of that site for the substrate to fit into as earlier, which ultimately slow down the reaction that is taking place. The reaction gets slowed down but never stopped. Non-competitive inhibition minimizes the turnover rate of enzyme instead of interfering with the quantity of substrate binding to the enzyme. As the inhibitor is not competing with the substrate, the inhibitor's effect cannot be withdrawn by increasing substrate levels. Heavy metal ions for example Ag+, Pb++, Hg++ etc. can inhibit the enzymes by binding non-competitively with cysteinyl sulfhydryl groups.[20] (Fig 3)

COVALENT AND NON-COVALENT INHIBITION

Covalent inhibition is rapidly evolving method in the area of drug discovery. Covalent drugs binding is irreversible, it specifically binds to a drug target and model a properly directed permanent bond with their target. Approximately; 30% of overall drugs in the market enzymes are covalent drugs. Inhibitory interaction is defined by the formation of covalent bond between electrophile moiety of inhibitor and the efficient side chain moiety of the inhibitor and the efficient side chain moiety of definite residues at the active site of enzyme target.[21]

Advantages

- Selective irreversible covalent inhibitors have been the focus of intensive, comprehensive exploration.
- Protein targets offer the amino acid residue for an appropriate covalent drug to directly affect the reaction mechanism.
- Covalent drug design is an increasing and promising areas; the amount and variety of covalent inhibitors and knowledge reaches in this field of drug discovery is increasing.
- There are plenty of strategies for covalent drug design development projects and computational chemistry technology can have a vital impact on covalent inhibitors design.

For non-covalent usually dependent on the development of small inhibitors that bind to a target non-covalently and the subsequent enhancement of potency and selectivity. Non-covalent drugs bindings is reversible, that interact with their target constantly through binding, rebinding and unbinding. It plays essential role in structure-based design of new substituents with specific properties. Non -covalent interaction like hydrogen bonding, hydrophobic interaction, Vander Waals interaction, electrostatic interaction and salt bridge has been the main focus in designing and improving drugs. Reversible noncovalent inhibitors, in most cases bind to the target's active site with relatively high affinity than that of natural substrate analogue.

DESIGN AND DEVELOPMENT OF ENZYME INHIBITORS

New medications are the products of a long medication growth process, the first step of which is often the growth of a new enzyme inhibitor. In the past the only way to discover these new inhibitors was by test and error, testing large collections of substances against a focus on enzyme and expecting that some useful brings would appear. This incredible power strategy is still effective and has even been prolonged by combinatorial substance make up techniques that quickly generate huge variety of novel compounds and high throughput testing technological innovation to quickly display these large substance collections for useful inhibitors.[22]

More recently, substitute strategy has been applied logical medication. Design uses of the compound three-dimensional framework of an enzyme's effective site to estimate which elements might be inhibitors. These forecasts are then tested and one of these tested may be a novel inhibitor. This new inhibitor is then used to try to acquire a framework of the compound in an inhibitor/enzyme complicated to demonstrate how the molecule is binding to the active site, enabling changes to be created to the molecule to try to optimize executed. This analyze and enhance pattern is then recurring until a completely effective chemical is created. Computer-based techniques of forecasting the appreciation of an inhibitor for an enzyme are also being designed, such as molecular docking and molecular techniques.

APPLICATION'SOF ENZYME INHIBITORS

Enzyme inhibitors can be synthesized in laboratory, and many are found in nature. Naturally obtain inhibitors are generally poisonous substances and use to kill animals in history. Synthetic inhibitors are used for treatment of number of diseases but many of them use to kill insects like malathion (insecticides), glyphosate (herbicides), and triclosan (disinfectants). Acetylcholinesterase inhibitors use as chemical weapon in warfare. [23]

Enzyme inhibitors in relation to chemotherapy

Enzyme inhibitors are promising agents for cancer chemotherapy. Leupeptin was originally isolated as an inhibitor against serine or thiol protease and soon it was found that leupeptin suppressed chemical carcinogenesis in rats. Pepstatin inhibits ascites accumulation caused by neoplastic diseases. Bestatin is a specific inhibitor against aminopeptidase B and leucine aminopeptidase.

The enzymes are located on the surface membrane in various kinds of cells including lymphocytes. Combined use of bestatin and other antitumor agents gave promising results in animal experiments. Bestatin is used for treatment of lung cancer. In anticancer treatment aminopeptidase inhibitors widely used in drug combination. Some examples of aminopeptidase N inhibitors (CD13) are bestatin, BC-02. BC 02 is a novel mutual prodrug of bestatin and 5FU, used in hepatocellular carcinoma (HCC).

Enzyme inhibitors in cardiovascular disease

Angiotensin converting enzyme (ACE) inhibitors inhibit the biosynthesis of Angiotensin II from angiotensin I. Examples of ACE inhibitors are ramipril, captopril, enlapril, perindopril and fosinopril.

Enzyme inhibitors in central nervous system

Acetylcholinesterase inhibitors also known as anticholinesterases. They act by enhancing the effects of acetyl choline at synapse by inhibiting its metabolism by inhibiting the Acetyl cholinesterase (AChE) enzyme. There are two classes of AChE inhibitors: Reversible inhibitors and Irreversible inhibitors. Examples of reversible inhibitors are Physostigmine, Neostigmine bromide, Pyridostigmine bromide, Tacrine and Ambenoniumchloride. Examples of irreversible inhibitors are Echothiophate iodide, Parathion and Malathion.

Table 3: Enzyme inhibitors use to treatment of various diseases

Sr. No.	Drugs	Targeted Enzyme	Use
1	Physostigmine, Neostigmine, Pyridostigmine, Edrophonium, Rivastigmine, Donepezil, Galantamine, Tacrine	Choline-esterase (Reversible)	Miotic, Myasthenia Gravis, Cobra Bite, Alzheimer's Disease, Post-operative Decurarization
	Dyflos, Echothiophate, Parathion, Diazinon, Tabun, Sarin, Soman	Choline-estrase (Irreversible)	
2	Aspirin, Ibuprofen, Ketoprofen, Flurbiprofen, Mefenamic acid, Diclofenac, Aceclofenac, Piroxicam, Tenoxicam, Ketorolac, Indomethacin, Phenylbutazone, Oxyphenbutazone	Cyclooxygenase (COX)(Nonselective)	Analgesic, Anti-pyretic, Acute rheumatic fever, Rheumatoid arthritis, Osteoarthritis, Post myocardial infection
	Nimesulide, Meloxicam, Nabumetone	COX-2 (Preferential)	
	Celecoxib, Etoricoxib, Parecoxib	COX-2 (Selective)	
	Paracetamol, Metamizol, Propiphenazone, Nefopam	COX	
3	Acarbose, Miglitol	α-Glucosidase	Diabetes
4	Finasteride, Dutasteride	5 α-Reductase	Testosterone Deficiency
5	Sildenafil, Tadalafil, Vardenafil,	Phosphodiesterase-5-	Erectile Dysfunction
6	Letrozole, Anastrozole, Exemestane	Aromatase	Breast Cancer
7	Disulfiram	Aldehyde dehydrogenase	Chronic Alcoholism
8	Carbidopa, Benserazide	Peripheral decarboxylase	Parkinson Diseases
9	Selegiline	MAO-B	Parkinson Diseases
10	Entacapone, Tolcapone	COMT	Parkinson Diseases
11	Moclobemide, Clorgyline	MAO-A	Antidepressant, antianxiety
12	Captopril, Enalapril, Lisinopril, Perindopril, Fosinopril, Trandolapril, Ramipril, Imidapril, Benazepril	Angiotensin converting enzyme	Hypertension, Chronic heart failure, myocardial infraction, diabetic nephropathy, scleroderma crisis
13	Amrinone, Milrinone	Phosphodiesterase III	Chronic heart failure
14	Acetazolamide	Carbonic anhydrase	Diuretics
15	Betrixaban, Apixaban, Rivaroxaban, Edoxaban	Factor Xa	Venous Thromboembolism, Pulmonary embolism
16	Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin	HMG-CoA reductase	Hypolipidemic drug
17	Trimethoprim	Dihydrofolate reductase	Various Bacterial Infections
18	Ciprofloxacin, Norfloxacin, Ofloxacin, Pefloxacin, Levofloxacin, Lomefloxacin, Gatifloxacin, Moxifloxacin	Bacterial DNA Gyrase	Various Bacterial infections like Gonorrhoea, Chancroid, Typhoid, Tuberculosis, and Meningitis.
19	Penicillin and Cephalosporins	Transpeptidase	Various Bacterial infections
20	Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir	Reverse transcriptase	Viral infection
21	Ritonavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir, Lopinavir	Protease	Viral infection
22	Allopurinol	Xanthine oxidase	Gout

CONCLUSION

Enzyme inhibitors are the compounds which play an essential role in pharmaceuticals, biochemistry, and pharmacology. Enzyme is present in whole body and associated with almost all metabolic processes that's why enzyme is best target for treatment. They are safe option for the treatment of various pathological conditions. They are safe option as compared to the cell targeted drug and compare to low dose required so side effects are lesser than it. On the basis of study, we can say that reversible inhibitors are good as compared to non-reversible inhibitors because non-reversible inhibitors can create toxicity. Allosteric inhibitors are the best inhibitor compared to other because they don't face any competition to binding site.

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